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Italian recommendations on enzymatic debridement in burn surgery

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ABSTRACT

Introduction: Nexobrid®, a bromelain-based type of enzymatic debridement, has become more prevalent in recent years. We present the recommendations on enzymatic debridement (Nexobrid®)'s role based on the practice knowledge of expert Italian users.
Methods: The Italian recommendations, endorsed by SIUST (Italian Society of Burn Surgery), on using enzymatic debridement to remove eschars for burn treatment were defined. The definition followed a process to evaluate the level of agreement (a measure of consensus) among selected experts, representing Italian burn centers, concerning defined clinical aspects of enzymatic debridement. The consensus involved a multi-phase process based on the Delphi method.
Results: The consensus panel included experts from Italy with a combined experience of 1068 burn patients treated with enzymatic debridement. At the end of round 3 of the Delphi method, the panel reached 100% consensus on 26 out of 27 statements. The panel achieved

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full, strong consensus (all respondents strongly agreed on the statement) on 24 out of 27 statements.

Discussion: The statements provided by the Italian consensus panel represent a "ready to use" set of recommendations for enzymatic debridement in burn surgery that both draw from and complete the existing scientific literature on the topic. These recommendations are specific to the Italian experience and are neither static nor definitive. As such, they will be updated periodically as further quality evidence becomes available.

1. Introduction

Surgical debridement/excision is currently considered the standard of care for eschar removal in burn patients. Early (within 48 h) eschar removal may improve the outcome of burn wound treatment. Nonetheless, surgical debridement often results in significant blood and heat loss, and it is hindered by poor selectivity, which means both viable and necrotic tissue may be excised [1–3]. To try and overcome these limitations, several alternative techniques for eschar removal have been developed over the years, including hydro-surgery and enzymatic debridement [2–5]. None has currently become standard of care.

Nexobrid®, a bromelain-based type of enzymatic debridement, has become more prevalent in recent years. Several published studies have assessed its efficacy and safety on burn wounds [5–9]. Its advantages, compared to the standard of care, include decreased surgical morbidity and blood loss, length of hospital stay, rates of infection, need for skin grafting, and costs [10,11]. More importantly, this product permits eschar removal without sacrificing viable or healthy tissue, returning entirely vital dermal or subcutaneous tissue.

We present the recommendations on enzymatic debridement (Nexobrid®)'s role based on the practice knowledge of expert Italian users. We acknowledge that European recommendations have recently been published [12,13]. We recognize the importance of international consensus as to the basis and starting point for defining more accurate, nation-specific consensuses and recommendations, as we did in our case, to better capture trends and variations to modus operandi that are often nation and region-specific. Only one Italian center participated in the European consensus. Therefore, it did not represent the full spectrum and knowledge of burn management with enzymatic debridement in Italy. In particular, the participating centers in the Italian consensus panel offer a combined experience of more than double the number of patients treated with enzymatic debridement by the centers included in the European consensus panel.

2. Methods

The Italian recommendations, endorsed by SIUST (Italian Society of Burn Surgery), on using enzymatic debridement to remove eschars in burn treatment were defined following a process to evaluate the level of agreement (a measure of consensus) among selected experts, representing Italian burn centers, concerning enzymatic debridement's clinical aspects. The consensus involved a multi-phase process based on the Delphi method [14]. This method involved selecting a group of experts by two principal investigators (IM, JM); these experts were subjected independently to a series of questionnaires, in successive phases, to collect the group's opinions systematically and reach an agreement on the main points under discussion.

2.1. *Expert selection*

The 2 principal investigators selected 20 participants in the consensus (panelists) based on their relevant knowledge and specialized skills on enzymatic debridement. Their expertise was defined as extensive, proven clinical experience with enzymatic debridement and previous peer-reviewed publications or congress presentations on the topic. The selected experts had wide and heterogeneous experiences with over 1068 patients treated from December 2015 to October 2018 and the relevant and consistent scientific production. The 20 experts represented the following burn centers: Catania, Bari, Brindisi, Cesena, Genova, Milano, Napoli, Palermo, Parma, Pisa, Roma, Sassari, Torino, and Verona. Each participating center was able to cast only one vote, regardless of the number of experts selected affiliated with each center. Therefore, while the cumulative number of experts was 20, they amounted to 14 valid votes (one vote per represented burn center). Following the Delphi method, the answers to the questionnaires were acquired in an anonymous form, avoiding the effects of the influence of leading personalities, as well as other bias deriving from an in-person, unblinded setting.

2.2. *The Delphi method*

Based on a systematic review of the literature (2000–17) regarding the use of the only drug (Nexobrid®) currently available for enzymatic debridement to treat burns, the two main investigators identified the main topics of interest related to enzyme debridement with Nexobrid®: indications for enzymatic debridement, pain management, application timing, application technique, post-enzymatic debridement wound care, and burn mass casualty disaster.

2.3. *Round 1*

During the first round, an open-ended questionnaire was submitted to the experts, asking them to provide information and suggestions concerning the specific topics based on their clinical experience. The investigators analyzed the information obtained during the first round to organize and categorize the proposed statements.

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2.4. Round 2

Based on a qualitative elaboration of the information obtained, the two principal investigators drew up a list of consensus statements submitted to the experts during the second round. The second round aimed to obtain quantitative information. In particular, experts were asked to express their degree of agreement/disagreement using a 5-point scale (Likert agreement scale, Table 1)[15] compared to such a series of clinical statements on enzymatic debridement. Based on the quantitative results of the second round, the main areas of agreement/disagreement of experts were identified concerning the topics addressed.

2.5. Round 3

During the third round, feedback on the previous questionnaire was provided to the experts. In particular, the two principal investigators provided the experts with a quantitative summary of the second round answers, highlighting the degree of disagreement of the group concerning the proposed clinical indications. Each represented burn center, informed about their position concerning the anonymized group's responses, had the opportunity to change their opinion on their degree of agreement/disagreement concerning the issues addressed.

All statements that scored at least 4 on the Likert scale for 90% of the panelists at the end of round 3 were included in the official SIUST-endorsed Italian recommendations on using enzymatic debridement in burn surgery.

Throughout the whole consensus process, surgical excision with tangential excision was considered the standard of care and, if applicable, compared to enzymatic debridement. Any aspect not explicitly related to enzymatic debridement should follow the current standard of care in burn management.

3. Results

The consensus process produced 27 statements that address the clinical features of enzymatic debridement and reflect the experience of the selected 14 centers in Italy, with 1068 cumulative cases treated as of the start date of the consensus process.

Table 2 provides the results, classified by main topics, under which each consensus statement is listed, followed by the distribution of the Likert scale responses to the statement and the percentage of achieved consensus (defined as cumulative % of Likert 4 and 5 responses) after rounds 2 and 3. In the following paragraphs, the statements are provided under the main topic's classification, followed by the Likert scale responses distribution (numbers of Likert 5/4/3/2/1 responses) and % of consensus (% of Likert >4 responses) after round 3.

To optimize enzymatic debridement's advantages, and thus experience the successful and beneficial results of this technique, users should follow the provided full consensus recommendation statements.

Table 1 – The Likert agreement scale.

Agreement	Value
Strongly Agree	5
Agree	4
Undecided	3
Disagree	2
Strongly Disagree	1

3.1. Indications to enzymatic debridement

1) Enzymatic debridement is not indicated in epidermal and superficial dermal burns, while it can be used in other degrees of burns (14) – 100%
2) Enzymatic debridement in the treatment of burns should only be used by experienced personnel after appropriate training (14) – 100%
3) Enzymatic debridement is a safe debridement tool for the removal of eschar in adult patients and can be safely used in compliance with the data sheet (14) – 100%
4) Enzymatic debridement can be used in pediatric patients with satisfactory results but is currently considered an off-label use (8/5/1) – 93%

Comment: Enzymatic debridement is a useful tool for selectively removing burn eschar, especially in deep and mixed depth burn patterns, where preservation of the viable dermis and deeper layers is essential but more challenging to obtain using the standard of care.

Enzymatic debridement is considered off label for pediatric patients (age <18 years); this is why many centers are currently more restrictive in this application. At the time of the consensus, eight centers had experience in treating pediatric patients. Until further studies validate this indication, the treatment of pediatric patients should be considered an individually tailored clinical decision, based on physician experience.

5) The use of enzymatic debridement can be very beneficial in the treatment of the face, hands, neck and décolleté in terms of saving vital dermal tissue; it is very useful in the treatment of the chest and abdomen for the reduction of bleeding (14) – 100%

Comment: The use of enzymatic debridement is particularly beneficial in areas with thin subcutaneous layers with underlying functional structures, where the risks of surgical burden and morbidity increase significantly. By literature data, enzymatic debridement is considered superior to the standard of care for hands and face [5,8,9]. All 14 centers had experience in treating these sites. They believe enzymatic debridement's main advantage is for treating large areas on the trunk, and advocate the need for further exhaustive evidence for face-neck and hands specific applications, when compared to the standard of care.

6) Clinical depth diagnosis of burns is sufficient indication to treat with enzymatic debridement (14) – 100%.

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Table 2 – Italian recommendation statements, Likert scale responses distribution and percentage of consensus agreement (defined as % of Likert values 4 and 5) per statement, after Round 2 and 3 of the Delphi method.

Italian recommendations on enzymatic debridement in burn surgery

Topic	Statement	Distribution of Likert scale responses – round 2	Consensus % – round 2	Distribution of Likert scale responses – round 3	Consensus % – round 3
Indications to enzymatic debridement					
1	Enzymatic debridement is not indicated in epidermic and superficial dermal burns, while it can be used in other degrees of burns	14 strongly agree	100% full strong consensus	14 strongly agree	100% full strong consensus
2	Enzymatic debridement in the treatment of burns should only be used by experienced personnel after appropriate training	14 strongly agree	100% full strong consensus	14 strongly agree	100% full strong consensus
3	Enzymatic debridement is a safe debridement tool for the removal of eschar in adult patients and can be safely used in compliance with the data sheet	14 strongly agree	100% full strong consensus	14 strongly agree	100% full strong consensus
4	Enzymatic debridement can be used in pediatric patients with satisfactory results but is currently considered an off-label use	8 strongly agree; 4 agree; 2 undecided	86% no consensus	8 strongly agree; 5 agree; 1 undecided	93% consensus
5	The use of enzymatic debridement can be very beneficial in the treatment of the face, hands, neck and décolleté in terms of saving vital dermal tissue; it is very useful in the treatment of the chest and abdomen for the reduction of bleeding	14 strongly agree	100% full strong consensus	14 strongly agree	100% full strong consensus
6	Clinical depth diagnosis of burns is sufficient indication to treat with enzymatic debridement	14 strongly agree	100% full strong consensus	14 strongly agree	100% full strong consensus
7	Enzymatic debridement can be safely applied in a single application over an anatomical area of not more than 15% of TBSA, but there are data indicating a single application on larger surfaces is safe	11 strongly agree; 3 agree	100% full consensus	11 strongly agree; 3 agree	100% full consensus
8	After the first application, not before 24 h, it is possible to reapply enzymatic debridement in the same patient on different anatomical areas	14 strongly agree	100% full strong consensus	14 strongly agree	100% full strong consensus
9	The main indication of enzymatic debridement is the removal of the eschar in thermal burns (flame, scalds, contact), while it is not indicated in the treatment of chemical and electrical burns	14 strongly agree	100% full strong consensus	14 strongly agree	100% full strong consensus
10	Enzymatic debridement is useful in the early removal of the eschar in circumferential burns of the limbs and extremities: in these patients a reduction in the use of escharotomies has been evidenced	14 strongly agree	100% full strong consensus	14 strongly agree	100% full strong consensus
Pain management					
11	Adequate pain management is necessary during all stages of treatment	14 strongly agree	100% full strong consensus	14 strongly agree	100% full strong consensus
Application timing					
12	Enzymatic debridement can be used immediately after the clinical evaluation of burns depth and wound cleansing: removal of blisters and keratin residues is necessary before application	14 strongly agree	100% full strong consensus	14 strongly agree	100% full strong consensus
13	In the early use of enzymatic debridement (within 72 h of the injury), standard wound cleansing and saline flushing immediately before application, without the need for a prolonged pre-soaking, are sufficient to allow for an effective debridement	14 strongly agree	100% full strong consensus	14 strongly agree	100% full strong consensus

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Table 2 (*continued*)

Italian recommendations on enzymatic debridement in burn surgery

Topic	Statement	Distribution of Likert scale responses – round 2	Consensus % – round 2	Distribution of Likert scale responses – round 3	Consensus % – round 3
14	Enzymatic debridement can be applied up to 5 days from the injury in the presence of moist eschars: late application requires adequate wound preparation through mechanical removal of the superficial layers and presoaking with wet dressings	14 strongly agree	100% full strong consensus	14 strongly agree	100% full strong consensus
15	The use of an antiseptic solution is necessary both in early as well as late applications in the presence of contaminated wounds	14 strongly agree	100% full strong consensus	14 strongly agree	100% full strong consensus
16	The use of enzymatic debridement is not recommended in case of clinical evidence of infection	14 strongly agree	100% full strong consensus	14 strongly agree	100% full strong consensus
Application technique					
17	The enzymatic agent must be applied for approximately 4 h	14 strongly agree	100% full strong consensus	14 strongly agree	100% full strong consensus
18	In adult and pediatric patients, the recommended application involves the use of about 2 g for 1% of TBSA or about 180 cm2, or about 3 mm thick layer	14 strongly agree	100% full strong consensus	14 strongly agree	100% full strong consensus
19	The standard application of the drug (direct spreading over the wound and delimitation with a physical barrier of Vaseline), can be optimized in terms of ease of use and surface contact with the burned area by first distributing the drug on a non-stick gauze in order to concentrate it more evenly on the lesion	8 strongly agree; 4 agree; 2 undecided	85% no consensus	8 strongly agree; 6 agree	100% full consensus
20	At the end of the enzymatic debridement phase, it is sufficient to use a blunt tool (tongue depressor) for the removal of tissue residues and of the residual enzyme mixture	14 strongly agree	100% full strong consensus	14 strongly agree	100% full strong consensus
21	To obtain a thorough removal of the tissue residues and of the residual enzyme mixture, the use of wet dressings is indicated, for 2–18 h	14 strongly agree	100% full strong consensus	14 strongly agree	100% full strong consensus
22	Wound bed color and bleeding pattern after moist dressing may help confirm the clinical diagnosis of burn depth	14 strongly agree	100% full strong consensus	14 strongly agree	100% full strong consensus
23	Enzyme debridement drastically reduces blood loss compared to surgical treatment	14 strongly agree	100% full strong consensus	14 strongly agree	100% full strong consensus
Post enzymatic debridement wound care					
24	After enzymatic debridement, in the presence of residual dermal tissue the optimal dressing to facilitate spontaneous healing, alternatively to homologous skin, is the use of dressings that maintain a moist environment	14 strongly agree	100% full strong consensus	14 strongly agree	100% full strong consensus
25	After effective enzymatic debridement, in the absence of vital dermal tissue, definitive coverage with an autograft should be performed, after appropriate preparation of the wound bed	14 strongly agree	100% full strong consensus	14 strongly agree	100% full strong consensus
Burn mass casualty disaster					
26		14 strongly agree		14 strongly agree	

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Table 2 (continued)

Italian recommendations on enzymatic debridement in burn surgery					
Topic	Statement	Distribution of Likert scale responses – round 2	Consensus % – round 2	Distribution of Likert scale responses – round 3	Consensus % – round 3
	Fast and selective enzymatic debridement should be considered as an optimal early treatment option in the case of burn mass casualties incidents		100% full strong consensus		100% full strong consensus
27	Any specialized burn center should stock and have available a minimal quantity of the drug in order to be able to provide an emergency treatment to a predefined number of burn victims and burned surface area (%TBSA)	14 strongly agree	100% full strong consensus	14 strongly agree	100% full strong consensus

Legend. full strong consensus: 100% Likert 5 responses; full consensus: 100% Likert between 4 and 5 responses; consensus: at least 90% of Likert >4 responses; no consensus: less than 90% of Likert >4 responses.

7) Enzymatic debridement can be safely applied in a single application over an anatomical area of not more than 15% of TBSA, but there are data indicating a single application on larger surfaces is safe (11/3) – 100%
8) After the first application, not before 24 h, it is possible to reapply enzymatic debridement in the same patient on different anatomical areas (14) – 100%

Comment: Burn wound assessment is performed by clinical evaluation, with no need for further technical measurements. Although application beyond 15% BSA per session is considered off-label use, sequential-deferred applications, each involving up to 15%TBSA on different areas, are considered on-label use. All centers had experience treating larger areas with sequential-deferred applications of 15% TBSA each. All participating centers had experience treating up to 25% BSA in one session. Additional fluids, invasive monitoring, and pre-treatment risk stratification are needed when treating patients on more than 25% BSA. The same patient can be treated in different areas after at least 24 h from the first application, due to fluid loss and systemic concerns. Reapplication in the same area is not recommended.

9) The main indication of enzymatic debridement is the removal of the eschar in thermal burns (flame, scalds, contact), while it is not indicated in the treatment of chemical and electrical burns (14) – 100%
10) Enzymatic debridement is useful in the early removal of the eschar in circumferential burns of the limbs and extremities: in these patients a reduction in the use of escharotomies has been evidenced (14) – 100%

Comment: Enzymatic debridement may be used for debridement and subcutaneous pressure release, effectively reducing the need for escharotomies. However, it will not release deeper compartment pressures. This factor does not modify current indications for escharotomy and fasciotomy. Early enzymatic debridement reduces the need for such procedures. Still, it does not substitute urgent escharotomies or fasciotomy when these are indicated per the standard of care.

Three centers had experience with treating chemical and/or electrical burns, with no significant and uncertain beneficial effects. Given the scarce experience and insufficient evidence, it cannot be recommended at present.

3.2. *Pain management*

11) Adequate pain management is necessary during all stages of treatment (14) – 100%

Comment: Enzymatic debridement is a painful procedure, requiring analgo-sedation or anesthesia, depending on the depth and extent of the burns.

In particular, adequate pain management is essential: at least 15 min before the application of enzymatic debridement, on-demand during the 4 h of application, and at the removal of the drug. Interdisciplinary pain management and appropriate monitoring together are advisable, according to the type of analog-sedation/anesthesia.

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3.3. Application timing

12) Enzymatic debridement can be used immediately after the clinical evaluation of burns depth and wound cleansing: removal of blisters and keratin residues is necessary before application (14) – 100%
13) In the early use of enzymatic debridement (within 72 h of the injury), standard wound cleansing and saline flushing immediately before application, without the need for a prolonged pre-soaking, are sufficient to allow for an effective debridement (14) – 100%
14) Enzymatic debridement can be applied up to 5 days after the injury in the presence of moist eschars: late application requires adequate wound preparation through mechanical removal of the superficial layers and pre-soaking with wet dressings (14) – 100%
15) The use of an antiseptic solution is necessary both in early as well as late applications in the presence of contaminated wounds (14) – 100%
16) The use of enzymatic debridement is not recommended in case of clinical evidence of infection (14) – 100%

Comment: Application of enzymatic debridement is recommended within 72 h of injury. If the wounds are not contaminated, immediate application may begin after wound cleansing; in these wounds, anti-infective agents are not superior to flushing and soaking compared to saline.

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

In both early and late cases of incomplete eschar removal by enzymatic debridement, additional eschar removal should be performed by the standard of care procedures.

3.4. Application technique

17) The enzymatic agent must be applied for approximately 4 h (14) – 100%
18) In adult and pediatric patients, the recommended application involves the use of about 2 g for 1% of TBSA or about 180 cm^2, or about 3 mm thick layer (14) – 100%
19) The standard application of the drug (direct spreading over the wound and delimitation with a physical barrier of Vaseline), can be optimized in terms of ease of use and surface contact with the burned area by first distributing the drug on a non-stick gauze to concentrate it more evenly on the lesion (8/6) – 100%
20) At the end of the enzymatic debridement phase, it is sufficient to use a blunt tool (tongue depressor) for the removal of tissue residues and of the residual enzyme mixture (14) – 100%
21) To obtain a thorough removal of the tissue residues and of the residual enzyme mixture, the use of wet dressings is indicated, for 2–18 h (14) – 100%

Comment: The application technique is of prime importance in eschar removal. Based on the expert experience, a shorter exposure time may be possible for more superficial burns. All centers have reported the treatment's efficacy and safety for applications longer than 4 h. The enzymes do not spontaneously inactivate after 4 h.

22) Wound bed color and bleeding pattern after moist dressing may help confirm the clinical diagnosis of burn depth (14) – 100%

Comment: The larger the diameter of the circular bleeding patterns in the dermis, the deeper the dermis is affected. Exposed fat after treatment is an indication for skin grafting as soon as possible. Assessing the wound for bleeding patterns should be performed after 2–18 h hours post debridement. Wet dressings may interfere with accurate assessment because bleeding can occur immediately after enzymatic debridement.

23) Enzyme debridement drastically reduces blood loss compared to surgical treatment (14) – 100%

Comment: as demonstrated in several studies in the literature, enzymatic debridement significantly reduces blood loss compared to the standard of care [6–8]. However, there is a risk of increased blood loss in the presence of anticoagulative treatment or disorders. Hemoglobin monitoring should always be performed.

3.5. Post enzymatic debridement wound care

24) After enzymatic debridement, in the presence of residual dermal tissue, the optimal dressing to facilitate spontaneous healing, alternatively to homologous skin, is the use of dressings that maintain a moist environment (14) – 100%
25) After effective enzymatic debridement, in the absence of vital dermal tissue, definitive coverage with an autograft should be performed as soon as possible, after appropriate preparation of the wound bed (14) – 100%

Comment: Post debridement care is essential to optimize outcomes and reduce unstable scarring. After enzymatic debridement, it is necessary to keep a moist environment to avoid desiccation.

The use of dressings capable of maintaining a moist environment effectively reduces the frequency of dressing changes, as well as pain. Also, it provides an optimal wound bed for the re-epithelization phase. When desiccation occurs from insufficient moisture, pseudo-eschar may result from degradation of proteins as well as residues from topical agents. When pseudo-eschar persists for more than 14 days, further debridement with the standard of care should be considered.

Skin grafting may become necessary in some deep-dermal burns with prolonged healing to reduce unstable scarring. It is always required for full-thickness burns (exposed subcutaneous tissue) after enzymatic debridement.

3.6. Burn mass casualty disaster

26) Fast and selective enzymatic debridement should be considered as an optimal early treatment option in the case of burn mass casualties incidents. (14) 100%

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27) Any specialized burn center should stock and have available a minimal quantity of the drug in order to be able to provide an emergency treatment to a predefined number of burn victims and burned surface area (%TBSA). (14) 100%

Comment: The American Burn Association has defined a burn disaster as any catastrophic event where the number of burn victims exceeds the local burn center's capacity to provide optimal care. Capacity includes the availability of burn beds, burn surgeons, burn nurses, operating rooms, blood transfusion, equipment, supplies, and related resources. Enzymatic debridement has helped overcome some of these limitations.

Enzymatic debridement can be applied at the time of admission by a trained surgeon but does not require an operating theater and associated surgical personnel. Per the European experience of a mass burn casualty incident in Bucharest, 39 severely burned patients were treated successfully in the first 48 h at 2 different hospitals. The potential limitations of using fast enzymatic debridement include lack of training and lack of Nexobrid® stock availability. In these emergent situations, the existence of national/international mass disasters burn networks, and the ability to dispatch both Nexobrid® and trained professionals to the disaster site to supervise and direct the operations helps to overcome the above limitations.

4. Discussion

The Italian recommendations for using enzymatic debridement in burn surgery are user-orientated recommendations based on the current available evidence in the literature, as well as on the direct experience of the participant centers and experts establishing the consensus panel.

It is a common feeling that, even if there is a good amount of evidence available, the enzymatic debridement procedure with Nexobrid® is still new and needs specific recommendations to guide physicians to optimize its use in terms of efficacy and patient management.

The consensus panel included experts from Italy with a combined experience of 1068 burn patients treated with enzymatic debridement. At the end of round 3 of the Delphi method, such panel reached consensus on all the 27 statements. The panel achieved a 100% consensus on 26 out of 27 statements and a full, strong consensus (all respondents strongly agreed on the statement) on 24 out of 27 statements (Table 2).

Pediatric use of enzymatic debridement did not reach full consensus (100% consensus): 8 strongly agree; 5 agree; 1 undecided. Treatment of pediatric patients (age <18 years) is considered an off-label use. This, along with lack of experience of some centers, might be why participants are more restrictive in this application. However, the eight centers that have been using it off label have reported consistently good results with excellent safety. Only partial data is currently available on the topic [6,7]. An undergoing clinical trial on pediatric patients [16] will further provide definitive data on this aspect. Until then, the decision to treat pediatric patients remains one based on individual clinical experience.

The statement on optimizing the application technique had a 100% consensus: 8 strongly agree; 6 agree. The current standard application of enzymatic debridement is considered simple and straightforward, leading to reproducible results. All centers had at least some experience with this newly proposed application method, evidencing advantages in terms of precision and consistency, as well as in terms of less spreading of the product, which translates in less wasting and more protection of the surrounding healthy tissues. Both application methods guarantee the full efficacy of the product. Lack of full strong consensus at present depends on the lack of experience of the centers that have not been using it consistently.

The recently updated European consensus recommendations complement, rather than replace, our set of recommendations. Specifically, the updated European consensus [13] focuses on enzymatic debridement application on special regions (such as hands, face and genitals), laser doppler imaging use, post interventional wound management, limitations in scald injuries and feasibility of outpatient use. Conversely, there is no mention to the off label pediatric use, nor is there a statement concerning the use in mass disaster events. However, the authors comment about an intense debate on the topic. Inevitably, as recommendations reflect the expert opinion (level of evidence 5) these are bound to differ among expert panels, reflecting country and author-specific practical clinical issues and experience rather than just literature data.

Areas that would benefit from future research and could change the current recommendations include reducing the local inflammatory response and optimizing perfusion and dermal layer preservation. Future research could also clarify enzymatic debridement's role in mass casualty events and systemic response after debridement, along with medium- and long-term outcomes compared to the standard of care, both in terms of patient scarring and quality of life. A comparative cost analysis may be helpful also.

The substantial number of patients treated (and therefore the cumulative experience of the participating Italian centers), as well as the reduced influence bias (given the modular structure and the anonymous reporting), are certainly strengths of this consensus panel. Individual influence on other respondents, as well as other influencing social factors, were, in fact, minimized thanks to the adoption of the Delphi method.

Stating limitations, on the other hand, we believe individual experience might potentially represent a bias, as it may sometimes lead to departures from current evidence-based practice. Furthermore, this consensus panel did not address complimentary topics related to enzymatic debridement, such as scar outcome prevention and training strategies. Future revisions of the Italian recommendations will thoroughly address these aspects. Finally, we recognize a possible indirect influence of the group (although anonymized) on the individual in round 3, as implied by the structure of the Delphi method.

In conclusion, the statements provided by the Italian consensus panel represent a "ready to use" set of recommendations available for enzymatic debridement in burn surgery, that both draw from and complete the existing scientific

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literature on the topic. These recommendations are specific to the Italian experience and are neither static nor definitive. As such, they will be updated periodically as further quality evidence becomes available.

Conflict of interest

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