Eschar removal by bromelain based enzymatic debridement (Nexobrid®) in burns: An European consensus

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ABSTRACT

Early debridement and/or eschar removal is regarded as a significant step in the treatment of deep partial and full thickness burns. It aims to control wound bioburden and allows early wound closure by conservative treatment or skin grafting. Preservation of viable dermis accompanied by early wound closure, is regarded as a necessary step to reduce scar related complication, e.g. functional limitations and/or unaesthetic scar formation. Aside from the classical techniques of surgical excision as tangential excision for eschar removal, hydrotherapy, maggots therapy, laser, enzymatic debridement have been described as additional techniques in the burn surgeon’s armamentarium. It is widely accepted that early eschar removal within 72h improves the outcome of burn wound treatment by reducing bacterial wound colonization, infection and length of hospital stay. In contrast, the right technique for eschar removal is still a matter of debate. There is increasing evidence that enzymatic debridement is a powerful tool to remove eschar in burn wounds, reducing blood loss, the need for autologous skin grafting and the number of wounds requiring surgical excision. In order to assess the role and clinical advantages of enzymatic debridement by a mixture of proteolytic enzymes enriched in Bromelain (Nexobrid®) beyond the scope of the literature

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1. Introduction

Early eschar removal is regarded as the key step in the treatment of deep partial and full thickness burns. Xiao-Wu et al. have demonstrated that early excision within 48h of injury can significantly reduce the rate of invasive infection, sepsis and length of hospital stay [1]. In accordance, Barret and Herndon showed that a significant reduction of bacterial colonization, bacterial counts and infection rate is possible by early excision within 24h of injury compared to later excision [2].

It is widely accepted that early eschar removal within 48h may improve the outcome of burn wound treatment. Nevertheless, the complexity of burn depth assessment within this time frame due to burn depth progression and late demarcation, as well as logistical reasons sometimes postpone the ideal time of eschar removal, which may lead to additional injury and loss of viable dermis. In summary, the optimal technique for eschar removal should selectively remove nonviable burned tissue, achieve minimal blood loss, allow for optimal clinical wound bed evaluation and treatment decisions resulting in faster wound healing by means of conservative treatment or early surgical coverage by autologous skin grafting in order to improve aesthetic and functional outcome and thus the quality of life.

The choice of the optimal technique is still a matter of debate. Aside from the classical technique of surgical excision, various other techniques have been developed, applied and validated for burn eschar removal, providing a level of evidence that ranges between 2 to 5: these techniques include hydro-surgery, maggot therapy, laser, collagenase based enzymatic gel treatment, special cauterity systems and Bromelain based enzymatic debridement [3-14].

It has been reported that classical surgical excisions done within the first 24h after burn injury may significantly reduce blood loss during eschar removal [15]. The procedure itself is regarded as a highly technical one, and a learning curve with training is necessary [16]. Special knives for tangential excision have to be fitted using varying thickness of skin guards to limit the thickness of excised tissue, and presence of pinpoint bleeding indicates the viable layer. Nevertheless, it is still recommended to include a thin adjacent layer of viable tissue into burn wound excision to enable safe transplant take and total excision of the burn wound. For hydro-surgery (e.g. Versajet®), there is evidence available that burn eschar excision has the capacity to significantly reduce the amount of excised viable dermis compared to standard of care, but further superiority to tangential excision could not been demonstrated so far [5-8]. In order to debride burn wounds more superficially, Dessy et al. demonstrated that the use of lubricants and a razor may reduce the pain during debridement compared to the use of sterile gauze for scraping the roof off, but no further superiority could be shown [17]. Fu et al. compared collagenase based gel (Iruxol® mono) to Vaseline treatment. They were able to show a reduction of necrotic tissue after a minimum of 14 days of application of collagenase gel in a randomized controlled trial (RCT) [12]. For the use of medical maggots, larvae and cautery knife with air spray in burn wound debridement only limited evidence is available from case series predominantly showing feasibility of these techniques without comparison to standard of care [3,13,14].

There is increasing evidence that enzymatic debridement is a powerful tool to remove eschar in burn wounds, reducing blood loss, the need for autologous skin grafting and the number of wounds requiring surgical excision [4,11]. In addition, it has been shown that enzymatic debridement can reduce the rate of burn wound infection and the length of hospital stay, which is mainly due to early application and timely selective eschar removal [10].

In order to assess the role and advantages of Bromelain based enzymatic debridement (Nexobrid®) beyond the scope of the existing literature and in view of users’ experience, a European Consensus Meeting was scheduled to provide statements for application.

2. Methods

European consensus guidelines on enzymatic debridement for eschar removal in burns were formulated by a multistep process, which included a systematic literature review (2000-2016), expert panel discussion and voting on panel statements, based on the only available approved drug Nexobrid®. Peer-reviewed literature was used as a basis for pre-formulated statements by the first and senior author (C.H. and U.K.). These statements were the basis for panelist discussions. A formal evaluation of the quality of the published evidence on
enzymatic debridement was conducted applying the Oxford Level of Evidence Classification System [18]. Due to the limited number of publications and the novelty of the treatment modality of enzymatic debridement in burns, systematic consensus measures (e.g., Delphi method) were not applied, and a modified consensus process was implemented.

2.1. Panelists

European expert panelists were selected by the first and senior author (C.H. and U.K.) based on the following criteria: clinical experience with the treatment regime of Enzymatic Debridement, prior publications on the topic, expertise and reputation in burn treatment, and role as key opinion leader. Selection of panelists was limited to Europe due to the medical approval of Nexobrid™. This included diversity of experience and practice patterns of more than 500 summarized patient cases in enzymatic debridement with Nexobrid™ from a variety of European geographic locations to provide a heterogeneous expert panel sample. Panelists were selected from Austria, Belgium, Germany, Italy, Slovak Republic, Spain, Switzerland and United Kingdom and encompassed plastic surgeons and burn surgeons. In order to serve the multi-professional aspects of enzymatic debridement in burns, one non-physician panelist (H.H.) also participated in the consensus meeting. Every participating center had one vote per statement, regardless of the number of participants present from the center.

2.2. Process

Prior to the face-to-face meeting (which was scheduled in January 2017 in Frankfurt, Germany), all panelists were provided with 68 possible, pre-formulated consensus statements on enzymatic debridement for eschar removal in burns based on peer-reviewed publications and clinical relevance on the following topics (10): indications, pain management and anesthesia, timing of application, technique of application, post-interventional wound management, skin grafting after Enzymatic Debridement, blood loss, summary of cost-effectiveness, training strategies and learning curve, areas of future research needs.

The consensus workshop was divided into two major sections:

The first section included the presentation of the systematic review on debridement and eschar removal in burns in order to synchronize the level of evidence for the years 2000-2016 in-between the panelists. The next major section consisted of the re-presentation and discussion on major issues of the clinical application of enzymatic debridement based on 68 possible, pre-formulated consensus statements followed by a final debate about which topics should be included in the consensus guidelines. Consensus statements were modified by the panelists during the discussion process. Ten voting centers representing eight European countries where enzymatic debridement is commonly used (Austria, Belgium, Germany, Italy, Slovak Republic, Spain, Switzerland and United Kingdom) were asked to mark agreement or disagreement with each consensus statement at the end of the debate.

All panelists were asked to reflect the consensus statements list and results by proof-reading of the consensus manuscript written and provided by C.H. and U.K. including a follow-up discussion via email. Panelists were encouraged to make comments and suggestions for changes to the manuscript. The final version of the manuscript was accepted and agreed for submission by all participants.

2.3. Consensus agreement

A systematic method for calculated consensus was not applied due to the novelty of enzymatic debridement. The methodology employed was an agreement algorithm based on a modification of the Willy and Stellar method [19]. The consensus model provided a classification scheme with cut-offs for consensus agreement (Table 1), allowing to assess degree of agreement for statement inclusion >50%.

The results of the consensus statements are provided in tables based on the major topics (Table 2), with the first column citing the consensus statement, followed distribution of “yes/no” responses to the statement and the percentage of for achieved consensus.

2.4. Standard of care

Throughout the whole consensus process, surgical excision with tangential knives and/or hydro surgery were regarded as surgical standard of care and if applicable compared to enzymatic debridement. The panelists agreed that everything that is not exclusively defined for enzymatic debridement, shall follow the standard of care for burn eschar removal.

3. Results

Based on the consensus process, 68 statements were generated. These address clinical routine of enzymatic debridement and include the experience of ten centers in eight European

<table>
<thead>
<tr>
<th>Rank</th>
<th>Agreement %</th>
<th>Agreement description</th>
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<tbody>
<tr>
<td>1</td>
<td>Strong consensus &gt;95% or participants agree</td>
<td>Statement should be included</td>
</tr>
<tr>
<td>2</td>
<td>Consensus &gt;75-95% of participants agree</td>
<td>Statement should be included</td>
</tr>
<tr>
<td>3</td>
<td>Majority approval &gt;50-75% of participants agree</td>
<td>Statement should be included</td>
</tr>
<tr>
<td>4</td>
<td>No consensus &lt;50% of participants agree</td>
<td>Statement should not be included</td>
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nations with more than 500 cases treated. In addition, statements were based on the available literature encompassing the years 2000-2016. The consensus statements as basis for the European Guidelines were sub-classified according to the following topics: indications, pain management and anesthesia, timing of application, technique of application, post-interventional wound management, skin grafting after enzymatic debridement, blood loss, summary of cost-effectiveness, training strategies and learning curve, and areas of future research needs.

In order to provide the published advantages of enzymatic debridement in burn eschar removal to the patients and experience successful and beneficial results of this technique, users should obey the provided strong recommendations during indication, treatment and further evaluation.

All consensus statements are listed in bold letters. In addition, the results of the consensus are listed in brackets after each statement. The following 68 statements are summarized in Table 2.

Table 2 – Consensus statements on enzymatic debridement in burns. (For interpretation of the references to color in this table legend, the reader is referred to the web version of this article.)

<table>
<thead>
<tr>
<th>Statement</th>
<th>Yes/no responses</th>
<th>Consensus</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Indications and setting</td>
<td></td>
<td></td>
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<tr>
<td>• Enzymatic debridement should only be applied by experienced burn teams after adequate training in enzymatic debridement.</td>
<td>(10/0)</td>
<td>100%</td>
</tr>
<tr>
<td>• Enzymatic debridement with Nexobrid is a safe and reliable alternative tool for early eschar removal in adults.</td>
<td>(10/0)</td>
<td>100%</td>
</tr>
<tr>
<td>• Enzymatic debridement may be applied in pediatric patients and is performed with satisfying results but this is currently considered as off label use.</td>
<td>(10/0)</td>
<td>100%</td>
</tr>
<tr>
<td>• In case of a moist burn eschar, enzymatic debridement may be applied to all burned surfaces.</td>
<td>(10/0)</td>
<td>100%</td>
</tr>
<tr>
<td>• Enzymatic debridement is advantageous in treatment for hands, feet and face.</td>
<td>(10/0)</td>
<td>100%</td>
</tr>
<tr>
<td>• Contact of enzymatic debridement to the eyes and the tympanum should be avoided.</td>
<td>(10/0)</td>
<td>100%</td>
</tr>
<tr>
<td>• Enzymatic debridement preserves viable dermis more efficiently compared to standard of care.</td>
<td>(10/0)</td>
<td>100%</td>
</tr>
<tr>
<td>• Enzymatic debridement as the only procedure for debridement should be limited to thermal burns, i.e. scald/flame/contact burns.</td>
<td>(10/0)</td>
<td>100%</td>
</tr>
<tr>
<td>• In additional trauma, such as high voltage injury, blast injury or crush burn, surgical techniques should be applied in order to release muscular compartment pressure and provide nerve decompression.</td>
<td>(10/0)</td>
<td>100%</td>
</tr>
<tr>
<td>• Enzymatic debridement cannot be recommended for eschar removal in chemical burns.</td>
<td>(10/0)</td>
<td>100%</td>
</tr>
<tr>
<td>• Pretreatment with silver sulfadiazine or betadine should be avoided.</td>
<td>(10/0)</td>
<td>100%</td>
</tr>
<tr>
<td>• Standard burn wound and depth assessment is sufficient prior to enzymatic debridement.</td>
<td>(9/1)</td>
<td>90%</td>
</tr>
<tr>
<td>• Frequent photography and wound documentation is strongly recommended to provide wound documentation for all members of the burn team.</td>
<td>(9/1)</td>
<td>90%</td>
</tr>
<tr>
<td>• Enzymatic debridement can be regarded as a useful tool in case of limited OR capacity.</td>
<td>(7/3)</td>
<td>70%</td>
</tr>
<tr>
<td>• Enzymatic debridement can be safely applied in up to 15% BSA in one session (label).</td>
<td>(10/0)</td>
<td>100%</td>
</tr>
<tr>
<td>• Up to 30% BSA can be treated by enzymatic debridement based on individual decision, but this is considered as off-label use.</td>
<td>(10/0)</td>
<td>100%</td>
</tr>
<tr>
<td>• Enzymatic debridement can be applied for early eschar removal in circumferential extremity burns to prevent surgical escharotomy as standard of care but not to replace fasciotomy.</td>
<td>(10/0)</td>
<td>100%</td>
</tr>
<tr>
<td>• The extremity should be monitored and surgical escharotomy and/or fasciotomy should be performed if signs of deterioration appear.</td>
<td>(10/0)</td>
<td>100%</td>
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2. Pain Management and Anesthesia

- Adequate pain management is essential before, during and after enzymatic debridement. (10/0) 100%
- Regional anesthesia is recommended for enzymatic debridement at the isolated (upper) extremity. (7/3) 70%
- Analgesics-based intravenous sedation or general anesthesia is recommended for enzymatic debridement at the trunk and if different regions are treated at the same time. (10/0) 100%

3. Timing of application

- Enzymatic debridement can be applied immediately after initial assessment and wound preparation. (10/0) 100%
- Later application (>72 hours from injury) is possible in selected patients after appropriate preparation. (10/0) 100%

4. Application of enzymatic debridement

- Preparation of the wound by blister removal and superficial debridement of keratin remnants is necessary prior to enzymatic debridement (before or after pre-soaking). (10/0) 100%
- A moist wound environment is essential prior to enzymatic debridement, because it does not work in dry wounds. (10/0) 100%
- A moist wound environment can be achieved by a pre-soaking phase of at least 2 hours in acute burns <72 hours from injury. (9/1) 90%
- Pre-soaking might not be required, if a moist wound environment is present prior to enzymatic debridement. (10/0) 100%
- Pre-soaking is not recommended in an emergency indication for the prevention of burn induced compartment syndrome. (10/0) 100%
- An additional mechanical cleaning step can be performed at the end of the pre-soaking phase. (10/0) 100%
- The enzymes should be applied for 4 hours. (10/0) 100%
- 2g/1% BSA should be applied in adult patients in order to achieve an active agent layer of approximately 1.5-3mm thickness. (10/0) 100%
- Even distribution of the enzymes over the entire wound area is required. (10/0) 100%
- The application of a moist dressing for at least 2 hours is recommended. (10/0) 100%
- Prolonged application up to 18 hours can improve the results of enzymatic debridement. (10/0) 100%
- Enzymatic debridement requires sterile occlusive dressings with minimal dead space. (10/0) 100%
- The dressing during enzymatic debridement includes: (10/0) 100%
- An adhesive local barrier (e.g. paraffine/vaseline vaseline gauze or ointment), or stoma paste is necessary should be applied 2-3 cm outside the treated area in order to prevent leakage of the active agent
  - Occlusive film
  - Bulky, protective dressing
- Complete eschar removal should be achieved within 7 days of injury.
- Re-application of Enzymatic Debridement after initial failure is currently not recommended.
- Wound assessment should be performed within 2 hours after Enzymatic Debridement.
- Post-Enzymatic Debridement wound bed color and bleeding patterns play a key role in diagnosing the resulting depth of the burn wound.
  - A uniform red or pink post Enzymatic Debridement wound bed represents high chances for spontaneous healing.
  - A uniform white post Enzymatic Debridement wound bed with pin-point punctate bleeding has good chances for spontaneous healing with acceptable results.
  - A post Enzymatic Debridement wound bed with large diameter red circles or oval patterns is associated with prolonged healing and skin grafting should be considered in these wounds.
  - Exposed fat post Enzymatic Debridement is a clear indication for skin grafting.

5. Post-interventional care of wounds after enzymatic debridement – wound management

- Debris and the residues of the enzymes and dissolved dermis should be removed by scraping.
- After ED, it is necessary to keep a moist environment to avoid desiccation.
- Pseudo-eschar is a specific layer sticking to the wound that may develop several days after Enzymatic Debridement.
- If an occlusive layer remains >14 days, re-debridement should be taken into consideration.
- Granulation tissue may develop in prolonged spontaneous healing after Enzymatic Debridement starting at day 14.
  - Hypergranulation is a sign of insufficient reepithelialization.
  - Granulation tissue requires topical treatment followed by secondary healing or surgical treatment.
  - Topical steroids can be recommended to avoid hypergranulation.

(continued on next page)
3.1. Indications and setting

3.1.1. Enzymatic debridement as an alternative tool compared to standard of care

- Enzymatic debridement should only be applied by experienced burn teams after adequate training in ED. (10/10)
- Enzymatic debridement with Nexobrid is a safe and reliable alternative tool for early eschar removal in adults. (10/10)
- Enzymatic debridement may be applied in pediatric patients and is performed with satisfying results but this is currently considered as off label use. (10/10)

Treatment of pediatric patients (age <18 years) is formally considered as off-label use so far, which is the major reason of the participants to be more restrictive in the application. Treatment of pediatric patients should currently be regarded a personal, clinical decision by the treating physician. 5/10 centers have treated young pediatric patients, while 10/10 have treated children <18 years, mainly adolescents >15 years of age. An approval study (https://clinicaltrials.gov/ct2/show/NCT022278718) is open for inclusion and is expected to provide further user relevant data on the application of enzymatic debridement in pediatric burns.
• In case of a moist burn eschar, enzymatic debridement may be applied to all burned surfaces. (10/10)

Enzymatic debridement advantages are most obvious in burned surfaces, which have thin subcutaneous layers with underlying functional structures and burned surfaces in which surgical techniques (standard of care) are limited, and when the risks of surgical burden and morbidity increase.

• Enzymatic debridement is advantageous in treatment for hands, feet and face. (10/10)
• Contact of enzymatic debridement to the eyes and the tympanic membrane should be avoided. (10/10)

For hands and face, enzymatic debridement is regarded to be superior to hydro-surgery or standard of care which is also reflected in the current literature [8,11,20,21]. Hydro-surgery is limited to smaller areas due to the relatively small cutting unit. Eyes should be carefully protected from the active agent by local measures, which include Panthenol based ointment on the cornea, stoma paste/vaseline and a dressing and tamponade by e.g. fatty gauze in the ear.

Hands and feet, lower and upper extremity, are regions that are ideal to start the learning curve with, due to the convenient fixation of occlusive dressing to keep the active agent in place.

2/10 participants have experience in treating male and female genitals and the perineum — locations which might benefit from enzymatic debridement due to limitations of standard of care in eschar removal in these regions, but there are technical issues regarded as drawbacks in applying and keeping the occlusive dressing on these areas during treatment phase of enzymatic debridement.

3/10 participants have experience in treating the axillary fold, where splints are helpful to keep the active agent in place.

3.1.2. Proposed role of enzymatic debridement for the preservation of dermis

• Enzymatic debridement preserves viable dermis more efficiently compared to standard of care. (10/10)

Enzymatic debridement is a powerful tool to selectively remove burn eschar especially in mixed depth burn patterns, where preservation of viable dermis and deeper layers is even more challenging by standard of care.

3.1.3. Patient selection

The following statements aim to help the user identifying the “ideal” patient and burn pattern to succeed in the treatment of enzymatic debridement and minimize pitfalls.

3.1.3.1. Mechanism of burn: flame, electricity, chemical?

• Enzymatic debridement as the only procedure for debridement should be limited to thermal burns, i.e. scald/flame/contact burns. (10/10)
• In additional trauma, such as high voltage injury, blast injury or crush burn, surgical techniques should be applied in order to release muscular compartment pressure and provide nerve decompression. (10/10)

Enzymatic Debridement may be used in these cases for debridement and subcutaneous pressure release, but it will not release deeper compartment pressures. It might be used as an additive procedure, when e.g. additional surface burns without deep extent are present in high-voltage injury, blast injury or crush injury.

• Enzymatic Debridement cannot be recommended for eschar removal in chemical burns. (10/10)

2/10 centers have experience in the treatment of 5 chemical burns, in which the power of early and selective eschar removal by enzymatic debridement did not become evident. As a consequence, due to limited evidence and unclear demarcation of chemical burns, it cannot be recommended.

• Pretreatment with silver sulfadiazine or betadine should be avoided. (10/10)

Based on the clinical trials and experience, pre-treatment with silver sulfadiazine or betadine should be avoided if possible. The suspected mechanism of interference with Enzymatic Debridement efficacy is thought to be the thicker layer on the eschar formed by these treatments or the heavy metals. If pre-treatment with one of the above mentioned agents is necessary due to in-house protocols and a lack of availability of water-based gel alternatives, the contact time should be kept as short as possible followed by sufficient rinsing and (prolonged) pre-soaking.

3.1.3.2. Burn wound assessment. Burn wound assessment is performed by clinical evaluation and can be followed by technical measures, e.g. Laser Doppler Imaging (LDI) [22]. Regularly burn wound photography and IT-based documentation provides improved comparability for optimal treatment [23].

• Standard burn wound and depth assessment is sufficient prior to enzymatic debridement. (9/10)
• Frequent photography and wound documentation is strongly recommended to provide wound documentation for all members of the burn team. (9/10)

Photography and decisive wound documentation during the implementation of enzymatic debridement is strongly recommended to shorten the learning curve for the whole burn team, and to have the chance to discuss wound evaluation and specific issues on enzymatic debridement and patterns.

The reasons for only a 9/10 consensus was the implementation of LDI as a standard diagnostic tool in one center where it serves as a diagnostic tool in addition to clinical evaluation before application of enzymatic debridement.

3.1.3.3. Role for mass casualty.

• Enzymatic debridement can be regarded as a useful tool in case of limited OR capacity. (7/10)

A unanimous recommendation for the use of enzymatic debridement in mass casualty events could not be reached (7/
10) due to concerns of 3 panelists of creating a situation where too many patients with open wounds requiring skin grafting exist simultaneously; 1/10 centers report advantages and remarkable logistic and therapeutic opportunities in a mass casualty event in 2016 where enzymatic debridement was used on multiple patients.

3.1.4. Body surface

3.1.4.1. TBSA treated.

- Enzymatic debridement can be safely applied in up to 15% BSA in one session. (10/10)
- Up to 30% BSA can be treated by enzymatic debridement based on individual decision, but this is considered as off-label use. (10/10)

6/10 participants have experience in treating up to 30% BSA in one enzymatic debridement session, but application beyond 15% BSA per session is currently regarded as an off-label use. Systemic aspects have to be considered in patients treated with more that 15% BSA, mainly due to fluid loss, which has to be recalculated in resuscitation fluids. Patients will require additional fluids, invasive monitoring and pre-treatment risk stratification.

Experience of the participants in treating >15% BSA ranges up to 36% in one session, but it remains consensus that it should not exceed 30% BSA per session.

3.1.4.2. Enzymatic debridement as a rapid tool for eschar removal to prevent escharotomies in extremity burns. Surgical escharotomies belong to the standard of care armamentarium in burn surgery and provide emergent decompression of circumferential eschar for the subcutaneous compartment and if necessary for the deep muscular compartment. Early ED may reduce the inflammation and edema formation and thus can be regarded as a tool to prevent need for surgical escharotomies by relieving the pressure in the subcutaneous compartment:

- Enzymatic debridement can be applied for early eschar removal in circumferential extremity burns to prevent surgical escharotomy as standard of care but not to replace fasciotomy. (10/10)
- The extremity should be monitored and surgical escharotomy and/or fasciotomy should be performed if signs of deterioration appear. (10/10)

9/10 participants have experience in the treatment of circumferential and near circumferential burns with eschar removal by enzymatic debridement to prevent surgical escharotomy. In case of suspected muscular compartment syndrome, enzymatic debridement is not recommended as a surgical fasciotomy is needed. 10/10 participants agree, that early application of enzymatic debridement after the burn trauma within the first hours is effective to prevent subcutaneous pressure increase, which may cause compartment syndrome. The participants reported that there was no incidence or necessity of conversion to surgical escharotomy after early eschar removal by enzymatic debridement.

Compartment pressure must be assessed if enzymatic debridement is applied in circumferential extremity burns after thermomechanical trauma or high voltage injury in order to assess the need of fasciotomy due to deep layer injuries.

3.2. Pain management and anesthesia

Enzymatic Debridement is regarded as a painful procedure and requires analgesia or analgo-sedation/anesthesia depending on the depth of burn and extent of BSA treated with enzymatic debridement.

- Adequate pain management is essential before, during and after Enzymatic Debridement. (10/10)
- Regional anesthesia is recommended for enzymatic debridement at the isolated (upper) extremity. (7/10)
- Analgesics-based intravenous sedation or general anesthesia is recommended for enzymatic debridement at the trunk and if different regions are treated at the same time. (10/10)

Enzymatic debridement causes significant pain during application and removal of the debris. For regional anesthesia, long-acting local anesthetic drugs (up to 8h) are recommended (e.g. Ropivacaine). If not available, catheter based techniques are necessary to provide long lasting anesthesia. Centers are recommended to develop interdisciplinary pain management concepts to implement the special aspects of enzymatic debridement. In case of total extremity burn, it is recommended to implement regional anesthesia through an unburnt area in order to prevent infection (e.g. scalene muscle level) or general anesthesia. Monitoring equipment is necessary according to the type of anesthesia.

There is limited experience in performing enzymatic debridement with local anesthesia (infiltration or tumescence), which has been applied by 1/10 of the participating centers. Some patients report of significant and prolonged pain after intervention.

3.3. Timing of application

Timing of eschar removal is a key factor in burn care in general, as it is with enzymatic debridement as well.

- Enzymatic debridement can be applied immediately after initial assessment and wound preparation. (10/10)
- Later application (>72h from injury) is possible in selected patients after appropriate preparation. (10/10)

Late application of enzymatic debridement benefits from special preparation of the burned surface in order to reduce dry surface and improve the effect of presoaking. This can be done by surgical removal of superficial burn layers followed by treatment and prolonged presoaking.

3.4. Application of Enzymatic Debridement

The technique of application is essential to achieve successful eschar removal.
3.4.1. Preparation of the wound

- Preparation of the wound by blister removal and superficial debridement of keratin remnants is necessary prior to treatment (before or after pre-soaking). (10/10)

3.4.2. Pre-soaking

- A moist wound environment is essential prior to enzymatic debridement, because it does not work in dry wounds. (10/10)
- A moist wound environment can be achieved by a pre-soaking phase of at least 2h in acute burns <72h from injury. (9/10)
- Pre-soaking might not be required, if a moist wound environment is present prior to treatment. (10/10)
- Pre-soaking is not recommended in an emergency indication for the prevention of burn induced compartment syndrome. (10/10)
- An additional mechanical cleaning step can be performed at the end of the pre-soaking phase. (10/10)

The participants agree (10/10) that anti-infective agents are not superior for pre-soaking, compared to saline or ringer solution. Solutions that are applied for pre-soaking by the participants: chlorhexidine 0.5% based solution (3/10), physiologic saline solution (1/10), sulfonamide based solution (1/10), Flamigel® (1/10) or polyhexanide based solutions (5/10). Gel based covers prior to treatment keep the wound bed moist, and thus an additional pre-soaking phase is not necessary.

If enzymatic debridement is applied for early eschar removal to prevent surgical escharotomy due to compartment syndrome, immediate application without pre-soaking should be performed in order to have a timely interaction of the enzymes.

Late burns with a dry eschar (>72h from injury) require additional preparation by mechanical removal of superfluous layers followed by prolonged pre-soaking up to 12h in order to improve the efficacy of debridement.

3.4.3. Product application

- The enzymes should be applied for 4h. (10/10)
- 2g/1% BSA should be applied in adult patients in order to achieve an active agent layer of approximately 1.5-3mm thickness. (10/10)
- Even distribution of the enzymes over the entire wound area is required. (10/10)

A reduction of exposure time to the enzymes is possible, but should be performed according to personal experience in order to maintain efficacy. A shorter exposure time may be possible when treating more superficial burns. 2/10 participants have experienced sufficient efficacy of enzymatic debridement with a minimum of 2h application. 2/10 participants have experienced an efficient and safe treatment when keeping the enzymes on for longer than 4h (mainly due to logistical reasons) without any side-effects. The enzymes do not undergo spontaneous inactivation after 4h. In general, after 4h there is no eschar left, which is the basis for the above-mentioned recommendation.

3.4.4. Initial phase after treatment (also known as “post-soaking phase”)

- The application of a moist dressing for at least 2h is recommended. (10/10)
- Prolonged application up to 18h can improve the results of enzymatic debridement. (10/10)

7/10 centers practice a prolonged initial post-treatment phase up to 12h, in order to remove the remnants in the next morning (due to logistic reasons). Prolonged post-soaking improves the removal of enzymes, gel and dissolved eschar remnants. The participants agree (10/10) that anti-infective agents are not predominantly necessary after treatment, compared to saline or ringer solution. In general, most participants apply the same solutions for the after phase as in the pre-soaking phase.

3.4.5. Debridement dressing

- Enzymatic debridement benefits from sterile occlusive dressings with minimal dead space. (10/10)
- The dressing during enzymatic debridement includes (10/10):
  - An adhesive local barrier (e.g. paraffin/vaseline gauze or ointment, or stoma paste) should be applied 2-3cm outside the treated area in order to prevent leakage of the active agent
  - Occlusive film
  - Bulky, protective dressing

3.4.6. Time to complete removal of eschar

- Complete eschar removal should be achieved within 7 days of injury. (10/10)

Application of enzymatic debridement is recommended within 72h of injury. In case of incomplete early eschar removal by enzymatic debridement, additional eschar removal by hydrosurgery or standard of care should be performed in order to complete eschar removal within the first 7 days after burn injury. This is necessary in order to reduce risk of colonization and infection, which has been also reported in literature [1,2,24,25].

3.4.7. Re-application of enzymes

- Re-application of enzymatic debridement after initial failure is currently not recommended. (10/10)

Re-application of the enzymes has been performed by 4/10 centers (single additional application), as a personal strategy based on the current off-label use. The participants agree that a re-application is not recommended. Failure of the initial application may be due to individual patient/burn- or
user-based, or to date unknown factors of which at least some must be addressed prior to re-application.

3.4.8. Wound bed assessment after Enzymatic Debridement

- Wound assessment should be performed within 2h after treatment. (10/10)
- Post- treatment wound bed color and bleeding patterns play a key role in diagnosing the depth of the wound. (9/10)
- A uniform red or pink post Enzymatic Debridement wound bed after treatment represents high chances for spontaneous healing. (10/10)
- A uniform white wound bed with pin-point punctate bleeding has good chances for spontaneous healing with acceptable results. (10/10)
- A wound bed with large diameter red circles or oval patterns is associated with prolonged healing and skin grafting should be considered in these wounds. (10/10)
- Exposed fat post Enzymatic Debridement is a clear indication for skin grafting. (10/10)

The larger the diameter of the circular patterns (skin appendages/fat) in the dermis, the deeper the dermis is affected. Exposed fat after treatment is a clear indication for skin grafting. Wound assessment for bleeding pattern should be performed at a standardized point of time. While 2/10 participants regard this as optimal 2h after treatment phase, 8/10 prefer evaluation straight after finishing enzymatic debridement. It is recommended to reassess the wound depth after removal of the post soaking as sometimes bleeding immediately after removal of Enzymatic Debridement may interfere with accurate assessment.

3.5. Post-interventional care of wounds after enzymatic debridement — wound management

Care after treatment is essential to provide optimal outcome of the technique, reduce instable scarring and keep the procedure as minimally-invasive as possible by reducing the number of unnecessary secondary procedures.

3.5.1. Enzymes removal

- Debris and the residues of the enzymes and dissolved dermis should be removed by scraping. (10/10)

3.5.2. Wound bed preparation after Enzymatic Debridement

- After enzymatic debridement, it is necessary to keep a moist environment to avoid desiccation. (10/10)

3.5.3. Pseudo-eschar: assessment and how to deal with it

- Pseudo-eschar is a specific layer sticking to the wound that may develop several days after treatment. (10/10)
- If an occlusive layer remains >14 days, surgical re-debridement should be taken into consideration. (10/10)

Pseudo-eschar results from exudate and the degradation of proteins as well as residues from topical agents and temporarily sticks to the surface. Spontaneous peeling of areas of the pseudo-eschar revealing epithelial islands underneath is a sign to not re-debride after 14 days. In general, pseudo-eschar is not an obstacle for spontaneous healing.

3.5.4. Role of granulation tissue

- Granulation tissue may develop in prolonged spontaneous healing after Enzymatic Debridement starting at day 14. (10/10)
- Hypergranulation is a sign of insufficient reepithelization. (10/10)
- Granulation tissue requires topical treatment followed by secondary healing or surgical treatment. (10/10)
- Topical steroids can be recommended to avoid hyper-granulation. (10/10)

In general, granulation tissue is expected to appear in areas of remaining very deep viable dermis sometime between 14-21 days after enzymatic debridement, where prolonged spontaneous wound healing is to be expected. In order to support epithelization, several days of topical steroids treatment are recommended in order to suppress granulation tissue as early as possible after its appearance.

The participants recommend temporary dressings and membranes to reduce the frequency of dressing changes, which provides comfort and reduces pain. In addition, it provides an optimal wound bed for the re-epithelization phase.

In case of clear punctate bleeding (assessment of an efficient debridement), temporary, hydrolysable membranes, allografts and xenografts for 10-14 days may reduce the frequency of dressing change and are suitable for preventing desiccation supporting spontaneous epithelization.

3.6. Skin grafting after enzymatic debridement

Skin grafting may become necessary in some deep-dermal (grade 2b) burns with prolonged healing to reduce instable scarring. It is always necessary in full thickness burns after enzymatic debridement.

Enzymatic debridement reduces the number and surface of skin grafting procedures. (10/10)

3.6.1. Timing

- Enzymatic debridement should be regarded as a debridement tool, and autologous skin grafting or other reconstructive procedures including application of dermal substitutes or flaps should be performed if stable healing cannot be expected. (10/10)
- In case of full thickness burns after treatment, autologous skin grafting should be delayed for at least 2 days. (10/10)
- Enzymatic debridement may allow good results even after a prolonged healing time. (10/10)
- Autologous skin grafting is advisable at latest after 21 days if there is no progress in epithelization. (7/10)
- Delayed healing might result in unstable scarring and insufficient functional and aesthetic results. (10/10)
If static wound dynamics are evident and epithelization does not proceed despite optimal topical treatment, re-debridement and autologous skin grafting have to be taken into consideration. There is a significant learning curve to assess timing and the track of prolonged spontaneous healing. There was an ongoing controversy regarding the appropriate time point to select patients for re-debridement and skin grafting. The participants agree that in case of prolonged healing without surgery, a watchful observation with frequent inspections is necessary not to miss the right moment of insufficient delayed healing. The combined experience of the panelists is that a delay of skin grafting for at least 2 days after enzymatic debridement is necessary in order to get a basic wound bed integrity to improve take rate. Superficial wound bed preparation in order to achieve pinpoint bleeding is necessary prior to skin grafting.

3.6.2. Use of dermal replacement matrices

- When enzymatic debridement is applied in full-thickness burns, dermal replacement matrices may be used. (10/10)

3.7. Scar prevention

Scar treatment (Massage, ointment, compression garments, silicon, etc.) should immediately start after healing. (10/10)

3.8. Blood loss

- Enzymatic debridement reduces blood loss compared to standard of care. (10/10)
- Enzymatic debridement might induce relevant blood loss in patients with coagulopathy or therapeutic anticoagulation. (9/10)

With reference to the systematic review, the participants agree to the potential of enzymatic debridement to reduce blood loss compared to standard of care. However if coagulopathy occurs or anticoagulative treatment is installed, there is a risk of increased blood loss and cautions should be taken. Monitoring of hemoglobin is mandatory even if limited blood loss is expected.

3.9. Training strategies and learning curve

Training strategies are essential in order to reduce the number of preventable pitfalls and build up a team to implement the use of enzymatic debridement.

- Enzymatic debridement benefits from standardized protocols and significant experience in the field of burn care and surgery. (10/10)
- Enzymatic debridement requires clear communication and multi-professional training. (10/10)
- Logistic requirements of enzymatic debridement have to be considered prior to implementation. (10/10)

The participants agree that the application of enzymatic debridement itself is a simple procedure that can be performed after minimal training, but the pre and post treatment assessment and treatment consequences are more complex, requiring experienced burn care teams and training in order to shorten their learning curves. Training programs and center specific standard of care documents should include preparation for enzymatic debridement and arrangement of logistics including multidisciplinary cooperation, wound bed assessment and treatment strategies, dressings after treatment (based on local supply) and indications for skin grafting after treatment.

4. Discussion

The provided consensus statements aim to serve as user-orientated recommendations for enzymatic debridement beyond the current available evidence in the literature. Peer-reviewed publications on enzymatic debridement were included to support the statements whenever appropriate, but this consensus document is not aimed to serve as a systematic review on enzymatic debridement. Although there is an increasing amount of evidence available on enzymatic debridement in burns [4,9-11], the technique per se is relatively new for widespread clinical application and requires a special strategy for successful implementation including technical training and wound bed evaluation compared to the standard of care. The consensus panel included experts from Europe with a combined experience of >500 patients treated with enzymatic debridement. The aim of this consensus paper is to prevent users from unnecessary pitfalls.

To start with, extremity burns (upper and lower extremity) followed by face burns are regarded as beneficial burnt surface areas in order to have an improved learning curve. In addition, for hands and face, Enzymatic Debridement is regarded to be superior to hydrosurgery or standard of care, which is reflected in the current literature [8,11]. Compared to the SOC, it is significantly important to provide a highly moist eschar prior to enzymes application, either by postburn application of gel based topical agents or a defined pre-soaking phase. Both before and after treatment, wound bed evaluation are key steps in achieving successful post-burn results, and require experience and training. An early application of enzymatic debridement in circumferential burns may prevent the need for surgical escharotomy, but is not an effective tool for decompression of deeper compartments in a combined mechanism of injury such as electrocution, crush-burn or explosion. The issues on enzymatic debridement achieving only 70% of consensus are indication and timing of skin grafting after partial thickness burns including the handling and interpretation of pseudo-eschar, the use of enzymatic debridement in mass casualties and the application of regional anesthesia for pain management. In view of timing of autologous skin grafting, it is regarded necessary to prevent instable scarring when prolonged secondary healing seems to occur. The best affordable consensus (7/10) for a general recommendation included autologous skin grafting to be performed at latest after 21 days if there is no progress seen in epithelialization, while some panelists even report on stable epithelialization >21 days after burn. Addressing the use of enzymatic debridement in mass-casualties, all participants...
agreed about the ability of enzymatic debridement to debride a large amount of burn patients within a small timeframe, i.e. increase surge capacity in a mass casualty incident. An unanimous recommendation for the use of enzymatic debridement in mass casualty events could not be reached (7/10) due to concerns of 3 panelists of creating a situation where many patients with open wounds requiring timely skin grafting exist simultaneously. However, the alternative of delayed eschar removal is detrimental, and the concerns expressed may be alleviated by temporary coverage, e.g. use of allo- or xenograft or other temporary covers. Concerns in the application of regional anesthesia in Enzymatic Debridement (7/10) mostly derive from experience of some centers with complications of regional anesthesia.

Relevant areas of future research have been identified by the expert panel and include reduction of the inflammatory local response, optimization of perfusion and drainage due to reduced posttraumatic edema, dermal layer preservation, patient satisfaction perspective, role in mass casualty and systemic response after enzymatic debridement.

We feel the need to state the limitations of a consensus panel with potential bias from individual experience and potential influence on other panelists during face-to-face discussions.

5. Conclusion

To the best of our knowledge, this is the first document summarizing user-oriented guidelines for enzymatic debridement, providing application recommendations and strategies in order to optimize the learning curve of this innovative technique. According to the Willy and Stellar scheme, all statements could be included. The degree of consensus is remarkably high, with a total consensus in 88.2% of statements, with the lowest degree of 70% consensus in only 3 out of 68 statements.

The statements obtained by the consensus panel provide a minimal set of guidelines available for the use of enzymatic debridement, and should be understood as such, in addition to the available evidence in the current literature. We believe that future readjustment and fine-tuning of these recommendations should be performed as further knowledge and evidence becomes available, which we expect will happen in the course of the next years.

Disclosures (potential conflict of interest statements)

Dr. Hirche is a consultant and speaker for MediWound, Germany; Integra Life science, France and is on the scientific advisory board of Kinetic Concepts, Inc., Europe; Dr. Citterio: No disclosures; Mr. Hoeksma has been a speaker for MediWound, Germany; Dr. Koller is a consultant for MediWound, Germany; Dr. Lehner: No disclosures; Dr. Martinez has been a speaker for MediWound, Spain; Dr. Monstrey: No disclosures; Dr. Murray received travel and accommodation expenses from MediWound, Germany; Dr. Ploch is a consultant and speaker for MediWound, Germany; Dr. Sander is a consultant and speaker for MediWound, Germany; Dr. Schulz is a consultant and speaker for MediWound, Germany; Dr. Ziegler has been a speaker for MediWound, Germany; Dr. Kneser has been a consultant for MediWound, Germany and has been a speaker for Acelity Inc.

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