Diploma thesis

Non-surgical Debridement in Plastic Surgery: A Systematic Review

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Graz, am 03.09.2019 *Alen Palackic eh*

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Zusammenfassung

Hintergrund: Für das Debridieren von chronischen Wunden und Verbrennungen werden chirurgische Methoden als Standardverfahren angesehen. Alternativen zum chirurgischen Debridement sind enzymatische, autolytische oder biomechanische Methoden. Diese systematische Übersichtsarbeit wurde mit Hilfe der PRISMA Guidelines erstellt, um herauszufinden, welche alternativen Methoden sich etabliert haben und deren Evidenz zu beschreiben.

Methoden: Das Review Protokoll wurde auf PROSPERO registriert (CRD42017057590). Im Oktober 2016 wurden mit vordefinierten MESH Begriffen zum Thema nicht chirurgischen Debridement die PubMed und Web of Science Datenbanken durchsucht. Ergebnisse wurden systematisch in Microsoft Excel Tabellen exportiert und Duplikate entfernt. Nach definierten Einschlusskriterien wurden nur diese Artikel eingeschlossen, welche den Kriterien entsprachen. Diese wurden dann nach ihrem Level of Evidence (LoE) I-V eingestuft. Artikel mit einem LoE I wurden in die systematische Übersichtsarbeit inkludiert.

Ergebnisse: Es konnten 8042 Artikel zu den MESH Begriffen identifiziert werden. Nach der systematischen Synthese wurden 8 Artikel, welche eine LOE I hatten, in die finale Analyse inkludiert. Drei Studien untersuchten die Therapie mit Larven und verglichen sie mit Hydrogelen. Sie zeigten, dass sie ein schnelleres Debridement ermöglichten als eine Behandlung mit Hydrogelen; jedoch war diese Behandlung mit stärkeren Schmerzen verbunden. Eine einzige Studie verglich die Larven Therapie plus Kompression mit Kompression ohne Debridement. Hier konnte gezeigt werden, dass sich die Therapie mit Larven in Bezug auf die Geschwindigkeit des Debridements gute Resultate erzielen ließen. In keiner dieser Studien zeigte das Debridieren mit Larven eine signifikant positive Auswirkung auf die Wundheilung. Eine Studie untersuchte Kollagenasen für das enzymatische Debridement von Diabetischen Fußulzera. Diese haben in dieser Studie bei allen Patientinnen eine signifikante Reduktion der nekrotischen Areale erzielt. Weiters wirkte sich das enzymatische Debridement mit Clostridium Collagenase positiv auf die Wundheilung aus. Eine Studie untersuchte das enzymatische Debridement mit Nexobrid bei Verbrennungen, und zeigte, dass sie den Gebrauch von konventionellen chirurgischen Methoden reduzieren konnten.

Diskussion: Mit der Ausführung dieser systematischen Übersichtsarbeit konnte gezeigt werden, dass es Literatur zu nicht-chirurgischen Debridement Methoden in der Plastischen Chirurgie, zur Behandlung von chronisch nekrotischen Wunden und Verbrennungen gibt. Bei Verbrennungen gibt es bis dato nur wenig Evidenz für das enzymatische Debridement. Das enzymatische Debridement mit Nexobrid sollte im Auge behalten werden; diese nicht-chirurgische Methode erzielte gute Ergebnisse für das Debridieren, mit gleichzeitiger Reduktion von invasivem chirurgischem Debridement. Weiters zeigten sich im Langzeitverlauf weniger Narben, da weniger Spalthaut benötigt wurde. Auch für die Behandlung von chronischen nekrotischen Wunden mit Enzymen konnten wenige Evidenzen gefunden werden. Das Debridement mit Larven zeigte gute und schnelle Ergebnisse, dennoch konnte kein positiver Einfluss auf die Wundheilung gezeigt werden. Diese Ergebnisse müssen noch in weiteren prospektiven randomisierten Studien bestätigt werden. Das Debridieren mit Kollagenase Salben zeigte ebenfalls gute Resultate bei der Behandlung von nekrotischen diabetischen Fußulzera, dennoch sind noch weitere Studien notwendig um dies zu bestätigen.

Abstract

Background: Many different non-surgical debridement methods are available for the treatment of chronic necrotic ulcers and burn wounds. So far, there is no existing systematic review describing these procedures in relation to each other for the field of plastic surgery. Hence, we conducted a systematic review to outline established therapy approaches and to see if there is evidence for the use of non-surgical debridement methods for chronic necrotic ulcers and burns.

Methods: The review protocol was registered on PROSPERO (CRD42017057590). In October 2016, pre-defined MESH terms on non-surgical debridement methods were used to search the PubMed and Web of Science databases. Results were systematically exported to an Excel spreadsheets and duplicates removed. Non-suitable articles were excluded following defined exclusion criteria and then classified according to their Level of Evidence (LoE) I-V. Studies with a LoE I were included in the systematic review.

Results: In total, 8042 articles could be identified using the pre-defined MESH-terms. After the systematic synthesis, 8 articles, which had an LOE I, were included in the final analysis. Three studies examined larval therapy and compared it to hydrogels. They showed that they enabled faster debridement than treatment with hydrogels; however, this treatment was associated with greater pain. A single study compared the larval therapy plus compression with compression without debridement. Here it could be shown, that the therapy with larvae achieved good results in regards to the speed of debridement. In none of these studies the therapy with larvae had a significantly more positive effect on wound healing. One study examined Clostridium Collagenase ointment (CCO) for the debridement of diabetic foot ulcers. In this study, all patients achieved a significant reduction in necrotic areas. In addition, enzymatic debridement with CCO had a positive effect on wound healing. One study investigated enzymatic debridement with NexoBrid (NXB) in burns, and showed that they could reduce the use of conventional surgical methods.

Discussion: This systematic review demonstrates that there is a lack of evidence for non-surgical debridement methods in the treatment of necrotic sloughy ulcers and burns. Based

on our results, larval debridement therapy seems to be faster than conventional methods using hydrogel. However, they don't improve wound healing, so they might be used for more acute complex wounds. More randomized trials are needed in order to confirm these results. NXB, an enzymatic selective debriding agent, seems to be a good alternative approach for deep and full thickness burns. Results showed that there is less debridement dependent blood loss, less scars and reduced need for surgical interventions in comparison with conventional methods.

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1. Introduction

1.1 Definition of Debridement

Debridement is the removal of dead (necrotic) or infected tissue and the removal of foreign matter in wounds, ulcers and burns. The goal is to improve the wound healing process and to prevent healthy tissue from a secondary infection or the progression of a previous infection. Prerequisite for the desired wound healing is an adequate blood circulation of the tissue.(1)

Any proper wound healing requires that non-functioning tissue is removed in order to rebuild a new tissue. Physiologically, the wound cleansing is accomplished by the inflammatory process and in special by neutrophil granulocytes and macrophages. The inflammatory cells remove the material by enzymatic digestion and phagocytosis and create an effective barrier on the wound surface to pretend germs for entering the organism. By elimination of confounding factors through extensive debridement in terms of necrosectomy, removing foreign matter, wound healing can be significantly accelerated. (1)

1.2 Summary of the Skin Anatomy

In this chapter I would like to describe the skin layers and give a short summary, because for the procedure of debridement the knowledge of the skin layers plays a big role in debridement of chronic wounds as well as in burn injuries.

The skin covers an area of just under 2m2 in adults. The skin (cutis) is divided into an epithelial portion (epidermis: keratinized multi-layered squamous epithelium) and a connective tissue portion (dermis). The cutis and underlying layer of connective and fatty tissue (tela subcutanea, subcutaneous tissue, subcutis) together form the dermal layer (Integumentum commune). (2)

1.2.1 Epidermis

The keratinized multilayer epithelium of the epidermis consists of keratinocytes. There are also pigment-forming melanocytes in the epidermis Langerhans cells and Merkel cells. The Epidermis again is sorted into four layers:

- Stratum basale: This layer consists of a layer of prismatic cells, directly sitting on the basal lamina. The basal layer is responsible for the constant supply of new cells. In the normal epidermis, only here mitosis of cells can be found. The stratum basale contains epidermal stem cells and progenitor cells and their offspring's ascend into the next higher layer.
- Stratum spinosum: The stratum spinosum (spiny cell layer) consists of multiple, usually 2-5 layers of polygonal cells, which show their typical spiny morphology in usual preparation, because of the shrinkage of their desmosome contacts.
- Stratum granulosum: This layer consists of cytoplasmatic aggregates of cytokine filaments and proteins (Profillagrin, Loricirin), which are related to the cornification process.
- Stratum corneum: The Stratum corneum consists of dead cells (corneocytes), which are held together by Desmosomes. The stratum corneum functions to form a barrier to protect underlying tissue from infection, dehydration, chemicals and mechanical stress. The thickness of this layer depends on the mechanical function and it varies from one skin area to another. (2,3)

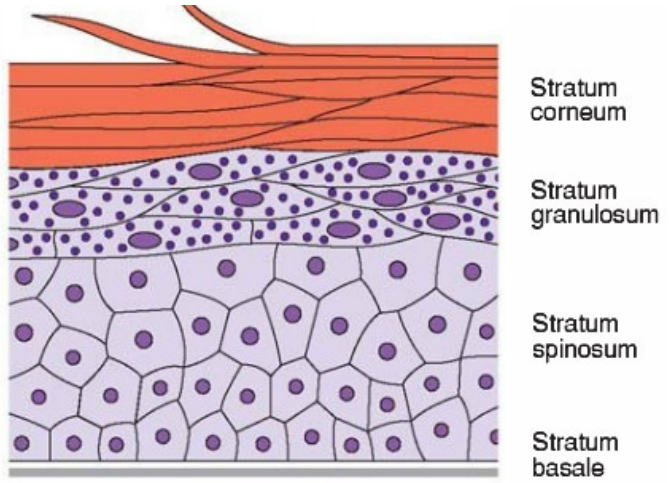

Figure 1: Layers of the epidermis (4)

1.2.1.1 Cornification process

In the course of differentiation, synthesis products appear in the keratinocytes, which are needed for the creation of the horny layer. In the stratum granulosum the huge protein Profillagrin occurs, which causes aggregation of cytokeratin filaments. At the beginning of the stratum corneum, Profillagrin is transformed into Fillagrin monomers, which causes the complete aggregation. The resulting material, which is resilient towards mechanical and chemical forces, is called keratin. (2)

1.2.2 Dermis

The corium (dermis) is the specific connective tissue of the skin, which is divided into a stratum papillare and a stratum reticulare:

- Stratum papillare: This layer is below the epidermis and forms connective tissue papillae. These papillae consist of fibroblasts, collagen fibres (type 1 and 3), elastic fibres and many cells, including cells for the defence, such as mast cells, macrophages and lymphocytes.
- Stratum reticulare: This thicker layer is beyond the stratum papillare. It contains very few cells and mainly consists of collagen type 1 and elastic fibre bundles. The reticular dermis gives the skin the mechanical resistance and it is also stretchable. The elasticity is caused by physical properties of the collagen fibres. (2,5)

1.3 Normal wound healing process

Due to the fact that debridement plays a big role in accelerating the wound healing process, a short summary will be given about the physiology of the normal wound healing process, which is a complex mechanism, in which many factors interact to achieve a regeneration of damaged tissue. After an injury, different pathways (intercellular and intracellular) must be activated in order to restore the damaged tissue. It is a dynamic, overlapped and coordinated mechanism, which normally proceeds in three stages:

1. Inflammation phase: The first stage starts immediately after tissue damage, which is needed to prevent blood and fluid loss, and complications like an infection. Therefore, dead tissue has to be removed. Initially, blood flow has to be stopped, by producing a blood clot composed of fibrin and fibronectin, which fill the tissue defect and including platelets, which thereby release multiple cytokines. These cytokines achieve a recruitment of inflammatory cells, fibroblasts and endothelial cells. Neutrophil granulocytes are then recruited to the wound and further monocytes differentiate into macrophages.

2. Proliferative phase: The main objective of this stage is to create new tissue and it takes place two-ten days after the injury. It is characterized by cellular proliferation and invasion of different cell types. The fibrin matrix has to be replaced by granulation tissue, which is achieved by fibroblasts and macrophages, with the goal to enable the keratinocytes the migration into this new matrix. Angiogenesis plays a big role at this stage of wound healing, because newly created capillaries support the proliferation of fibroblasts, by delivering nutrients to the wound. The most important regulators of angiogenesis are vascular the endothelial growth factor A (VEGFA) and the fibroblast growth factor 2 (FGF 2). Fibroblasts get activated and differentiate into myofibroblasts, which are capable of contracting the edges of the wound. The contractile qualities of myofibroblasts are due to the acquisition of α-smooth muscle actin. Furthermore they produce an extracellular matrix, which forms the bulk of the mature scar. (6,7)

3. Rebuilding phase-scar formation: The rebuilding phase normally starts two-three weeks and lasts individually up to a year or even more. All processes, which are included in the first and second stages slow down and endothelial cells, macrophages and myofibroblasts undergo apoptosis, which is a physiological

mechanism of controlled cell death. The matrix metalloproteinases (MMP), which are produced by fibroblasts, macrophages and endothelial cells, play a big role in this stage. Their task is to remodel collagen type 3 types into collagen type 1 and therefore strengthen the repaired tissue. In diabetic foot ulcers, for instance, there is an excess of MMP´s and decrease of tissue inhibitors of the MMP´s (TIMP´s). This imbalance is probably the cause of impaired wound healing. All processes are coordinated and complex, but nevertheless the skin quality of the repaired tissue would never reach the same quality as an uninjured tissue. (6–8)

1.4 Indications for Debridement

As described in chapter 1.1, debridement is the removal of necrotic (dead) or infected tissue and the removal of foreign matter in wounds, ulcers and burns. In this chapter I would like to describe the indications for this type of procedure would profit most from it. Debridement is a procedure that is used in many disciplines such as dentistry, orthopaedics, general surgery, dermatology and plastic surgery. Due to the fact, that this thesis deals with non-surgical methods of debridement in plastic surgery, indications will be described for which debridement is needed in general, especially in plastic surgery.

The spectrum of plastic surgery is different worldwide, but basically you can say that this discipline is confronted with the treatment of chronic wounds, ulcers of various genesis, as well as acute burns, therefore debridement plays an essential role in this field of medicine.

1.5 Chronic Wounds

Due to the aging demographics more and more people are affected by chronic wounds and the incidence increases with age and reaches 40-50% in patients beyond the age of 80. There are certainly some causes for chronic wounds in elder people such as: (9,10)

- Numerous comorbidities (Diabetes mellitus, cardiovascular diseases)
- Consuming disease
- Limited mobility

- Malnutrition
- Cellular and biochemical changes of aging (9,10)

1.5.1 Explanation of Terms: Wound-Ulcer

Wounds are acute tissue defects, which are caused by trauma (injury, surgical procedure), in primarily healthy, not previously damaged skin. They generally show a good healing rate. Ulcers, however, are deep defects reaching the Dermis or even subcutaneous tissue in previously damaged tissue, which show a bad wound-healing tendency. (11)

The successful healing severely requires the removal of the causes of wounds and their confounding factors. (12)

1.5.2 Biology of Chronic wounds

In chronic wounds the physiological phased healing is disrupted and the process remains usually within the inflammatory phase or the proliferative phase. Variations and disorders in any factor of the complex wound healing mechanism can lead to significant changes in the entire process. It is also affected by excessive inflammation, tissue damage by oxygen radicals, cell aging, disease specific factors, such as metabolic disorders (e.g. Diabetes Mellitus) or malnutrition. Also necrotic tissue, exudate and infections hinder the wound healing sustainability.(9)

By eliminating the interference factors such as necrotic tissue and exudate and therefore maintaining the healing process, the debridement plays such an essential role in wound management of chronic wounds.

The fibroblasts play a major role in the pathophysiology of chronic wounds and ulcers with venous origin. It appears that long-standing venous insufficiency leads to premature aging of fibroblasts. Aged or senescent fibroblasts have a reduced motility, have an arrested capacity for proliferation, respond poorly to growth factors and have an abnormal protein production. (13)

Chronic wound fibroblasts also have a different morphology compared to normal skin fibroblasts. They are described as larger and polygonal instead of being spindle shaped. (10)

A prolonged inflammatory response, a defective Extracellular Matrix (ECM) and a failure of re-epithelization further characterize these wounds. These events are a consequence of the presence of senescent cells, defective ECM synthesis and altered proteolytic remodelling of the ECM. Furthermore, this is also affected by environmental factors, such as bacteria, reactive oxygen (ROS) and nitrogen species. Nitric oxide (NO) is known to combine with hydroxyl free radicals to form peroxynitrate, a potent free radical that causes tissue destruction. NO over-expression may be in the pathogenesis and delayed healing of chronic wound ulcers. (10,14)

Due to the abnormalities and factors, which affect the wound healing process, necrotic tissue and slough tend to accumulate in chronic wounds continually. Necrotic tissue, which is a result of inadequate blood supply, contains dead cells. Slough is yellow fibrinous tissue, that consist of fibrin and pus. The accumulation of necrotic tissue and slough concludes to a bacterial colonisation and prevents the complete repair of the wound. Furthermore it prolongs the inflammatory response and mechanically obstruct the process of wound contraction.(10)

This is the part were debridement plays an imperative part for the acceleration of the wound healing process and prevention of secondary infections.

Matrix metalloproteinases (MMP) is another huge factor, which is part of the pathophysiology of chronic wounds. MMP´s belong to the family of zinc endopeptidases and are capable of degrading all components in the ECM. They eliminate damaged protein, destroy the provisional ECM, probably affect the angiogenesis and also influence growth factors. MMP´s and the tissue inhibitor of MMP`s (TIMP) are essential in the physiological wound healing process and are finely regulated, by the decrease of MMPs and increase of TIMP. Whereas chronic wounds contain a significantly higher level of proteases and pro-inflammatory cytokines, as well as a decrease in growth factors, which are essential for the tissue rebuild.(8)

Chronic wounds and ulcers certainly have different aetiologies, such as venous, arterial and diabetic neuropathy, which will be described in the next chapter.(15)

1.5.3 Causes of chronic wounds and ulcers

The clarification of the causes of chronic wounds and ulcers tend to be difficult, but essential for further wound treatment. It requires more than specific knowledge, but also knowledge in general medicine. For instance, a so-called venous ulcer can also be a tumour, a vasculitis or some infectious process. There are many different causes of chronic wounds and ulcers, which are often overlapping, so a chronic venous insufficiency can be associated with Diabetes, or atrophy of the skin through long-term intake of cortisone. The following tables, should give you a visualized summary of some causes of chronic wounds and ulcers. (16)

95% of the ulcers
• **Ulceration in Peripheral Arterial Occlusive Disease (PAOD)** • **Venous Ulceration** • **Diabetic Ulceration** • **Ulceration in skin infections** • **Livedovaskulitis (Atrophy blanch)** • **Pressure ulcers**

Table 1: 95% of the ulcers(16)

Lower limbs
Most frequent
• **Venous ulceration** • **PAOD** • **Diabetes**
Infection
• **Ulcer after erysipelas** • **Ekhtymata**
Systemic Disease
• **Lupus erythematodes** • **Rheumathoid Arthritis** • **Giant cell arteritis** • **Panarteritis nodosa**

Table 2: Causes of Ulcers in Lower Limbs(16)

1.5.4 Lower Extremity Ulcers

Due to the fact, that the clinical trials, which were included into my systematic review, are about debridement in burns and lower extremity ulcers, I would like to give a short summary about the approach to lower extremity ulcers and then move on to acute burns, in the following chapters.

Lower extremity ulcers affect millions of people every year, representing a major health risk and an economic burden. They comprise a diverse group of diseases with different pathogenesis and manifestation. To treat them effectively, clinicians have to figure out the diagnose and manage the aetiology. The most frequent cause of leg ulcers is within the category of venous disorders, with about 70 to 80 %. The most frequent foot wound is caused by diabetes. Foot ulcers are limb - and life - threatening for diabetic patients. After an initial amputation, the incidence for another amputation increases with a 5-year mortality. (15,17)

1.5.4.1 Venous leg ulcers

1.5.4.1.1 Pathophysiology

The cause for venous leg ulcers is in general a chronic venous insufficiency (CVI). The blood flow is no longer sufficient. This is caused by the failure of the calf muscle pump function and in addition shows a retrograde flow or reflux. It further leads to venous hypertension, which results in extension of the capillary walls and enables macromolecules to spread into the dermis or subcutaneous tissue. Fibrinogen then polymerizes into Fibrin, which hinders the diffusion of oxygen and nutrition and results into hypoxia of the tissue, which subsequently leads to ulcerations. This previously described mechanism is also known as the „fibrin cuff“ hypothesis. (17,18)

Secondly, another hypothesis suggests that macromolecules spread into the tissue, which is caused by a leaking of the capillaries as a result of venous hypertension. These macromolecules hinder growth factors and matrix material, which then becomes unavailable for tissue repair. (17,19)

An additional hypothesis suggests that white cells become trapped in the capillaries in response to slowing down the circulation, which leads to more vascular resistance and subsequently to occlusion. These trapped white cells then release proteolytic enzymes and superoxide radicals, which causes endothelial damage. (20)

1.5.4.1.2 Risk factors

There are several risk factors for venous leg ulcers, which have to be given special attention. The main problems are longstanding, large ulcers, as well as recurrences. The ethnicity might also play a role, but this is controversial, because the predominance of a certain ethnicity in studies are influenced by the population in which the study is being conducted. Nevertheless, venous leg ulcers are often seen in male, Caucasian and obese patients aged >40 years. Furthermore a high number of patients suffer from lipodermatosclerosis. (21)

Typical risk factors are as follows:

- Age: >55 years(22)
- Male sex (22)
- History of superficial/deep vein thrombosis and pulmonary embolism (22)
- Previous history of ulcers (21)
- Lipodermatosclerosis (21)
- Time since first ulcer episode ≥ 2 years (21)
- Higher body mass index (22)
- Physical inactivity (22)

1.5.4.1.3 Physical Examination

Venous leg ulcers are usually present on the lower third of the leg, on, or above the medial malleolus, but can also be present laterally or posteriorly. Usually they are superficial, with fibrinous material and slough. (17)

1.5.4.2 Diabetic Foot Ulcers

1.5.4.2.1 Pathophysiology of the diabetic foot

Several biochemical factors influence the formation of Diabetic foot ulcers (DFU). In general, DFU´s are caused by neuropathy, ischemia, or both, further by inflammatory cytokines and infection. Persons with diabetes mellitus (DM) tend to have neuropathy, with sensory, autonomic and motor components, which leads to nitric oxide blocking and the Maillard reaction. Pathological conditions like hyperglycaemia, dyslipidaemia, or oxidative stress lead to cellular damage, endothelial dysfunction and several complications, through numerous pathways. Nitric oxide is inhibited by hyperglycaemia, which results into a higher level of superoxide. Through a complex biochemical pathway in terms of the conversion of the superoxide, it results into platelet aggregation, abnormal intimal growth, inflammation, and atherothrombosis formation. The Maillard reaction is a complicated pathway, which leads to structures, known as advanced glycation end products (AGE`s), which are decisive in the pathophysiology of Diabetic complications. (23)

As mentioned above, patients with DM suffer from neuropathy, with sensory, autonomic and motor components. Especially the peripheral sensory component, plays a huge role in the formation of diabetic foot ulcers and amputations. Pain is a primarily natural warning system, which leads the patient to pay more attention of a specific body part. This warning system is defective, so that injuries are not noticed, until full-thickness wounds result. Furthermore clinical signs of infections are too subtle, which overall lead to necrosis and finally to ulceration. (24)

In addition, micro and macro vascular disease play another factor in the development of Ulcers and amputations, because it impairs the healing process. The capillary walls are inelastic and have a limited capacity for vasodilatation, which leads to ischemia. Last but not least, as mentioned above, once a Diabetic foot ulcer has developed , the natural barrier is faulty, which leads to a higher susceptibility for infections. (23)

1.5.4.2.2 Staging and Classification

There are different classifications or tools for lesions of DFU, which give a good reference point for further treatment and prognostics. Especially two classifications for DFU were established, by Wagner (25) and Armstrong (26).

The classification according to Armstrong is a good tool for appraisal of threatening amputations. The following tables should give you a visual overview about the classifications:

Degree 0	No open lesions; possible deformities
Degree I	Superficial ulcerations
Degree II	Deep ulcerations to tendons, joint capsule, or bone
Degree III	Deep ulcerations with abscess, osteomyelitis, joint involvement
Degree IV	Isolated gangrene; Forefoot or heel
Degree V	Gangrene of the entire foot

Table 3: Wagner Classification (25)

Degree 0	Pre. -or post ulcerative lesions, epithelisation
Degree I	Superficial Ulceration
Degree II	Deep ulcerations to tendons or joint capsule
Degree III	Deep ulcerations to bones or joints

Stadium A	Uncomplicated
Stadium B	Infection
Stadium C	Ischemia
Stadium D	Infection and ischemia

Table 4: Texas University Classification (26)

1.5.4.2.3 Risk factors

There are several established risk factors for Diabetic foot ulcerations; usually the development results from a combination of neuropathy and ischemia caused by a peripheral artery disease. It is important to understand the risk factors for diabetic foot ulcers, in order to react, and to prevent the patient from developing new foot ulcers, or the need for amputations. (27)

There are other identified factors, which have a relation to the development of diabetic foot ulcers. Following characteristics are related to a higher risk of developing foot ulcers: (27–29)

- Greater height and weight
- Longer diabetes duration
- Insulin use
- Greater plasma glucose
- HbA1c
- Lower ankle blood pressure
- Claudication with walking less then one block
- History of vascular bypass surgery
- Diagnosed peripheral vascular disease
- Symptoms of neuropathy

- History of foot ulcers and amputations
- Absent Achilles tendon reflex
- Special foot wear
- Charcot deformity

So as mentioned multiple pathological mechanism play a role in DFU. However, it is obviously important to pay attention to these different aetiologies, for the best prevention against further damage.

1.5.4.3 Arterial „ischaemic “ulcers

1.5.4.3.1 Pathophysiology and Risk factors

There are different reasons for arterial ulcerations, however the most common reason is an occlusion of the arteries proximally to the ulcer formation. The occlusion then prevent the delivery of nutrients and oxygen to the foot. (17)

The most common aetiology for occlusion is atherosclerosis, which is a slowly progressive arterial disease, in which the intima of the vessel is thickened through fibrous deposits. Fatty streaks are the earliest visible sign of atherosclerosis; they are a sub-endothelial accumulation of large fatty cells. Later, fibrous plaques develop, which cause the clinical manifestation of atherosclerosis. These plaques are an accumulation of monocytes, macrophages, foam cells, T-lymphocytes, tissue debris and cholesterol crystals. (30)

Of the major risk factors, five can be influenced: (17,30)

- Hyperlipidaemia
- Hypertension
- Smoking
- Diabetes Mellitus
- Hyperhomocysteinemia

Non-influenceable risk factors are: (17,30)

- High age
- Male sex
- Genetic burden

Other further factors are obesity, poor movement and a stressful lifestyle. (17,30)

For the description and classification of the severity of peripheral artery diseases, the Rutherford classification is commonly used, which is shown in Table 5.

STAGE	FEATURE
0	Asymptomatic
1	Mild claudication
2	Moderate claudication
3	Severe claudication
4	Rest pain
5	Ischemic ulceration not exceeding ulcer of the digits of the foot
6	Severe ischaemic ulcers or frank gangrene

Table 5.: Rutherford classification of peripheral arterial diseases (31)

1.5.4.3.2 Physical Examination

Usually Arterial „ischaemic “ulcers are located on the foot, especially on the toes. They can also be present proximally, such as on the ankle, heels, or even on other parts of the leg. Usually the extremity presents to be paler and colder and tend to be dry.

1.5.5 Debridement of chronic necrotic wounds

Due to exogenous (foreign bodies, infection, hematoma) or endogenous (disturbed micro and macro circulation) influences, a wound can possibly remain in one phase. The goal of wound treatment in this particular situation is to direct the wound towards a physiological healing process, by debriding it. Basically, there are five different types of debridement available, which can also be used in combination (1):

- Surgical Debridement
- Physical Debridement
- Enzymatic Debridement
- Autolytic Debridement
- Biological Debridement

1.5.5.1 Surgical Debridement

Surgical debridement offers the fastest and most effective way for removal of less perfused or necrotic tissue and wound coverings. By removing the necrotic tissue, the local circulation is improved and the bacterial load significantly reduced. Surgical debridement is essential in advanced infections or septic patients. To avoid aftereffects from less perfused tissue, comprehensive surgical debridement is essential, especially in posttraumatic wounds, which includes uncompromising removal of all less perfused or already avascular tissue, whether soft tissue or bones. The development of plastic-surgical flap techniques for defect coverage and the possibilities for bone replacement, allow uncompromising radical removal of avital tissue. The surgical debridement of chronic wounds is the first step of phase-adapted wound base conditioning.

A disadvantage of surgical debridement is the frequently required analgesia by regional anaesthesia or intubation anaesthesia and the risk of bacterial scattering during the surgery. (1)

1.5.5.2 Physical Debridement

Physical debridement is a mechanical wound cleaning with gauze compresses, wound irrigations and baths. Cleaning with dry and damp gauze compresses is the simplest form of mechanical wound cleansing, which results in mechanical detachments of the scab. The disadvantage here is the frequent pain stress of the patient and the damage of newly formed granulation tissue. Wound irrigation has shown to be effective at removal of bacteria and cell debris. Wound rinses with hydrogen peroxide or iodine-containing solutions should not be used anymore, because of its cytotoxic effects on vital tissue. (1)

1.5.5.3 Enzymatic Debridement

Enzymatic debridement is done with help of protein splitting enzymes, due to degradation of fibrin coverings and necrotic layers, without damaging the intact tissue. These enzymes are from bacterial or animal origin and need a moist and warm environment for sufficient activity. An application on dry necrosis therefore does not lead to the desired success. It is recommended for easy wound cleansing, but it cannot replace surgical debridement in terms of efficacy. The bacterial collagenase is made out of Clostridium histolyticum and can dismantle all known collagen types. In addition, these resulting collagen fragments stimulate fibroblasts and Macrophages, which accelerate the necrosis degradation. Two other enzymes, streptokinase and streptodornase, also result in necrosis degradation. The advantage of enzymatic wound cleansing is in it´s simple and secure application and further in painless dressing change. The disadvantages are the higher treatment costs and longer treatment times, compared to surgical debridement. (1)

1.5.5.4 Autolytic Debridement

Hydrogels or moist wound dressings are used for autolytic debridement, to create a physiological wound environment, which promote the release of endogenous enzymes, such as collagenase or elastase. In addition to the increased enzyme release, the proliferation, synthesis, migration and diffusion processes in the humid wound are supported. Whereas excessive absorption of dry dressings, lead to un-physiological

conditions of the wound. Several studies have proved the superiority of moist wound therapy versus dry wound treatment. The debridement by means of autolysis is painless, effective, safe and easy in the implementation. However, the time until necrolysis is significantly extended, compared to the other methods. (1)

1.5.5.5 Biological Debridement

The use of the sterile golden fly larvae Lucilia sericata on wounds is referred to as bio-surgery and has largely replaced the negatively charged concept of maggot-therapy. In general, there are three mechanisms, which have a positive effect on the wound: Firstly it´s the ability to debride and the cleansing of the wound. This does not come by an immediate removal of the necrotic tissue by the maggot, but by the proteases in the saliva secretions of the maggot. Secondly, it has an antibacterial effect. The ammonia and calcium carbonate content of the digestive secret additionally shifts the pH-value of wound exudate from an acidic to an alkaline area, which furthermore inhibits bacterial growth. Thirdly, it improves and stimulates the wound healing process. For better acceptance and less disgust for the patient, maggots can be brought on the wound in so-called biobags. These are closed bags, similar to a tea bag, which guarantee a sufficient oxygen and moisture supply. The bio-surgical debridement provides a painless method of debridement under the complete protection of healthy tissue. (1,32)

1.6 Burns

Burn injuries face overwhelming physiologic and psychological challenges. The debridement of burn wounds represents an essential step in the wound treatment. Through the early removal of necrotic tissue (within first 48h), septic progression can be significantly reduced. Before explaining the conventional treatment options in the debridement stage and non-surgical debridement methods for acute burn injuries I will give a short summary of the basic knowledge of burn-wounds in terms of burn depth and zones. The skin layers are described above in section 1.2.

1.6.1 Causes

The main causes of thermal trauma are scalding with hot water and oil. In most cases infants and toddlers are the victims, by removing hot boiling water pot from the stove. In Austria, around 8500 people annually are affected by such severe burns or scalds, who have to be treated in hospitals. 45 percent of the victims are under five years old. 3,700 out of the 8,500 injured are toddlers, which means that every day about ten toddlers suffer a burn injury, at home. (33)

A thermal trauma is caused by flame, contact with hot surfaces, or gases, electricity or arc injuries, by radiation, as well as by scald with hot liquids. The severity of the damage depends on the temperature, the time of exposure and of the extend of the affected body surface. While in the group of children and geriatric patients, scalding plays the major cause, burns in is most prominent in adults and is mostly caused by flames, hot gases after explosions, or by electricity and arc injuries. (34)

1.6.2 Expansion

Heat leads to denaturation of tissue proteins. Depending on temperature, heat transporting medium and exposure time, more or less tissue is destroyed. The resulting necrotic areas are surrounded by damaged cells (Stase zone). The objective of medical aid is to improve the circulation and the oxygen transport, and prevent afterburning. . (33)

1.6.3 Burn depth and zones

As mentioned above, heat leads to denaturation of proteins and damage of the cell membranes. The temperature and the duration of contact have a synergistic effect, so that after a contact time of one second at 69 degrees, or a contact time of one hour at 45 degrees, cell necrosis will occur. (35)

The classification of burn injuries in 3 zones by Jackson 1953 still has its validity and describes the onion-bowl shaped structure of the burn wound:

The **necrosis zone** is in the centre of the wound, where no viable cells remain. The **stasis zone** is located adjacent, which is characterized by diminished tissue perfusion and

consists of viable and non-viable cells, ischemia, capillary vasoconstriction. This zone can change into necrosis, with hypoperfusion, edema and infection. This kind of process is called „afterburning “, which can be stopped or reduced by proper wound care management. Factors, like advanced age or diabetes can put this zone into higher risk for „conversion “. The outermost layer of the wound, the **hyperaemia zone,** is characterized by viable cells, and vasodilatation, caused by local inflammatory mediators. Commonly, the tissue of this zone recovers completely. (36,37)

As already stated, the primary tissue loss is caused by a protein denaturation, which is accompanied by inflammatory mediators, especially in the well-perfused zone. Oxidants and peptidases add further damage to endothelial cells and so reinforce the ischemic tissue necrosis. (38)

Furthermore, the combustion grade determines the type of treatment and also the outcome and it plays an essential role for further local and surgical treatment in burn wounds. The following table shows the combustion grades of the skin.

GRADES

I/ SUPERFICIAL	Limited to epidermis. Skin redness and swelling. Tension and Touch sensitive. Scarless healing.
IIA/ SUPERFICIAL PARTIAL THICKNESS	Damage to the epidermis and superficial dermis parts. Redness, formation of fluid-filled, blisters. Risk of infection. Hair roots, glands and receptors of the skin remain intact, causing severe pain. Healing process over two to three weeks. No scarring but possible occurrence of pigmentary disorders.
IIB/ DEEP PARTIAL THICKNESS	Damage to the epidermis and low level of the dermis. Blistering. Moist to dry wound ground, increased consistency and whitish to red areas. Damage to sensation due to damage of pain and tactile receptors. Healing with scarring

III/ **FULL THICKNESS**	Damage of all skin layers to the subcutis. Greyish to yellowish waxy discoloration of the skin with visible thrombosed blood vessels. Complete loss of tactile and pain receptors. Healing under scar and keloid formation. Possible emergence of contractures in joint areas. Special form: Charring (formerly grade IV burn) with possible involvement of muscles, tendons or bones

Table 6.: Combustion grades of the skin (37)

The most challenging part, is the decision, how to respond to burns that are intermediate in depth. These wounds heal in three weeks, depending on a few tenths of a These burns are called indeterminate as their healing potential becomes evident with serial assessments in the course of a few days. Initial evaluation by experienced surgeons as to whether an indeterminate burn wound heals within three weeks is only 50-70% accurate. (37)

1.6.4 Total body surface area burns

Another essential factor is the estimation of the total body surface area (TBSA) burn, which is even more important than the burn depth in the initial assessment. The percentage of TBSA (%TBSA) is decisive for further fluid and nutritional substitution, which can be immense in severe burn injuries. (39)

As stated, it is crucial for calculation of nutrition delivery, as well as for fluid requirements. There are several different methods existing for the estimation of the %TBSA burn. The rules of nine and the Lund and Browder charts are the most commonly used tools.(39)

The „rules of nine “method is a very simple and rapid, but therefore an imprecise method for the estimation of burn wounds. With this tool, nurses, doctors and even experts in this field tend to overestimate the wound size. It is unworkable for patients under 15 years of age. The simplicity and quickness make it popular in emergency situations. The Lund and Browder chart requires more time, but in contrast to the „rules of nine“, it is feasible for different ages and sexes and offers a more accurate estimate of the burned wound area. (40,41)

1.6.5 Systemic response to burn injuries

Due to the fact, that the skin plays a major role with its barrier function, the systemic response to burn injuries is associated with fluid loss and decreased resistance to infections, caused by vasoactive mediators with secondary interstitial edema and organ dysfunction. Initially the burn tissue is clean, but it is rapidly colonized by bacteria and from bacterial overgrowth, which is caused by vasoactive mediators and protein coagulation in the eschar, which further leads to a systemic infection process. Certainly, it depends on the percentage of burned tissue and the depth of the burn. Usually in burned patients with <20%TBSA burn the Systemic infection process is well tolerated, but with no early excision, which will be described in further chapters, the chance of survival decreases in patients with >40% TBSA burn.(42) Infection is the leading cause of death in patients with burn injuries.

1.6.6 Treatment of acute burns- Debridement stage

After describing the basic knowledge about burns, a short summary will be given about the history and the debridement methods for these kinds of injuries. This is done in order to point out the importance of this kind of procedure.

An effective removal of the burn eschar (debridement) is a crucial part of the treatment in burn injuries. It is the initial action to prevent eschar related complications, such as a systemic infection or the burn-induced compartment syndrome (BICS), which also can be life-threatening. Furthermore it certainly promotes the wound healing process. (1,42,43)

The timing and method of the debridement depends on depth of the burn wound. However, early and initial debridement can be a lifesaver in serious, third grade full-thickness burns of more than 50% TBSA. (42)

In indeterminate burns, as described in chapter 1.7.3, debridement is commonly executed two-four days after the injury, although it may shift up to two weeks, until the clear depth of the wound has been evaluated. Early debridement in the first days has to be surgical, as no other method is fast enough. (43,44)

1.6.7 Debridement factors and assessment in burns

The factors, that determine the common value of debridement means and methods are as follows (43):

- Safety: no systemic side effects, trauma or bleeding
- Selectivity: no damage to surrounding local viable tissues
- Efficacy: complete debridement in a single use, with release of BICS
- Speed: Debridement completed as fast and as soon as possible, within hours of admission
- Cost-efficiency and simplicity: minimal specialized facilities and personal required

All these mentioned factors are very important and even more so in children, elderly patients and patients with burns to the head, neck, hand and feet.

1.6.8 Surgical debridement

As mentioned, the eschar in burned wounds has to be removed (Debridement) to provide the patients from further complications. Janzekovic (45) set a milestone as she reintroduced the process of early tangential excision of the necrotic tissue and initial closure of the wound with split thickness skin grafts. The main goal of the early excision is to remove all of the necrotic tissue and to prepare the wound for skin grafting. It is crucial to remove all of the devitalized tissue in order to achieve a successful skin-graft healing. Tangential excisions are executed with special knives to control the thickness of the cut. (44)

The initial nercrosectomy after a thermal trauma (within 6-8 hours after the injury) has been abandoned, because of logistical problems (staff availability, operating rooms (OR), Another reason is the condition of the patients (hypothermia, unstable circulation). Instead the early necrosectomy (72h post trauma) is the most common procedure nowadays. In any case, patients with large burns have to be treated in several serial sessions, as only 25% of the total body surface can be debrided within one single session. (34)

The main advantage of the early excision of the necrotic tissue, is in the shorter time interval, in which the patient is exposed to a higher risk for wound infection.(34)

1.6.8.1 Tangential necrosectomy

This procedure consists of a tangential removal of all burned skin layers, until a vital, well bleeding wound surface is reached. This vital surface is characterized by capillary bleeding, deriving from the dermal plexus. If the combustion extends to the subcutaneous tissue, tangential necrosectomy can be performed as well. In general, this procedure allows better healing results, by leaving a better wound surface. Furthermore, important structures, like veins and nerves are achieved and a better-preserved body contour turns out. A disadvantage is certainly the blood loss, caused by the removal of the burned tissue. (34)

1.6.8.2 Epifascial necrosectomy

Epifascial necrosectomy is a surgical approach for a large area of infected skin, as well as for patients with >50%TBSA. This consists of the removal of all layers above the muscle fascia, wherein the capillary-rich layer should be remained. This kind of procedure is most commonly performed with an electrocautery. This approach has its advantages, as there is less bleeding, it is faster and additionally it requires less skin grafting. Adversely it results in severe cosmetic deformity and, because of the excision down to the muscle fascia, leads to destruction of cutaneous nerves thus to a reduced sensitivity. (34,44)

1.6.8.3 Adverse effects of surgical debridement

Bleeding is one of the most feared complications in the process of surgical debridement. For the reduction of bleeding during debridement, the well-circulated subcutaneous tissue can be infiltrated with epinephrine. Other possibilities are the use of haemostatic spray, fibrin sealant or vasopressin. Nevertheless, despite these listed approaches, debridement can cause severe bleeding. (44)

Another common complication in patients with large burn wounds are infections, systemic as well as localized, which complicate the skin grafting. Staphylococcus aureus, Pseudomonas aeruginosa, are a risk for patients with burns, because of their capabilities of antibiotic resistance. (46)

1.6.9 Non- surgical debridement

Surgical debridement is traumatic, associated with severe blood loss, non-selective and dependent on the diagnosis. Non-surgical methods do not have the same efficacy as conventional methods, but they are not dependent on the diagnosis, less traumatic and more selective. These „conservative "methods are based on autolytic processes, which involve different topical medications, combined with showers, removal of debris and dressing changes. These methods reduce the inflammatory process, but they slow down the separation of eschar. In consequence the debridement stage is extended, which may also lead to complications. The burn wound might get deeper, as the partial-thickness burn can transform into full-thickness burn. Furthermore, the inflammatory-infectious process can lead to a formation of granulation tissue, which can result into heavy scars. Besides the adverse effects, it has its benefits, as it is selective, diagnosis independent, simple to practice and it does not involve surgery. (43)

The idea of using different enzymes, or ointments instead of surgical methods, which dissolve the necrotic eschar, is not new, but throughout history it could not replace surgery in any way. Idealistically, these products would be the first option of treatment, which selectively remove the burn eschar, without damaging any other tissue and further provide a surface for healing, or skin grafts. There have been different approaches for alternative debridement methods throughout history. In first attempts an enzymatic mixture was used, containing „papain ", which is a vegetable pepsin prepared from the juice of the Carica papaya („melon tree ") for the removal and debridement of necrotic tissue. Several studies showed, that it has no effect on healthy tissue and did not cause any systemic side effects. Nevertheless, it is not applicable for thick leathery crusts. Furthermore, it requires daily application for up to three weeks. Nevertheless it is still in use nowadays. (43,47)

Later on, Acids were expected to improve the approach towards non-surgical debridement. Pyruvic acid was in use for this purpose and before application incisions had to be made to

enhance the action of the acid. It was assumed that the separation of the sloughs could be accelerated, by lowering the ph-levels down to 1.9. Trials back then showed, that the wound was ready for skin grafting within a week. In addition, it was also assumed, that this paste also killed bacteria. In the 1960`s Pyruvic acid was replaced by Phosphoric acid, as it showed similar efficacy and the Pyruvic acid was difficult to obtain. Nevertheless, this alternative method was ineffective in deep burns and additionally it was painful and could cause acidosis in patients with large burns. However, the indication for acids was not actually the ability to remove necrotic tissue, but rather it`s antibacterial properties. (47)

The first treatment with proteolytic enzymes of bacterial origin (Clostridium histolyticum, streptokinase and Pseudomonas (Varidase) were tried and abandoned in the early 1950´s. Overall, they showed disappointing results in patients with full-thickness burns, because of its insensitivity toward these enzymes. Later on, in the 1970´s several clinical trials were executed involving Sutilains, a neutral proteinase derived from filtrates of Bacillus subtilis (Travase). Additionally, tangential excisions had to be made to ensure successful skin grafting and debridement of full-thickness burns. Overall this process took a week until completion. It was postulated, that the advantage of debridement with Varidase was to debride wounds soon after the accidents. In practice though, it was used about five to seven days after the accident, to ensure a better effect and to avoid any epithelial damage. However, this could lead to excessive fluid loss and potential bacterial invasion. (43)

Collagenase ointment from Clostridium histolyticum (Santyl) has been in use since the 1950`s and is still in use nowadays. The completion of the debridement varies from several days, up to 2 weeks. Investigations have shown, that it is only effective in dermal burns and not in burned subcutaneous fat or muscle. It was postulated, that Collagenase ointment may assist in decision making for early excisions, to assess the burned area, whether it is a partial-thickness or a full-thickness burn injury. Other agents as such as Trypsin, Chemotyrpsin, blowfly larvae extracts were too slow for acute burn injuries and therefor attracted relatively short attention. (43,47)

1.6.9.1 Bromelain extracts

In recent years there have been several animal and human studies with a bromelain-derived debriding preparation (Debridase, Debrase, NexoBrid). Several animal studies in pigs showed their efficacy and speed of eschar removal, selectivity, preservation of zone of stasis as well as beneficial effects on re-epithelization of partial-thickness burns. In few multinational clinical trials this product showed it`s efficacy in completely and selectively debriding partial, deep or full-thickness burns within a 4-hour time window after initial application. This kind of non-surgical debridement is performed at patients' bedsides under analgesia. Early debridement and evaluation of the real wound depth allows better planning in terms of the further wound closure phase. A preliminary report by Rosenberg et al. (48) showed that the debridement with Nexobrid started and ended on the day of admission, compared to standard of care group, which completed the debridement in 6-12 days. Furthermore 15% of the enzymatically treated burn wounds needed additional surgery, compared to 62% in the SOC group. Another huge advantage is that it is much less traumatic, as it only shows half of the blood loss. (43,49,50)

1.7 The goal of the review

As you can see in the introduction of this thesis, there are several different indications for debridement as well as different non-surgical debridement methods available. On the one hand you have chronic wounds and on the other hand you have acute burn injuries, which have to be treated by plastic surgeons. Because of its variety it is important for plastic surgeons to stay up to date about the present therapy modalities and approaches. Therefore, a systematic review was conducted, to point out the main differences between non-surgical debridement methods, and also to visualize the differences between these procedures. The aim of this review is to point out the main clinical differences between non-surgical methods of debridement, to outline established therapy approaches and to provide evidence for using non-surgical debridement methods for chronic ulcers and burns.

2 Material and Methods

In this chapter of the thesis I want to describe the strategy of applying the final results and the formation of the systematic review. All aspects of the working process will be described in detail, in order to give an understanding of the procedure.

2.1 Systematic review

A systematic review, or simply review, is a scientific work in form of a literature review, which tries to collect, summarize and critically evaluate the actual scientific knowledge, referring to a specific question. The core of each review is the published literature.

As mentioned, our goal was to conduct a systematic review on non-surgical debridement methods in plastic surgery, based on the PRISMA (51) checklist for systematic reviews of 2009. Before starting with the literature search, a project proposal was created, which was reviewed by my supervisors and then registered on PROSPERO (CRD42017057590) (52) (International Prospective Register of Systematic Reviews), to make it official, that we are currently working on a systematic review on non-surgical debridement methods in plastic surgery.

2.2 Search strategy

We conducted this systematic review to identify all available studies in this field of expertise. The next step was to define MESH words for the literature search, using PubMed (accessed 10/7/2016) and Web of Science (accessed 10/7/2016) interface. With following Mesh terms, I searched in PubMed and Web of Science interface:

Debridement
AND
(Larva OR Enzymes OR Treatment)

Table 7: MESH Terms for PubMed

(TS =(Debridement)
AND
TS= (Larva OR Enzymes OR Treatment))

Table 8: MESH Terms for Web of Science

I limited the literature search referred to the interest to our key question, to reduce the number of studies. Therefore, our results included studies, which were "published in the last 10 years "and which were in "English ".

Afterwards I imported the results from each interface into an Excel 2010 spreadsheet (Microsoft, Richmond, VA, USA). After automatic and manual removal of 638 duplicates I obtained a total number of 8041 articles.

After reading the titles, or when necessary the abstracts, I could exclude all articles, which were not related to the topic, nor in the English language. I flagged all articles, which were not in English and did not match with our inclusion criteria (non-surgical debridement methods in plastic surgery) with a red mark and I was able to identify all articles, containing non-surgical debridement in plastic surgery and further flagged them with a green mark. The green marked articles (N=178) were then exported into an extra Excel Spreadsheet to create an overview and to assess the full-text articles for eligibility.

2.3 Categorization process

Due to the fact that these articles did not match exactly with our inclusion criteria, I had to categorize the full-text articles into subgroups. We focused exclusively on clinical trials on non-surgical debridement in plastic surgery. These subgroups were as follows: animal studies, reviews and non in vivo human studies. I was able to identify them and to accord them to the subgroups, by reading the abstracts, or when necessary the full-text.

I used different colour markers to differ the studies and counted them in order to accord them to the subgroup. Table 8 shows you, which type and number of studies we excluded and were not in interest to our key question.

EXCLUDED	NUMBER
1) ANIMAL STUDY	N=31
2) REVIEW	N=42
3) EX VIVO/IN VITRO STUDY	N=30
INCLUDED	**Number**
1) TOPIC SUITABLE	**N=75**

Table 8: subgroups excluded

In the next step, again I exported only the included articles (N=75) into an extra Excel spreadsheet, which allowed a qualitative analysis of the remaining articles.

2.4 Rating of Level of Evidence

In the next stage of this process I had to rank the remaining studies according to their Level of Evidence. Only High-quality, randomized controlled trials with an adequate power were included in our systematic review. We performed a qualitative analysis by ranking the studies, according to a scale, which was developed by the American Society of Plastic Surgeons for prognostic and therapeutic studies (53) in 2011. Therefore, all articles with a Level of Evidence lower than I, were excluded. Again, I marked them with different colour markers.

Evidence Rating Scale for Therapeutic Studies Level of Evidence	**Qualifying Studies**
I	High-quality, multi-centred or single-centred, randomized controlled trial with adequate power; or systematic review of these studies
II	Lesser-quality, randomized controlled trial; prospective cohort or comparative study; or systematic review of these studies
III	Retrospective cohort or comparative study; case-control study; or systematic review of these studies
IV	Case series with pre/post-test; or only post test
V	Expert opinion developed via consensus process; case report or clinical example; or evidence based on physiology, bench research or "first principles"

Table 9: ASPS Evidence Rating Scale (53)

After filtering and organizing, as described above, we obtained a result of eight articles. To get an visual overview of the review process, a flowchart based on the PRISMA guidelines (54) was created in PowerPoint 2010 (Microsoft, Richmond, VA,USA).

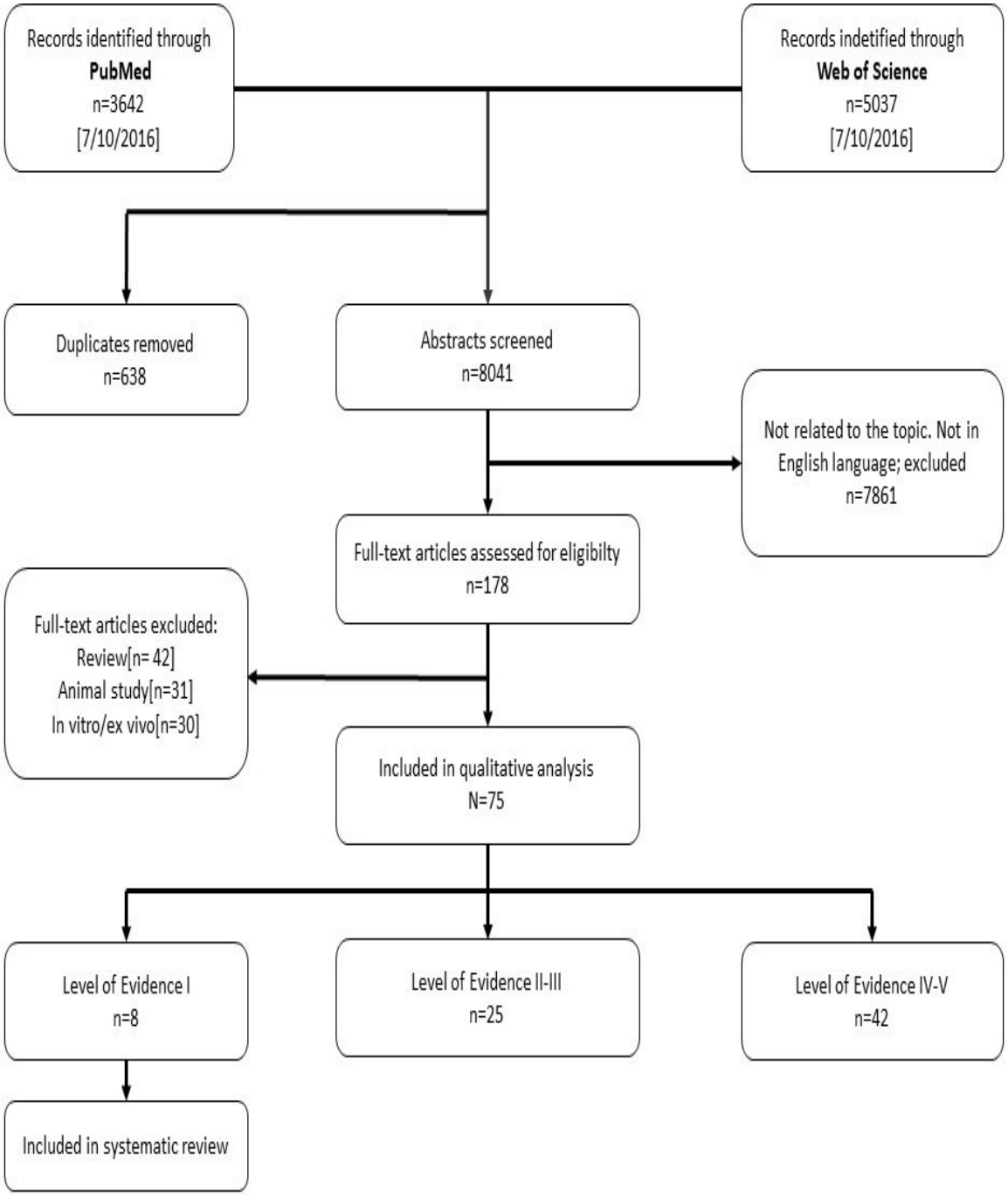

Figure-2.: Flow chart depicting the organisation of search results

3 Results

3.1 Overview of the search results

Overall, we could obtain 8679 articles with our defined MESH terms, as illustrated in table 7 and table 8, using PubMed and Web of Science interface. Duplicates [638] were removed automatically and manually and so 8041 articles were ready to be screened. As illustrated in the Flow Chart [Figure 4] a lot of articles were excluded, because they were not related to the topic and therefore not suitable for the systematic review. Articles, which were not in English, reviews, animal studies and in vitro/non vivo studies were also excluded. It could also be noticed, that a lot of the articles, were about debridement in other specialities, like dental medicine, or orthopaedics.

Overall 75 studies were included for the qualitative analysis, which were graded according to their Level of Evidence. After this process of filtering, a huge number of articles, which did not match precisely with our inclusion criteria, was eliminated. We finally obtained 8 articles ranked as Level of Evidence I, which we included in our systematic review, with a collective cohort containing 911 subjects in total.

Overall four studies investigated larval debridement therapy. Opletalova et al. (32) discussed the comparison between maggot debridement and conventional methods. Seven studies discussed non-surgical debridement therapy of ulcers, either arterial or venous aetiology. One study discussed non-surgical debridement methods in burns. Rosenberg et al. (55) compared Nexobrid, a selective enzymatic agent to the conventional sharp debridement. Two studies evaluated the efficiency of autolytic debridement dressings. Only one study investigated Clostridium Collagenase ointment (CCO), an enzymatic debriding agent for the debridement of DFU. The Table below shows all selected articles for the

Source	*Title*	*Authors*
PubMed/WoS	Evaluation of two fibrous wound dressings for the management of leg ulcers: results of a European randomised controlled trial (EARTH RCT) (56)	Meaume S, Dissemond J, Addala A, Vanscheidt W, Goerge T, Perceau G, Chahim M, Wicks G, Perez J, Tacca O, Bohbot S.
PubMed/WoS	A randomized controlled trial of larval therapy for the debridement of leg ulcers: results of a multicenter, randomized, controlled, open, observer blind, parallel group study (57)	Mudge E, Price P, Walkley N, Harding KG.
PubMed/WoS	Clinical and economic assessment of diabetic foot ulcer debridement with collagenase: results of a randomized controlled study (58)	Tallis A, Motley TA, Wunderlich RP, Dickerson JE Jr, Waycaster C, Slade HB
PubMed/WoS	A novel rapid and selective enzymatic debridement agent for burn wound management: a multi-center RCT (55)	Rosenberg L, Krieger Y, Bogdanov-Berezovski A, Silberstein E, Shoham Y, Singer AJ.
PubMed/WoS	Maggot therapy for wound debridement: a randomized multicenter trial (32)	Opletalova¡ K, Blaizot X, Mourgeon B, Chaene Y, Creveuil C, Combemale P, Laplaud AL, Sohyer-Lebreuilly I, Dompmartin A.
PubMed/WoS	An RCT to compare a bio-cellulose wound dressing with a non-adherent dressing in VLUs (59)	Alvarez, O. M.; Phillips, T. J.; Menzoian, J. O.; Patel, M.; Andriessen, A.

PubMed/WoS	Larval therapy for leg ulcers (VenUS II): randomised controlled trial (60)	Dumville JC, Worthy G, Bland JM, Cullum N, Dowson C, Iglesias C, Mitchell JL, Nelson EA, Soares MO, Torgerson DJ; VenUS II team.
PubMed/WoS	Maggots as a wound debridement agent for chronic venous leg ulcers under graduated compression bandages: A randomised controlled trial (61)	Davies CE, Woolfrey G, Hogg N, Dyer J, Cooper A, Waldron J, Bulbulia R, Whyman MR, Poskitt KR.

Table 10: Final studies with Level of Evidence I [8]

3.2 Describing of each included study

At the beginning of the review process we planned to conduct a systematic review and a meta-analysis, to create a big cohort number, in order to achieve a statistically significant statement for non-surgical debridement methods in plastic surgery. Nevertheless, these included trials differed in indications, measurements, as well as interventions and therefore it was not possible to create a meta-analysis and compare these studies to each other. Thereafter we decided to describe each single study and then point out the differences of the outcomes and analyse them.

1. **Evaluation of two fibrous wound dressings for the management of leg ulcers: results of a European randomised controlled trial (EARTH RCT):** (56)

Subjects:

This randomised controlled trial by Meaume et al. (56), took place in 37 centres in France, Germany and the UK. Patients, who suffered from chronic leg ulcers with mixed aetiologies in their sloughy stage, were included into this trial. This was measured by ensuring the ABPI (Ankel Brachial Pressure Index), which had to be between 0.7 and 1.3 for the target limb. The ulcer period had to be within 3 and 36 months and the wound area had to range between 3 and 30 cm^2 with sloughy tissue in the wound surface area. Subjects, who had ulcers with infection, dry wounds or necrotic tissues were excluded. In addition, subjects, who had a bad health situation, treated with chemotherapy, radiotherapy or immunosuppressant drugs, were excluded as well.

Study design:

This clinical trial was performed as an open-label, multicentre, controlled, randomised, clinical trial (RCT). After the ABPI measurement with a Mini Doppler, the Subjects were randomised into two groups, either the test dressing (UrgoClean) or control dressing (Aquacel) for a six- week period, with weekly assessment.

The demographic parameters and the medical history, such as surgical and leg ulcer history were documented. In addition, a detailed wound status was performed by physicians. The exploration was performed, by the investigating physicians, in the six-week follow-up. It was executed on a weekly basis during the first four weeks and then again in week six. Over the course of the study, the acceptability of the two dressings and the characteristics of the treatment by the nurses, were evaluated, by using open- ended questions. In week six, the investigator, executed the final clinical evaluation, by using the EuroQol-5D Questionnaire, which is a Quality of Life assessment. Furthermore, the investigators used a Global Performance Score for evaluation, which had a range between 0 and 36. The higher the score, the better the performance, which was based on the calculation of nine questions, using a scale of five points (very poor, poor, fair, good, very good).

Measurement:

The reduction of the wound area (WAR in %) was the judgement criteria. All wounds were measured, by two non-participating clinicians, using a digital software. In addition, the secondary endpoints were based on the comparison between the two dressings, which included the percentage of granulation and the sloughy tissue on the wound bed. Furthermore, it was based on the GPS, the characteristics of the debridement, the frequency of changing the dressing and parameters of acceptability (e.g. comfort, bleeding after removing).

Study Result:

In this clinical trial, 159 patients were recruited and randomised in a period of 15 months. The dropout rate was low and the patients were well balanced into these two groups. 83 patients were allocated to the UrgoClean group (test group) and 76 were placed to the Aquacel group (control group). 134 patients (84 %) were followed-up until week six or until re-epithelisation. After a treatment period of six weeks, the surface area was reduced by 36.9% in the test group and 35.4% in the control group. The relative reduction of sloughy tissue was calculated. In the test group the surface area was covered by 82.6% and in control group by 80.8% by sloughy tissue. The relative reduction in the UrgoClean group was 65.3 % vs. 42.6% in the Aquacel group, which was a statistically significant difference. The percentage of debrided wounds in the test group (52.5%) was higher than in the control group (35.1%).

Key message:

The fastest and most direct form of debridement is certainly the surgical excision, but not always the best option. This trial evaluates non-surgical debridement methods. They compared a micro-adherent absorbent dressing (UrgoClean) with a hydro fibre dressing (Aquacel) in the management of venous ulcers, especially during the debridement phase. To sum up the results, there is a similarity between those two dressings in terms of efficacy, based on the healing process. The test dressing (UrgoClean) was superior to the control dressing (Aquacel) in terms of autolytic debridement capacity.

2. **Clinical and economic assessment of diabetic foot ulcer debridement with collagenase: results of a randomized controlled study:** (58)

Subjects:

The participants were recruited in a period between April 2010 and May 2011. Patients, who were 18 years or older with a diagnosis of Diabetes of type 1 or 2 were included into this trial. These subjects had neuropathic foot ulcers with a surface area of 0.5 to 10 cm^2.

Study design:

This trial was performed as a randomized, controlled, parallel group, multicentre, open-label, 12-week study in seven sites in Arizona, Nebraska, Texas and Pennsylvania. 48 patients with neuropathic DFU, were randomized into two groups. All participants were treated by surgical debridement and then randomly assigned to a treatment either with CCO or SMG. In either case the patients were treated for four weeks and they were followed up for another eight weeks. The participants were seen every week during the treatment and during the follow-up period. They were instructed to using either CCO or SMG.

Measurements:

For the analysis they used a standardized wound assessment tool, including wound edge appearance, necrotic tissue type, necrotic tissue amount, exudate type, exudate amount, peri wound skin colour and granulation tissue appearance. This was done at all visits with the intention to treat the population. Furthermore, the secondary efficacy was measured manually in percentage of the wound area change from the baseline during the 4-week treatment and after the follow-up period. Lastly, they measured the response rate of the two debridement modalities after the 12^{th} week at the end of the study. The following table shows, how they categorized the results, in order to measure the response, in order to compare the two groups:

Reduction of the wound surface area (WSA)	Wound classification
WSA<=10%	Stalled wound
WSA >10%<=50%	Moderate response
WSA >50%	Large response

Table 11: Analysis on the response rate for the debridement modalities

At the end they performed a cost-effectiveness analysis to compare these two methods using following formula:

CU=cm² x PA x pCO x 28 days

CU=Collagenase use

Cm²= WSA (2.7cm²)

PA= Proper application (0.2 cm thick, daily)

PCO= Density of the CCO (=0.8g/ml)

Study results:

As mentioned, a total of 48 patients were randomized at seven sites. Both, the CCO and SMG groups had significantly improved wound assessment scores after four weeks of treatment. There was no significant difference between those two methods. In most cases (60%) the ulcers were located at the plantar surface with a mean surface area of 2.7cm². Secondly there was no significant difference in the characteristics of the wounds. Eight patients dropped out before the study ended (n=5 in CCO group and n=3 in SMG group).

As mentioned, they used a wound assessment tool to score the wound, which included eight subscales. Each subscale had a possible score of 1 to 5 (1= intact skin; 5=worst skin). In combination of these subscales the score could range between 8 (intact skin) and 40 (ulcer with no granulation tissue). The mean wound assessment scores were neither

significantly different, at any of the treatment periods, nor at the last visit after the follow up. Both groups had a similar number of large responses at the end of the study visit (week 12). There were more stalled ulcers in the SMG group (n=5) compared to the CCO group (n=1) and more moderate responses in the CCO group (n=6), compared to the SMG group (n=1). These differences in between these two non-surgical debridement methods in terms of clinical response were statistically significant ($P<0.05$).

The number of surgical debridement performed during the whole study (treatment and follow-up) was 6.9 for the SMG group and 1.0 (baseline debridement) for the CCO group.

In terms of economic outcomes, the mean cost of debridement for physician office per patient in the SMG group was more than six-fold higher than in the CCO group for the management of Diabetic Foot ulcers. The wound clinic facility mean cost of debridement per patient SMG group was seven-fold higher than in the CCO group.

Key message:

In this trial A. Tallis et al. (58) evaluated the clinical benefit of clostridium collagenase ointment (CCO), especially in Diabetic Foot Ulcers (DFU). They compared it with standard debridement using serial sharp debridement and saline moistened gauze (SMG).

The results of this trial demonstrated the efficacy of CCO in achieving the removal of non-vital tissue. The utility is comparable to SMG plus additional serial sharp debridement. Furthermore, the benefit of using CCO was the absence of additional serial sharp debridement, whereas the SMG group received surgical debridement during the follow-up period.

Relating to the cost effectiveness, the analysis proved that the costs for the SMG group was higher than in CCO group, and therefore the therapy with CCO offers a cost-effective non-surgical debridement method for Diabetic foot ulcers.

3. An RCT to compare a bio-cellulose wound dressing with a non-adherent dressing in VLUs: (59)

Subjects:

49 subjects were included into this trial, 48 were randomized (1 not randomized (n=1 lost to follow-up). Patients were eligible for inclusion, if they had a confirmed, non-healing VLU, which was defined as no healing after four weeks of compression and standard VLU care. The minimum ulcer duration had to be at two months with no upper limits. In opinion of the investigators the ulcers had to require autolytic debridement. Participants were excluded if they had any clinical signs of infections, cellulitis, osteomyelitis, uncontrolled Diabetes and any other conditions that would cause a negative influence on the wound healing (e.g. hepatic, neurologic, immunological disease). Furthermore subjects, who received corticosteroids, radiation or chemotherapy, were also excluded.

Study design:

This trial was performed as a randomized, multicentre, parallel group, comparative, open trial, conducted in four centres in New England, from November 2003 to November 2005. The Patients were assigned to two groups. One was the intervention group (BWD and compression n=25) and the second one was the control group (nonadherent contact layer and compression n=25). All patients received compression therapy, regardless of the group they were included in. The intervention group received the BWD (Surasorb X) and the control group a sterile, non-adherent cellulose acetate gauze (Systagenix). During any point of the study, surgical, mechanical or enzymatic debridement was not allowed. This kind of treatment was practised on a weekly basis during a period of 12 weeks, or until healing.

Measurements:

The primary endpoint was the autolytic debridement efficacy of the dressings. Investigators compared wound bed conditions at the baseline (week 0) and weekly over the 12-week study period, per patient, per treatment group and between the treatment groups. The digital photographs were made by clinicians, who were blindfolded.

Secondly, the time for 75-100% of granulation and time for >=50% epithelialisation was evaluated by comparing the wound bed condition at the baseline (week 0) and week six and 12, per patient, per treatment group and between those treatment group. In addition, the investigators reported the ulcer pain before every dressing removal, using a validated visual analogue scale (VAS), in a score range of zero (no pain) to ten (extreme pain) or a verbal rating scale (no pain, mild pain, moderate pain, severe pain)

Study results:

	BWD(n=25)	Control (n=23)
Sex (m/f)	13/12	12/11
Age (years)	69.0+-8.3	63.0+-10.3
Ulcer duration (months)	10.9+-2.2	8.9+-1.2
Ulcer size in mm^2		
• **Mean**	743.9+-103.8	629.0+-106.9
• **Median**	785	627

Table 12: Demographics and ulcer characteristics

As you can see in Table 13 no significant differences were found between the two groups. During the study seven patients (28%) were withdrawn from the BWD group and eight (35 %) from the control group. So therefore 33 patients (n=18 BWD group; n=15 control) were included into the analysis. At the end of the study 15 VLU (84%) in the BWD group achieved a 75-100% granulated wound bed, in comparison to 4 (26%) in the control group. The median time to achieve over 75% granulation was shorter for the BWD group (25 days), compared to the control group (36 days). The median time to achieve a >50%

reepithelialisation was faster for the BWD group (36 days), compared to the control group (50 days). The mean percentage reduction was 83% greater for the BWD group at week six (44% vs 24%) and 37% larger at week 12 (74% to 54%). Of the 33 patients, who were included into this analysis, 14 achieved full healing (N= 7 [39%] BWD, N=7 [47%]) controls. According to the pain related scales (VAS and VRS) the patients who received treatment with BWD reported no or just mild pain, in comparison to the control group. In week seven, there was a significant difference ($p<0.05$). By the end of the study period, the investigators reported a cleaner looking ulcer bed in the BWD group, compared to the control group, which was not statistically significant ($p=0.005$).

	BWD (n=18)	Control (n=15)
75-100% cleansing of the wound by week 12 (n)	15 (84%)	4 (26%)
Time to >=75% granulation (days)	25 (12-57)	36 (15-60)
Time to >=50% epithelialisation (days)	36 (8-99)	50 (22-91)
Mean ulcer is reduction (%)		
• **Week 6**	44+-15%	24+-10%
• **Week 12**	74+-11%	54+-14%
Ulcers fully healed (n)	7 (39%)	7 (47%)

Table 13: Autolytic debridement results

Key message:

In this trial Alvarez et al.(59) compared a bio-cellulose wound dressing with a non-adherent dressing in venous leg ulcers (VLU) under a compression system. The study results showed faster and more effective autolytic debridement for VLU patients, treated with BWD in comparison to the control group. Better, but not statistically significant, results were noted in terms of ulcer pain reduction in favour for the BWD group.

4. **A novel rapid and selective enzymatic debridement agent for burn wound management: A multi-center RCT:** (55)

Subjects:

In this clinical trial, an overall of 190 patients were screened, and subsequently 182 enrolled between 2006 and 2009. 26 subjects were Nexobrid (NXB) training patients, 156 participants underwent randomization. Patients aged 4-55 years with good health conditions and with deep partial and full thickness burns, covering 5-30% of their total body surface are (TBSA) were enrolled. They were hospitalized in special burn centres. Patients, who were pregnant, lactating, suffered smoke inhalation or had severe comorbidities, were excluded from the study.

Study design:

This study was a prospective, randomized, multi-centre, open label, controlled, phase three clinical trial, that was executed in 26 burn centres in 13 countries. Before the subjects were randomized, they got allocated into two groups based on the size of the burn area, because due to its influence on the outcome. This study performed a randomization ratio 1:1 between NXB and Standard of Care (SOC), using limited blocks, prepared and managed by an independent statistician. The pre and post debridement patients and the wound management were identical to both groups (NXB and SOC). The only difference was the eschar removal strategy (enzymatic vs surgical and non-surgical SOC). Prior to the debridement all subjects received a routine treatment, such as analgesia, wound cleansing, and the burn areas were soaked by a hypertonic saline. In one group they used NXB as debriding agent. It was applied topically for 4h, followed by a 2h soaking period, using the same product as in the pre debridement stage. If the debridement was incomplete, they applied it again for 4-h. In the other group the patients received a surgical debridement SOC (tangential excision, dermabrasion or hydro surgery). Non-surgical SOC included the application of topical therapies (e.g. silver sulfadiazine).

Measurements:

The early measurements were the number and percentage of treated burn wounds, that were surgically debrided, excised, as well as the wound area (in TBSA %) that was excised and/or autografted. The reduction of surgical interventions reflected the efficacy of NXB and the reduction of autografts reflected the selectivity. Second endpoints were the time to complete eschar removal (>=90%), time to wound closure, increased compartment pressure and blood loss. The loss of blood was measured by subtracting the haemoglobin and haematocrit levels before and 24h after debridement. These endpoints were only measured in randomized, non-training patients. Scar quality were measured by senior burn surgeons. The scar quality was measured by using the Modified Vancouver Scar Scale (MVSS), which has a range of 0(best) to 13(worst). The quality of life was evaluated by using the short form -36 in adults and the Burn outcome questionnaire in children.

Study Results:

75 participants were treated with NXB and 81 were treated with SOC. In total 20 patients were lost in follow-ups, but the rates of follow-ups were similar between these two groups (10.9% vs.11.1 in the NXB and SOC group). The time to complete the eschar removal was statistically significantly shorter in the NXB group (2.2 days) compared to the SOC group (8.7 days); ($p<0.0001$). Of all NXB treated wounds, only 6.8% (11/163) required a second 4h application or a complete debridement. Furthermore, NXB significantly decreased the need for surgical excision (24.5% vs. 70.0%; $P0<0.0005$) as well as the percentage of the burnt area, which was surgically excised (13.1% vs 56.7%) compared to the SOC group. The need for autografting in deep partial thickness burns were significantly lower in NXB treated wounds. The blood loss, which is related to debridement stage, was also significantly reduced in NXB treated patients. The time of wound closure was not significantly higher in NXB treated patients (3.6 days longer). The time of wound closure was significantly shorter in children and hand burns, treated by NXB in comparison to SOC. 89 patients could be contacted and returned for the follow up. The subjects were well balanced between those two follow up groups (n=54 in NXB group; n=78 in SOC group). The mean MVSS between these two groups was similar (3.12 in NXB group vs 3.38 in SOC group; P=0.88)

Key message:

To sum up the results, the study showed enzymatic debridement with NXB. This resulted in reduced need for and extend of surgery in comparison to the Standard of Care. Furthermore, the study demonstrates that the resulting long-term scars are not worse than the wounds treated with SOC.

5. **A randomized controlled trial of larval therapy for the debridement of leg ulcers: results of a multicenter, randomized, controlled, open, observer blind, parallel group study:** (57)

Subjects:

In this trial Mudge E et al.(57) compared the effectiveness of larval debridement therapy to a hydrogel dressing in relation to the time of debriding leg ulcers with venous (VLU) or mixed aetiology (MLU). Overall 88 subjects had to be recruited for this trial, based on a previous study to achieve an 80% power. Patients, who had an ankle brachial pressure of >= 0.05 mmHg and contained over 25% sloughy and/or necrotic tissue were identified and recruited (n=88).

Study design:

This study was performed as randomized, multicentre, controlled, open, observer blind, parallel group study. The subjects (n=88) were randomized and divided into two groups. One group was treated by the larval therapy (n=46) while the other received a hydrogel dressing (42). Before treatment with either a larva dressing or a hydrogel dressing, the wound bed was cleaned with saline solution. Patients were treated to a maximum of 21 days, or until the debridement was completed. All three-four days patients were visited and the wound bed and surrounding skin were assessed by blindfolded investigators. At every visit the wound bed was reviewed and a photograph was taken. At the end point the assessors evaluated if the wound was debrided or not.

Measurements:

In this trial Mudge E et al.(57) compared the time of complete debridement of a referent ulcer (>=25% sloughy/necrotic tissue, >= 2cm² in area) between the two groups. Furthermore, they compared the percentage of complete debrided ulcers, after excluding the withdrawn patients. Debridement was further analysed by ulcer size and ulcer duration at the baseline.

Secondly, they measured the pain caused by the treatment by using self-administered Visual analogue scale (VAS), which had a range between zero (no pain) and ten (worst pain).

Study results:

Of the 88 subjects, 46 (52%) were randomized to the larval group and 42 (48%) to the hydrogel dressing group. Of the 46 patients in the larval group, 31 ulcers (67,4%) and of the 42 patients in the hydrogel group 11 ulcers (26.2%) were fully debrided. In relation to the number of wounds, which were fully debrided in the intervention phase, the larval treatment was superior, which was with a statistical significance (P=0.001). Furthermore, after excluding the withdrawn subjects, the percentage of fully debrided ulcers in the larval group was 96.9%, compared to the hydrogel group (34.4%).

A statistically significant difference was noted for wound size at baseline (P=0.003), most of the ulcers, which had a size of less than 25cm² towards 100cm² did not debride during the intervention phase.

In relation to the pain both groups had similar scores. For all patients in both groups, the score decreased after the final visit. There was a statistically significant difference between the pain score at the beginning and the pain score at the final evaluation visit.

Key message:

This trial compared larval therapy with a hydrogel dressing in leg ulcers (venous or mixed aetiology). It shows that larval therapy debrided slough and necrotic tissue from a wound bed in a statistically significant ($p<0.001$) shorter period than the hydrogel dressing. Furthermore, it shows lower incidence of local infections, when using larva debridement therapy.

6. Maggot therapy for wound debridement: a randomized multicenter trial: (32)

Subjects:

This trial lasted from 1st of March 2005 to 31st of December 2008. 105 patients who had a non-healing sloughy wound of 40cm² or less on the lower limb and with an ankle brachial index of 0.8 or higher, were included into this clinical trial. Subjects with pregnancy, lactation, neuropathy, and/or a perforated ulcers, dementia, or previous hospitalization because of non-healing wounds, were excluded.

Study design:

This study was a randomized, multicentre, controlled, prospective, single- blinded, phase 3 trial, which was performed in two hospitals in Cannes and Lyon (France). The randomized subjects were allocated into two groups. One group was treated with a maggot therapy twice a week for a two-week period. Therefore, they used a bag, which was filled with 80 maggots.

The other group was treated with conventional methods, which included surgical debridement three times a week with a scalpel, using topical anaesthesia. Furthermore, they received hydrogel dressings, if the wound was dry, or fibre-based dressings if the wounds were oozing. To ensure that the patients did not know, which therapy they received, they wore a blindfold during the dressing changes. For evaluation the patients were referred to one of the two mentioned centres for a two-week period. After these two weeks they were discharged on day 15 and on day 30 there was a follow up visit.

Measurements:

Digital photographs of the wound were taken on day 1, day 3,8,15 and at the follow-up visit. With a software package they could quantify the percentage of slough in the wounds. They could also quantify if the wound was dry or oozing, the wound surface area and the presence of MRSA or Pseudomonas aeruginosa, recorded in clinical and microbiological evaluations. Furthermore, they measured the duration of the wound care (in time) and the ulcer related pain by using a visual analogue scale (VAS), which has a range from zero (no pain) to ten (worst pain).

The most focus was on the slough percentage, which was measured by the mentioned software. All these digital photographs were evaluated by a blinded assessment.

Study results:

After randomization and exclusions, 51 received maggot debridement therapy (MDT) and 51 the conventional therapy. After mentioning that the focus was on the slough percentage, the evaluation showed, that there were no statistically significant differences between two groups in Day 1,15 and 30, but yet at day 8. With a mean decrease of the wound surface area of 14.6% in the MDT group and a mean decrease of 8.2%, there was a significant difference in relation to healing rates. Furthermore, the number of infected wounds decreased from day 1 to 15 in the MDT group, but not in the control group. Mentioning the wound duration, this study showed that the control group certainly took more time, because of the surgical debridement (30 min. of anaesthesia).

Key message:

In this clinical trial Opletalova K. et al. (32) tried to compare the effectiveness of maggot debridement in comparison to conventional methods. In general, there was no significant benefit, using maggot debridement therapy at day 15, compared to the conventional method; however, it is statistically significantly faster than the conventional method. After 1 week and the applications of 2-3 maggot debridement therapies, there is no benefit in continuing the treatment and so they suggest a change to another dressing for further treatment.

7. Maggots as a wound debridement agent for chronic venous leg ulcers under graduated compression bandages: A randomised controlled trial: (61)

Subjects:

Overall 601 Subjects were assessed for eligibility. Patients who had an Ankle Brachial Pressure Index (ABPI) between 0.85 and 1.25 (measured by Doppler Ultrasound), a venous ulcer ranging between of 4 and 100 cm^2 in size, and a surface covered by 20% or more of sloughy tissue. If a participant suffered from more than 1 ulcer, the biggest one was included into this study. The following table shows the subjects, who were excluded:

EXCLUDED	REASON	NUMBER
ULCER	<4cm² or >100cm²	N=359
SLOUGH	<20%	N=96
ABPI	Not 0.85-1.25	N=84
	No venous Reflux	N=38
	Unable to consent	N=13
	Declined to participate	N=10
	Pressure ulcer to foot	N=1

Table 14: Reasons and numbers for exclusion

Study design:

This study was a two-arm, parallel group, randomized controlled trial, which was performed from November 2008 to July 2012. After the assessment of eligibility, 40 subjects were randomly allocated into two groups. The control group received treatment with standard multilayer compression bandages and the other group received the same standard treatment plus the larval treatment. So, all participants received a compression bandage on day zero and the larval group was treated additionally with sterile larvae. On day zero the measurements were executed and on day four the subjects returned into the clinics to repeat the procedure, by changing the dresses and performing the measurements. All subjects were followed up every two weeks. The total follow-up was 12 weeks or sooner, if the wound healed before.

Measurements:

The focus was on the measurements of the sloughy tissue on the wound surface area at day zero and four. This was performed using a portable digital planimetry system. The measurements were executed by a specialist nurse and debridement was defined as the reduction of the sloughy wound surface area. Secondly the wound healing was evaluated, again by using the portable digital photography system.

Study results:

Overall, both groups showed a good outcome concerning the reduction of sloughy tissue at day four. In the control group the median reduction was 3.7 cm^2 and median percentage debridement of 50%. In the larval group the reduction was 4.2 cm^2 and 84%. Both results were statistically significant. Nine participants suffered adverse events. Five of them had wound infections, three did not tolerate the compression well and one got eczema.

Key message:

In this clinical trial C.E. Davies et al. (61) tried to assess the clinical effectiveness of MDT under a multilayer compression, by comparing it to compression therapy without larval treatment in chronic venous sloughy ulcers. It seems to be an effective alternative method for wound debridement, but on the other side it did not improve wound healing.

- **8. Larval therapy for leg ulcers (VenUS II): randomised controlled trial:** (60)

Subjects:

267 patients with at least one venous or mixed venous and arterial ulcer with at least 25% coverage of slough or necrotic tissue, and an ankle brachial pressure index of 0.6 or more were recruited. If a patient had multiple ulcers, the biggest one was chosen and included for the trial. The participants were excluded for this trial, if they were allergic to hydrogel, pregnant or lactating, suffered from uncontrolled diabetes, grossly oedematous legs, ulcer $<5cm^2$, or aged<18, or were in therapy with anticoagulants.

Study design:

This was a multicentre, randomized, open trial with equal randomization, carried out in 22 centres in the United Kingdom from July 2004 until May 2007. The patients, who participated, were randomized to receive a treatment with loose larvae, bagged larvae, or a hydrogel dressing. The larvae group received sterile Lucilica sericata larvae, which were left on the ulcer locally for three to four days. Patients in the control group received hydrogel, covered and like in the larvae group also a compression bandage depending on the Ankle Brachial Pressure Index (ABPI). The randomized treatment was conducted in

the debridement phase, which ended either when debridement was completed, or when it was stopped before treatment. The maximum length of follow-up was 12 months.

Measurements:

The primary outcome was the healing time of the ulcer, which was defined as epithelial cover of the wound. It was assessed by two independent nurses. They took digital photographs in order to document and assess the process. Secondly, they measured the time of debridement of the ulcer, which was defined as a completely clean wound. Again, they used photographs in order to assess the debridement status. Further they measured the quality of life by using the short-form-health-survey (SF-12). For analysing the bacterial load, they took swabs from the baseline, after each debridement and then, when the ulcer was healed, or the trial completed. Laboratory analysis measured the bacterial load, as well as the presence or absence of MRSA.

Study results:

In terms of time for the ulcer to heal up there was no difference between the groups, and after further analysis also any difference between the two larvae groups. The median time to healing in larvae group (results are presented for both larvae groups) 236 days and in the hydrogel group it was 245 days. The time to debride the wound was statistically significantly different between the three groups. The median time to debridement with loose larvae was shorter (14 days) than with bagged larvae (28 days) and hydrogel (72 days). The data collected from the swabs showed no evidence of any difference in bacterial load over the time between the combined larvae group and the hydrogel group. The mean ulcer related pain (24 hours before removal of the first debridement therapy) for the larvae groups were double compared to the hydrogel group. It was statistically significant more pain experienced in the combined ($P<0.001$) larvae groups than in the hydrogel group.

Key message:

To sum up the results, this trial shows no evidence that loose or bagged larvae, shortens the time of healing ulcers compared with hydrogel. There was also no difference in terms of bacterial load between these groups. However, they showed that larvae are a more effective debriding agent than hydrogel.

3.3 Results in detail

Clinical trial	Cohort number (N)	Care setting	Period of treatment	Follow up	Treated wounds
2014, Meaume et al.	159	In 37 active centres in France, Germany und UK	6 weeks	6 weeks	Venous or mixed aetiology leg ulcer
2013, Tallis et al.	48	7 sites in Nebraska, Arizona, Pennsylvania, Texas	4 weeks	8 weeks	Diabetic foot ulcer
2012, Alvarez et al.	48	4 clinical centres in New England	12 weeks	Not reported	Venous ulcers
2014, Rosenberg et al.	156	26 burn centres from 13 countries	6-8h	Followed until closure and additional 3 monthly visits; long -term: 2-4 years after injury	Burn wounds
2014, Mudge et al.	88	General hospital	3 weeks or until heal	7-14 days after final visit	Ulcer with mixed aetiology (venous/arterial)
2012, Opletalova et al.	105	Multicentre Trial in Cannes and Lyon	2 weeks	Visit at day 30	Venous Ulcers
2015, Davies et al.	40	Wound healing research unit and General hospital	4 days	12 weeks	Venous ulcers
2009, Dumville et al.	267	18 leg ulcer centres in the UK	Until debridement occurred or withdrawn	Maximum 12 weeks	Ulcers with mixed aetiology (venous/arterial)

Table 15: Characteristics of each included trial

Clinical trial	Inclusion criteria	Exclusion criteria	Intervention 1	Intervention 2
2014, Meaume et al.	ABPI between 0.7 and 1.3; ulcer period between 3 and 36 months; ulcer area with sloughy tissue between 3 and 30 cm^2	infection, dry wounds or necrotic tissue bad health situation, treated with chemotherapy, radiotherapy or immunosuppressant drugs	UrgoClean dressing	Hydro fibre dressing (Aquacel)
2013, Tallis et al.	18 years or older with a diagnosis of diabetes of type 1 or 2;	Not reported	Clostridial Collagenase dressing	Standard of care with saline moistened gauze
2012, Alvarez et al.	Non-healing VLU after 4 weeks of treatment.	clinical signs of infections, cellulitis, osteomyelitis, uncontrolled diabetes; receiving corticosteroids, radiation or chemotherapy	Bio cellulose wound dressing	Non adherent dressing
2014, Rosenberg et al.	4-55 years with good health condition and with deep partial and full thickness burns, covering 5-30% of (TBSA)	pregnant, lactating, suffered smoke inhalation or had severe comorbidities	Nexobrid (enzymatic)	Standard of care (surgical)
2014, Mudge et al.	ankle brachial pressure of >= 0.05 mmHg and contained over 25% sloughy and/or necrotic tissue	Not reported	Maggot debridement	Hydrogel dressing
2012, Opletalova et al.	Non-healing sloughy wound of 40cm^2 or less on the lower limb and with an ankle brachial index of 0.8 or higher	pregnancy, lactation, neuropathy, and/or a perforated ulcer of the foot, dementia, or previous hospitalization because of non-healing wounds	Maggot Debridement	Conventional Method (surgical+Hydrogel dressing or fibre-based dressing)
2015, Davies et al.	Ankle Brachial Pressure Index (ABPI) between 0.85 and 1.25 (measured by Doppler Ultrasound), a venous ulcer in size between of 4 and 100 cm^2, and a surface covered by 20% or more of sloughy tissue	Ulcer <4cm^2 or>100cm^2 Slough <20% ABPI Not 0.85-1.25	Maggot debridement + compression bandages	Compression bandages without Debridement

2009, Dumville et al.	venous or mixed venous and arterial leg ulcers (assessed as an ankle brachial pressure index ≥0.6) with at least 25% of the wound covered by slough or necrotic tissue, ulcers with an area of 5 cm^2 non-healing	pregnant or lactating, were allergic to hydrogel, had grossly oedematous legs, or were taking anticoagulants (contraindicated with larval therapy).	Loose/bagged larvae	Hydrogel

Table 16: Summary of inclusion, exclusion criteria and interventions

4 Discussion

In this chapter of my thesis I want to summarise all results, discuss them and point out which non-surgical methods might have been established and describe their evidence. Further I want to refer to qualitative characteristics, such as adverse effects, cost-effectiveness of debridement methods, follow up and treatment period.

As mentioned above, we wanted to compare these trials and planned a meta-analysis to create a single pool of cohorts. This was done in order to create a significant statement. Unfortunately, due to the fact, that we only included studies with Level of Evidence I and therefore lesser quality randomized, retrospective, case studies, as well as the letter(s) to the editors were excluded, it could not be carried out. Furthermore, these trials differ in interventions, wound applications, treatment period and follow-up time, which would have been necessary for a meta-analysis. Finally, our systematic review is limited to studies linked to the PubMed and Web of Science interface. In table 15-16 all results are shown in detail.

Debridement is an essential part in the wound management as well as in acute burn injuries. Clinicians use various wound debridement methods. The surgical approach is the most direct form of debridement. For patients, who are poor candidates for this procedure, as well as for patients, who don't have access to surgeons, other non-surgical debridement methods are available. They are more selective and less harming for vital and healthy tissue. The goal of this systematic review was to see, if there is evidence for the use of non-surgical debridement methods for chronic necrotic ulcers and burns.

4.1 Wound application

4.1.1 Leg ulcers

Debridement of chronic wounds is considered essential for optimizing wound healing. They often contain sloughy or necrotic tissue, which hinder the wound healing process. As table 15 shows, several different non-surgical methods were used as an intervention for different chronic necrotic ulcers. These ulcers showed various aetiologies and surgical or non-surgical methods where compared. In total seven RCT´s (32,56–61) investigated non-surgical debridement methods for chronic necrotic leg ulcers. Mudge et al. (57) and Dumville et al. (60) used MDT as an intervention for venous or mixed leg ulcers and compared it with a conventional debridement technique using hydrogel. Little evidence exists comparing debridement with no debridement in treatment of leg ulcers, which was investigated by Davies et al. (61). Meaume et al. (56) compared two autolytic methods using a new dressing UrgoClean in comparison with a common hydrogel dressing. Debridement of non-vital tissue in Diabetic foot ulcers has been used for decades for wounds to improve their healing capacities, to prevent infections and to create an ideal environment. Tallis and colleagues (58) compared CCO, an enzymatic debriding agent with serial sharp debridement and saline moistened gauze for the treatment of Diabetic foot ulcers. Furthermore, they evaluated the cost effectiveness, tolerability and cost of Clostridial collagenase ointment.

4.1.2 Burn wounds

Especially deep and full thickness burns are serious injuries with serious consequences. They are associated with significant morbidity and mortality. In these burn wounds necrotic tissue is presented, which leads to local and systemic complications and therefore the necrotic tissue has to be removed. Serial sharp debridement followed by autografting was established as the standard treatment of deep and full thickness burns, but it is associated with consequences, such as bleeding, damage of functional tissue, requiring specialized staff and facilities. (55)

The idea of using different enzymes, or ointments instead of surgical methods, which dissolve the necrotic eschar, is not new, but throughout history it could not replace surgery in any way, because they are inefficiently slow. Idealistically, these products would be the first treatment option, which selectively remove the burn eschar, without damaging any other tissue and further provide a wound bed for healing, or skin grafts. (43).

Rosenberg and colleagues (55) have developed an enzymatic debriding agent, NexoBrid, which is mixed with a carrier gel forming debriding gel dressing. They carried out a clinical trial to evaluate enzymatic debridement and to compare it to conventional methods.

4.2 Non-surgical debridement methods

4.2.1 Enzymatic Debridement

In total two studies evaluated the performance of an enzymatic debridement method. At this point of my review I want to elaborate on the trial by Rosenberg et al. (55), which differ in a certain manner to the other trials. As mentioned above in the detailed descriptions of my results, they performed a randomized trial to evaluate the efficiency of an enzymatic debriding agent, especially in deep and full thickness burns. Furthermore, it is the only study, which compares non-surgical method to a surgical method in burn wounds. This specifically concerns deep and full thickness burn. They developed an enzymatic debriding agent, NexoBrid, which was tested in preliminary studies in animals and humans, which showed it`s efficacy by removing burn eschar selectively after a 4h single application, which led to a clean wound bed, and less time to complete the debridement studies in animals and humans.(55)

It was a high-quality trial, which showed similar effects and seems to be a good alternative and fast method for eschar removal with additional clinical benefits. It reduced the need for surgical interventions (24.5% NXB vs. 70.0% SOC; $P < 0.0001$), reduced debridement dependent blood loss in the wounds treated with NXB in comparison to the SOC. Furthermore, less autograft from a donor area was needed, which resulted in less scars. The time to complete the eschar removal was statistically significantly shorter in wounds treated with NexoBrid compared to SOC (2.2 days vs. 8.7 day; $P < 0.0001$).

Due to the fact, that it was the only trial, using this agent, we could not point out it´s efficacy objectively. This trial has its limitations too, as reported: they were unable to mask physicians to treatment assignment, so is might be possible, that the open label nature influenced the surgeons to be less aggressive in performing the surgical debridement, especially after the treatment of patients who required NexoBrid. Furthermore this study was performed in a burn centre with special-trained burn surgeons, so the results might not generalize to other less specialized surgeons.(55)

Furthermore, there are a poor number of studies containing enzymatic debridement for deep and full thickness burns. It is not possible to state, that a non-surgical method of this kind, is well established. For burn wounds, the treatment with a rapid enzymatic agent using NexoBrid, seems to be promising for the future, but there is necessity of prospective randomized clinical trials.

The same applies to the treatment of Diabetic foot ulcers (DFU), by Clostridial Collagenase ointment (CCO), an enzymatic debriding agent, which removes non-vital tissue selectively, without harming vital and healthy tissue. Tallis et al. (58) investigated the efficacy of enzymatic debridement using Clostridial collagenase ointment (CCO) in comparison to a conventional method using saline moistened gauze (SMG) and sharp debridement in DFU. The results show, that the debridement efficacy using CCO is as effective as SMG with serial sharp debridement, as there was no significant difference in wound assessment scores. This study shows, that CCO promotes the wound healing process. Both groups had significant improvements in the wound bed in the first four-week treatment period, however in the eight weeks follow up period the SMG group remained static. The CCO group had a 54% reduction in the wound surface area in comparison with a lacking decrease in the SMG group. Despite this there was no additional sharp debridement in the CCO group, which might lead back to the effects of collagenase during the follow up period.

4.2.2 Autolytic Debridement

In total, two studies investigated wound dressings and assessed the efficacy of autolytic debridement in non-healing venous ulcers. There was no study, which compared an autolytic debriding dressing to mechanical debridement. At this point I have to point out

the significance of these studies. Certainly, a higher cohort number means a more significant result. Meaume et al. (56) randomized 159 subjects, whereas Alvarez and colleagues (59) randomized 48 subjects. However, in relation to the reduction of wound surface area, both studies showed similar results. In terms of reduction of sloughy tissue and therefore in the debridement stage, the UrgoClean, a new micro-adherent absorbing dressing showed statistically significantly better results than the Aquacel control group and the BWD group showed better results too. Meaume and colleagues (56) reported, they additionally used mechanical debridement, but they mentioned, that it was much easier to perform, after treating patients with autolytic debridement.

In my point of view the pain levels of these alternative treatment methods play a vital role, because it should be a gamechanger to surgical procedures. In respect to the trial of Meaume et al.(56) the pain measurements were poorly addressed in contrast to Alvarez et al. (59), who used the Visual Analog Scale (VAS) to measure pain during the treatment with the two dressings. They demonstrated, that patients treated with BWD reported mild or no pain, which was statistically significant at week seven of the treatment period ($p<0.05$)

Overall the studies show, that autolytic debridement methods are well established for treating chronic venous ulcers, as these two studies (58,61) compared new dressings to conventional methods, which also include autolytic dressings as well. Due to the fact, that there are only two studies, which test new dressings, there is still room for improvement for new autolytic dressings and their establishment on the market for chronic venous ulcer treatment.

4.2.3 Larval debridement therapy

Four studies assessed the effectiveness of larval therapy for chronic, sloughy or necrotic ulcers, with either venous or mixed aetiology. In total, three studies (32,57,60) compared them to conventional methods using a hydrogel dressing. Opletalova et al.(32) showed that Maggot Debridement Therapy (MDT) has no significant benefit until day 15. However, it demonstrates that it is significantly faster in the first week of treatment in comparison to surgical debridement and hydrogel. It was also demonstrated by Dumville and colleagues (60), as well as by Mudge et al.(57). This study (60) investigated the treatment with loose

as well as bagged larvae in comparison to hydrogel, in contrast to the other two mentioned studies. They showed that the time to debridement with loose larvae was shorter than with bagged larvae and hydrogel in the first week. Furthermore, it was the only study, which measured the bacterial load and the presence or absence of MRSA. Bacterial load decreased in both groups over time of treatment but no difference was shown between the two groups. In these two studies (32,60) the healing rates could not be improved.

The study by Davies et al. (61) was the only one, which assessed the efficacy of larval debridement therapy (LDT) under multilayer compression bandages compared to no debridement and the compression system alone. It demonstrates that debridement with larvae and compression is more effective than multilayer compression bandages alone. Furthermore, it also demonstrates in the secondary outcome, that LDT plus compression bandages did not improve the wound-healing rate for venous leg ulcers compared to the standard treatment of compression alone.

In my point of view time to debridement, plays an essential role in the treatment of complex and necrotic wounds. Due to the fact, that LDT is faster than conventional methods and additionally it saves more time, by skipping the local anaesthesia for surgical debridement, it seems to be a useful alternative debridement method for wounds, in need of a fast debridement, however, it does not improve the wound closure.

As mentioned above, the pain levels during these treatments play an essential role. Mudge et al. (57) showed that subjects, who were treated with Maggots, had more pain during their treatments and furthermore it was the main reason for withdrawal. Likewise it was demonstrated by Dumville et al. (60), where statistically more pain was experienced by participants in both larvae groups than in the hydrogel group.

Overall Maggot debridement seems to have potential as a non-surgical debridement method, but due to the fact, they do not improve wound healing, they could be used for more acute cases to debride wounds, because they are faster than conventional methods. Furthermore, the use of LDT could also depend on the ulcer size, as in one study large ulcers could not be debrided, and therefore the ulcer size might have an influence on the choice of the debridement method.

Due the fact, that there are only four studies about LDT for chronic necrotic ulcers, further research is required to explore if LDT is a better option for debriding chronic necrotic wounds.

The following table shows the improvements according to their study protocol for chronic necrotic ulcers, using different non-surgical debridement methods.

Ulcers	Reduction of sloughy tissue	Pain	Wound surface area	Adverse events	Drop outs
Opletalova et al. (32)	MDT>surg.Deb. +Hydrogel	Mild in both groups	Surg.Debr. +Hydrogel>MDT at Day 15 Similar at day 8 and 30	3 in control group	Not reported
Davies et al. (61)	4LB+Larvae>4LB	Not reported	similar	6 in 4LB and 3 in 4LB+Larvae	None
Mudge et al. (57)	MDT>Hydrogel	MDT>Hydrogel	similar	14 in larval arm 10 in hydrogel arm	24
Meaume et al. (56)	UrgoClean>Aquacel	similar	similar	7 in UrgoClean; 9 Aquacel	25
Tallis et al. (58)	CCO similar to SMG	Not reported	similar	23 patients experienced 61 adverse events	
Alvarez et al. (59)	BWD>control	BWD>control	Not reported	6 in BWD group,8 in control group	15
Dumville et al. (60)	Loose larvae>bagged larvae>hydrogel	Both larvae groups>hydrogel	similar	131 patients had 340 adverse events	Not reported

Table 17: The table shows the improvements according to their study protocol for chronic necrotic ulcers.

4.3 Study quality and point of criticism

All previously described studies were ranked as Level of Evidence I and therefor quality factors like randomization, blinding and prospective study design are not in further discussion. Remaining qualitative factors like adverse events, follow-up, cost effectiveness will be discussed in closer detail.

Adverse events:

Adverse events have a huge impact on the outcome for treatment options and their value and are therefore an important parameter for comparisons. In these eight studies, which investigated different non-surgical debridement methods in chronic necrotic ulcers and burns, adverse events were reported as follows.

For the investigation of larval debridement therapy all three studies, which compared LDT with hydrogel revealed adverse events like infection, increased slough and pain. In all three studies, more pain was experienced by participants in the LDT group. Dumville et al. (60) categorized adverse events as serious and non-serious, which was judged by treating nurses. Then health professionals judged, if the adverse events were related to trial treatment. Furthermore, they established a list of possible treatment related to adverse events on the basis of previous literature (maceration, pressure damage, excoriation, infection, ulcer related pain, ulcer deterioration). The study (61), which compared LDT with only compression bandages reported no serious adverse events. However, nine participants experienced adverse events like infection, eczema and intolerance to compression.

In the case of the two studies, which investigated autolytic debridement methods, the study by Meaume et al. (56) demonstrated rare and non-specific adverse events. A total of 16 local adverse events were reported, of those eczema and pain represented being the main reason for treatment discontinuation.

In the case of the study by Tallis et al. (58), which investigated CCO, an enzymatic debriding agent for the treatment of DFU, adverse events were reported, but not described precisely. None of them were considered to be related to the treatment. In the study by Rosenberg and colleagues (55), who assessed the efficacy of NXB, all subjects were

monitored for local and systemic adverse events. There was no statistically significant difference in adverse events between treatment with NXB and SOC. Pain scores were similar in both groups. As there is less need for skin graft and no difference in pain levels after the treatment with NXB, this non-surgical, enzymatic, selective debriding agent might be a promising alternative approach for deep and full thickness burns. Since it is the only study, which assessed the effectiveness for this alternative treatment method, further clinical prospective randomized studies should be performed, in order to give advice for treatment options.

Costs:

Millions of people suffer from chronic necrotic and burn wounds, representing an economic burden to our society. Therefore, costs for new treatment approaches should be taken into consideration. Meaume and colleagues (58) evaluated the costs of Clostridial collagenase ointment (CCO) in comparison to surgical debridement and saline moistened gauze in treatment for DFU. Their results showed, that the treatment with CCO is more cost effective than with SMG and serial sharp debridement and furthermore demonstrated better results in terms of wound debridement, at similar costs of care. I want to point out, that this was the only study, which evaluated the costs of a non-surgical debridement method, however, Dumville et al. (60) referred to a different study (62), where they analysed the cost effectiveness of larval therapy in comparison to hydrogel in the management for leg ulcers, based on the data from the included study. This analysis demonstrates, that debridement with larvae have similar health benefits, as well as similar costs, in comparison to hydrogel, in the management of chronic, sloughy leg ulcers. Finally, I would like to point out, that treatment costs are certainly an important factor for decision making, as there are several different methods available for wound debridement. Therefore, further research is recommended to ensure, that the most cost-effective treatments are used.

Treatment period and follow up:

Due to the fact, that these included studies investigated different non-surgical methods in the management of different wounds, the treatment and follow-up periods vary a lot. In the case of the three studies, which compared LDT to hydrogel for leg ulcers, the treatment period was similar, with 15 and 21 days, which is adequate. Wound healing was also a

point of interest, which requires a long follow up period to ensure a good long-term outcome. The last follow up visit of the studies by Opletalova et al. (32) and Mudge et al. (57) was two weeks after the last treatment day, which is too short, in order to make a statement about the wound healing benefits. The study by Dumville et al. (60) used a follow up period between six and 12 months, which is adequate. The two studies, which evaluated autolytic debriding dressings used an intervention and follow up period of six and 12 weeks, which is long enough to evaluate the debriding efficiency and wound healing benefits of autolytic debridement methods in the treatment of venous leg ulcers. The study by Tallis et al. (58), which assessed the efficiency of CCO in the treatment of DFU, was a 12 week trial with a 12 week follow up. Again, in terms of wound healing this trial is comparatively short, considering that other DFU healing trials have a treatment duration of >20 weeks. Interestingly, Rosenberg et al. (55) conducted a long term follow up of subjects two-four years after the trauma, in order to assess the scar quality, which was not part of the original study. They demonstrated, that the size and number of scars were reduced in the group, which was treated with NXB.

5 Conclusion

This systematic review demonstrates, that there is a lack of evidence for non-surgical debridement methods in the treatment of chronic ulcers and burns. Based on our results, larval debridement therapy seems to be faster than hydrogel. However, they showed no improvement in wound healing and further randomized trials are needed, in order to confirm these findings. Subsequently, evidence for autolytic debridement methods in the treatment of venous leg ulcers is still lacking. In the case of using non-surgical debridement methods for deep and full thickness burns, Nexobrid showed, that there is less debridement dependent blood loss, less scars and a reduced need for surgical interventions in comparison to conventional methods. However, this debriding agent has to be evaluated in further randomized clinical trials. There is insufficient evidence for Clostridium collagenase ointment, an enzymatic debriding agent, for the treatment of diabetic foot ulcers. This study demonstrated similar efficiency in terms of debridement in comparison to a serial sharp debridement method and saline moistened gauze. Overall, there is a need for further prospective randomized trials to compare non-surgical debridement methods.

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