

Chapter

Enzymatic Debridement in Burns: Methods, Indications, Contraindications, and Results

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Abstract

Enzymatic debridement for the treatment of moderate- and deep-thickness burns has seen rapid global uptake in recent years. This growing interest stems from the high selectivity of proteolytic enzymes in removing only non-viable tissue, in contrast to conventional surgical methods. Bromelain—extracted from both the fruit and stem of *Ananas comosus*—has proven exceptionally effective in enzymatic debridement. It is a composite of proteolytic enzymes and non-enzymatic constituents exhibiting anti-inflammatory, fibrinolytic, anti-oedematous, antithrombotic, analgesic, and immunomodulatory properties. The advantages of bromelain-based enzymatic debridement, marketed as NexoBrid® (NXB; MediWound Ltd., Yavne, Israel), have led to its incorporation into treatment protocols for deep burns, challenging the historical gold standard of surgical excision followed by precise grafting. National and European consensus guidelines—as well as numerous reports worldwide—have demonstrated the efficacy of enzymatic debridement (ED) in both adults and children. This study has precisely defined the indications, application technique, contraindications, and anatomical-region-specific considerations for enzymatic debridement, tailored to burn aetiology and depth.

Keywords: burns, enzymatic debridement, bromelain, epitelisation, skin grafts

1. Introduction

Burns cause irreversible protein denaturation in the skin. Thermal injury acts on the skin, most conspicuously on collagen, with consequent disruption of its native triple-helical architecture. This conformational collapse is observed within a narrow thermal window—60 to 65°C—after which the denatured collagen matrix becomes highly susceptible to subsequent proteolytic degradation [1].

Tangential excision of the burn eschar within the first 48 hours after injury represents a critical intervention in the management of partial- and full-thickness burns. Early removal of devitalised tissue significantly diminishes the risks of microbial colonisation, invasive infection, and sepsis, while concurrently shortening the interval to re-epithelialisation and, by extension, the overall length of

hospitalisation [2]. The combined approach of tangential excision followed by immediate autologous split-skin grafting was first described by Zora Janzekovic in 1970 and has since become the prevailing therapeutic paradigm for deep dermal and full-thickness burns [3].

Excision of the burn wound can be performed with an electric dermatome, electrocautery, or a conventional scalpel. It is estimated that 30–50% of the excised specimen by these methods often comprises viable, healthy tissue, principally dermis, which is the primary source of epithelial cells essential for spontaneous wound closure [3]. Recognition of the need to conserve this viable dermal matrix has spurred the development of more selective, tissue-sparing modalities. Among surgical selective options, high-speed dermabrasion and hydro-surgical debridement achieve incremental preservation of the dermis, albeit at the cost of prolonged operative times and the requisite use of general anaesthesia [4, 5]. In cases where surgical debridement leaves little or no dermis, immediate coverage of the remaining defect is imperative. The overarching objective to maximise viable tissue preservation has, in turn, catalysed the adoption of non-surgical, selective debridement techniques, which achieve tissue removal without the trauma and sequelae inherent to traditional surgery [6, 7].

2. Debridement

Debridement is the purposeful removal of non-viable tissue, foreign material, contaminated debris, and any bone fragments that may lie within the wound bed. By clearing these barriers, the clinician restores a clean surface and gives the wound the biological conditions it needs to heal. Whatever the underlying cause—thermal, mechanical, vascular, or otherwise—timely debridement remains a cornerstone of modern wound care and an essential prerequisite for reliable closure [8, 9].

Therapeutic wound care unfolds in four inter-locking phases: D – debridement of devitalised tissue; I – control of inflammation and infection; M – optimisation of moisture balance; and E – continual reassessment of the wound micro-environment and progress of epithelialisation. Together, these elements make up the well-established DIME framework, a set of principles embedded in every modern wound-care protocol [10].

The principal aim of debridement is to purge the wound bed of devitalised tissue, thereby creating the physiological conditions required for repair [11]. In addition, debridement is pivotal in disrupting microbial biofilm, removing accumulated biological detritus, and clearing senescent cells that hinder regeneration. Best-practice guidelines therefore advocate performing debridement as early as possible after the inciting trauma—and repeating it serially whenever the wound’s appearance or biology warrants—to optimise healing, especially in burn wounds [12, 13].

Debridement is a pivotal step in contemporary wound management because it conditions the wound bed for re-epithelialisation. Devitalised and necrotic tissues provide a nutrient-rich niche for microbial proliferation, thereby amplifying the risk of infection [14]. At the same time, necrotic tissue forms a physical barrier that blocks epithelial migration and prevents topical therapies from reaching viable tissue where they can exert their intended effects [15]. Its continued presence disrupts essential repair mechanisms—including angiogenesis, granulation-tissue formation, epidermal resurfacing, and orderly extracellular-matrix (ECM) remodelling—and can even obscure the clinician’s ability to assess the true depth

and severity of the lesion, masking incipient or established infection [16]. Taken together, these factors highlight why the prompt and, when necessary, iterative removal of non-viable tissue remains indispensable to optimal wound healing [17]. Over the years, a spectrum of debridement strategies has been described for clearing devitalised tissue: autolytic debridement, biological (larval) debridement, surgical debridement, and enzymatic debridement [18].

2.1 Autolytic debridement

Autolytic debridement is a natural, physiological process in which the body's own phagocytic cells and proteolytic enzymes break down necrotic tissue. Highly selective, it targets only devitalised material and leaves healthy tissue unharmed [19].

Achieving effective autolysis requires a consistently moist wound environment and adequate systemic immune support; moist dressings speed cleansing by softening and loosening areas of necrosis, while irrigation, chemical cleansing, and gentle mechanical debridement further promote detachment of devitalised tissue [20].

The method's efficiency depends on both the amount of necrotic burden and overall wound size, and—being inherently slow—it may take several days to produce visible results. If no meaningful reduction of necrotic tissue is evident after 24–48 hours, an alternative debridement strategy should be considered [20].

2.2 Biological debridement

Biological debridement—more widely recognised as larval therapy—relies on the controlled application of sterile *Lucilia sericata* (green-bottle fly) larvae. The method is particularly advantageous for extensive wounds in which painless removal of necrotic tissue is required [16].

Once placed on the wound bed, the larvae secrete a cocktail of proteolytic enzymes that liquefy non-viable tissue; simultaneously, they ingest the resulting detritus together with resident bacteria, release ammonia that elevates local pH and suppresses microbial growth, and disrupt established biofilms while preventing the formation of new ones—all of which hasten wound resolution [21]. Larvae may be applied directly onto the wound surface or enclosed in a permeable “biobag”; experimental data show that free-range larvae complete debridement in approximately 14 days, twice as fast as biobag-contained larvae (≈ 28 days) and far quicker than autolytic hydrogel dressings (≈ 72 days) [22].

Contraindications include wounds communicating with the intraperitoneal cavity, lesions of pyoderma gangrenosum in immunosuppressed patients, and ulcers adjacent to joints affected by septic arthritis [21–23].

2.3 Surgical debridement

Surgical debridement encompasses all operative manoeuvres undertaken by the surgeon to excise necrotic tissue from a wound, using instruments such as scalpels, scissors, curettes, and, in the case of burns, electrodermatomes or Watson dermatomes [16, 24].

Because these procedures are inherently painful and often highly haemorrhagic, they must be performed in the operating theatre under strict aseptic conditions and with adequate anaesthesia, which may need to be continued into the immediate postoperative period for optimal patient comfort [25].

Anaesthetic techniques range from general anaesthesia with orotracheal intubation to regional blocks—such as infraclavicular, supraclavicular, or axillary plexus—and spinal anaesthesia, selected according to the location of the wound or burn [16].

Effective postoperative pain control is equally critical and typically combines systemic analgesics and anti-inflammatory agents with prolonged regional anaesthesia when warranted—for example, an epidural catheter when burns involve the lower abdomen, buttocks, or lower limbs, or a continuous peripheral plexus catheter (e.g., Contiplex®) for upper-extremity burns [25]. Surgical debridement inevitably causes bleeding of variable magnitude, so meticulous haemostasis is essential to avert major blood loss and haemodynamic destabilisation. All of these procedures must be carried out by personnel specifically trained in burn surgery and critical care [26].

2.4 Enzymatic debridement

Enzymatic debridement—acknowledged since the 1998 International Society for Burns Injuries (ISBI) meeting in Jerusalem as a “Minimally Invasive Modality” (MIM) of burn care—is distinguished by its high degree of selectivity [27]. The technique employs a proteolytic enzyme to dissolve devitalised tissue while sparing viable structures [28]. Over the years, a variety of protease sources were explored. Ultimately, a bromelain-based preparation that met FDA requirements was developed and approved, and it is now being incorporated increasingly into standard burn care protocols [29].

Current burn care protocols recommend enzymatic debridement for deep partial- and full-thickness injuries of moderate to large extent [30]. Nevertheless, it is contra-indicated in patients with known hypersensitivity to any component of the formulation and in wounds that are already in an advanced reparative stage [31]. It is relatively contra-indicated in heavily infected wounds. In addition, collagenase preparations must not be combined with silver-based dressings or with Dakin's solution, as these agents inactivate the enzyme and nullify its therapeutic effect [32].

3. Enzymatic debridement

3.1 Brief history

Over the decades, many forms of enzymatic debridement have been explored. To identify an agent that is both effective and practical, several benchmark criteria were set: it had to act rapidly and efficiently; be highly selective, leaving intact skin unharmed; contain no allergenic, toxic, or irritant components; possess a chemically stable, easy-to-prepare formulation; and, ideally, be affordable.

Investigators therefore tested a wide array of proteolytic sources.

In the 1950s, Tillett experimented with streptococcal enzymes [33, 34], while Connell introduced a protease called debricin along with other fungal- and bacterial-derived enzymes [35].

In 1951, Altemeier, Hummel, and McMillan evaluated clostridial enzymes from *Clostridium histolyticum* and *Bordetella pertussis* and described a mixed papaya-fruit protease preparation [36]. None of these early efforts produced a clinically viable product, but they paved the way for bromelain-based agents.

In 1957, Heinicke and Gortner isolated a novel protease from pineapple—bromelain—opening a new line of investigation [37].

The following year, Burke and Golden proposed a papaya-enzyme formula combined with urea and chlorophyll, and in the 1960s researchers evaluated proteases obtained from filtrates of *Bacillus subtilis* [38].

Bromelain's therapeutic promise was first demonstrated by Levine in 1971 [39] and later confirmed by Levenson in a porcine burn model [40]; Klein and co-workers likewise reported its efficacy as a burn debriding agent [41, 42].

Building on this body of work, the bromelain-based preparation NexoBrid® received regulatory approval in 2012 as a minimally invasive option for enzymatic debridement of deep partial- and full-thickness burns [43].

The first multicentre study detailing its clinical use in burn care was published by Rosenberg and colleagues, marking its transition into routine practice [44].

3.2 Proteolytic enzymes enriched with bromelain: Nexobrid® (NXB; MediWound Ltd., Yavne, Israel)

Bromelain is an extract derived from the pineapple (*Ananas comosus*), present in both the fruit and the stem. It is a composite of proteolytic enzymes and non-enzymatic constituents whose anti-oedematous, anti-inflammatory, antithrombotic, analgesic, and keratolytic properties have been scientifically validated [45–47].

The mechanisms underlying its activity involve the kallikrein–kinin pathway, arachidonic-acid metabolism, and cell-mediated immune responses [48]. Both fruit bromelain (BAA21848) and stem bromelain (CAA08861) are classified as cysteine proteases; they are active across a pH range of 5.5–8.0 and consist of protease subunits with molecular masses of 20–35 kDa [49].

The anti-inflammatory action of bromelain stems from its modulation of prostaglandins and cytokines, which leads to diminished oedema. In burns, it lowers pro-inflammatory mediators such as TNF- α and select interleukins, thereby reducing swelling, erythema, and pain [48]. By promoting fibrin degradation, it exerts a fibrinolytic effect that enhances local circulation and thus accelerates healing. At the microvascular level, bromelain decreases platelet aggregation, reducing thrombus formation and sustaining tissue perfusion [49]. Antimicrobial activity against *Escherichia coli* and *Staphylococcus aureus* has also been demonstrated, suggesting an additional antibacterial effect [49–51]. Beyond wound care, bromelain is recognised for its mucolytic action in sinusitis and bronchitis and for its role in protein digestion as a component of digestive-enzyme supplements [51].

Although bromelain-based preparations are effective for non-surgical debridement, adequate analgesia is essential during their application, and the surrounding intact skin must be carefully protected [52].

Bromelain selectively digests denatured collagen and necrotic protein matrices without harming nerves, blood vessels, or hair follicles. The bromelain formulation approved in 2012—NexoBrid® (NXB; MediWound Ltd., Yavne, Israel)—contains 0.09 g of bromelain per gram of product. It has secured FDA approval for burn management and is now used widely across Europe and elsewhere [43].

3.3 Indications and method of use of the bromelain-enriched proteolytic enzyme mixture NexoBrid® (NXB; MediWound Ltd., Yavne, Israel)

Peri-operative bromelain therapy has demonstrated efficacy across multiple medical disciplines—including orthopaedics, obstetrics, otorhinolaryngology, dentistry, ophthalmology, sports medicine—and, topically, for the debridement of wounds and burns [43].

Consequently, bromelain constitutes a validated enzymatic alternative to surgical debridement [9, 10]. Enzymatic debridement with NexoBrid® (NXB), a bromelain-enriched proteolytic enzyme mixture, is indicated for patients with deep-partial-thickness (grade II B) and full-thickness (grade III) burns. The original label limited use to adults (>18 years) and to grade II B injuries, but since 2025 NXB has been approved for children of any age, and its indication for grade III burns was endorsed following the 2020 update of the 2017 European consensus [30, 53].

There is no specific age limit that contraindicates the use of enzymatic debridement. This method can be safely employed in the treatment of deep partial-thickness and full-thickness burns caused by scalds, steam, or flames, provided the injury does not extend through the full depth of the skin to the underlying muscle or beyond.

In high-voltage electrical burns, where there is a defined entry and exit point typically represented by deep necrotic lesions, enzymatic debridement may be used in an initial step. However, due to the depth and complexity of these burns—as is also the case with flame burn—enzymatic debridement may need to be followed by surgical debridement and definitive coverage using split-thickness skin grafting.

In chemical burns, whether caused by acids or alkalis, enzymatic debridement is generally not recommended. Despite immediate irrigation with copious amounts of water, chemical agents can remain active for extended periods.

The product used for the enzymatic debridement is supplied in two vials: one containing lyophilised powder and the other a gel vehicle. Reconstitution is achieved by gradually adding the powder to the gel and stirring with a spatula for several minutes until a smooth, lump-free suspension forms; the preparation must be applied to the burn surface within 15 minutes of mixing (**Figure 1**).

Each standard kit provides 2 g of bromelain-enriched concentrate (0.09 g active enzyme per gram of product after reconstitution) suspended in 22 g of gel. A mixture of 2 g powder with 20 g gel treats approximately 1% of total body surface area—about 180 cm²—while larger vials (5 g powder plus 50 g gel) suffice for roughly 450 cm². These calculations assume an application layer 1.5–3 mm thick [7, 43, 54].

The first European consensus on bromelain use in deep-partial and full-thickness burns was adopted in 2017, and NXB has since been incorporated into the standard of care for selected burn types [30]. The consensus recommends application from the first hour up to 72 hours post-injury [30].

Moti Harats et al. later reported favourable outcomes when bromelain was applied between 72 hours and 5 days after the burn [55]. Bromelain has also proved effective in chemical and electrical burns, including paediatric cases; however, its efficacy appears to wane beyond the fifth post-injury day, probably because eschar permeability progressively declines [56].

Initial prescribing guidance limited bromelain application to no more than 15% of total body surface area (TBSA) in a single session, with the option to repeat treatment after 24–48 hours—provided the product is not reapplied to the same anatomical site. The 2017 European consensus on bromelain-based enzymatic debridement (NexoBrid®) was revisited in 2020; the updated statement permits use on any region of the body, including the face, perineum, and genitalia [30, 53].

The most recent (2025) paediatric update allows NexoBrid® at all ages, but restricts treated surface area to ≤15% TBSA in children aged 4–18 years and to ≤10% TBSA in infants and toddlers aged 0–3 years [57].



Figure 1.
 A. Gel-based vehicle (excipient), B. Combine the gel base with the bromelain powder, C. Thoroughly homogenise the two components (gel/powder), D. Apply the resulting preparation evenly across the burn wound.

3.3.1 Method of application

Although the introduction of NexoBrid[®] was initially met with scepticism, its clinical value has since been demonstrated in many countries, where it now yields consistently favourable outcomes.

Topical application of the bromelain preparation can reduce—or even eliminate—the need for split-thickness skin grafting by conserving as much viable dermis as possible. The procedure is performed at the patient's bedside, is quick and efficient, and results in substantially less blood loss than conventional surgical debridement [43, 46].

The technical sequence for applying and subsequently removing the debriding agent has been standardised and recommendations for use are made by the manufacturer [58]:

1. *Assessment of burn area and depth.* After obtaining microbiological screening swabs, the burns are irrigated and cleansed with saline. Depth is then determined by clinical examination and, when necessary, echo-Doppler imaging.

Clinical burn assessment and depth grading rely on three bedside cues: skin colour, the presence of blisters, and the nature of their fluid. Clear, straw-coloured serum points to a superficial-partial injury (grade II-A), whereas a sero-sanguinous exudate suggests a deeper partial-thickness burn (II-B degree). Areas of stiff, leathery eschar—brown-black or pearly white—denote a full-thickness injury (grade III).

From a clinical standpoint, depth is refined beyond visual cues by testing capillary refill and revascularisation time and by mapping sensation: a sharp, stinging pain is typical of superficial burns, while dull or absent sensation points to deeper injury. On hair-bearing skin, the “hair-pull test” is informative: in full-thickness burns the follicular bulb is destroyed, so hairs detach with a light wipe of gauze or minimal traction with forceps.

Once burn depth and total surface area have been established, the team decides whether enzymatic debridement is appropriate, taking into account associated injuries, comorbidities, and the patient’s current haematological profile.

Echo-Doppler imaging can then corroborate bedside findings, delineating well-perfused zones versus regions of diminished or absent flow, in keeping with the graduated loss of vascularity seen as burns deepen (**Figure 2**).

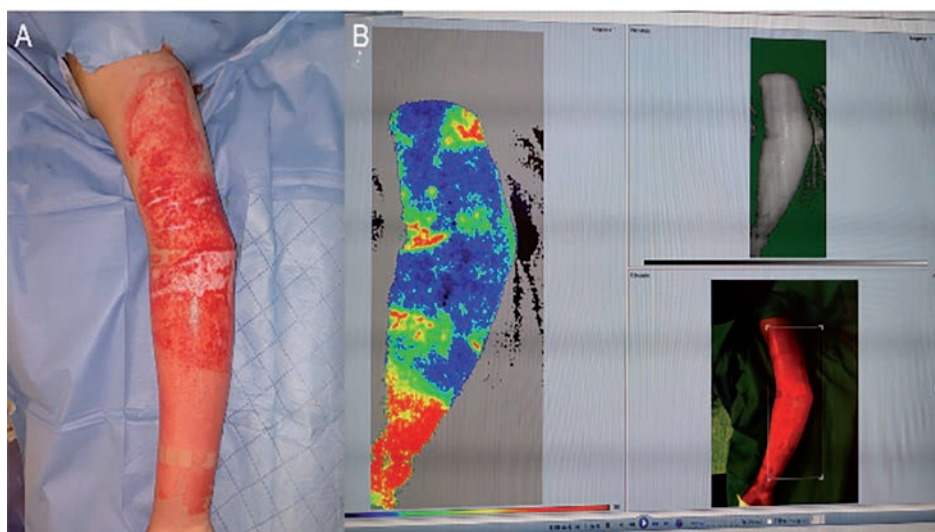


Figure 2.
Assessment of burn depth using Doppler ultrasound.

For Nexobrid® to work optimally, the target burned surfaces—deep-partial-thickness (grade IIB) and even full-thickness (grade III) injuries—must first be adequately hydrated. No silver-sulfadiazine creams or povidone-iodine (Betadine®) dressings should be applied beforehand, as these agents can inactivate the enzyme complex.

Immediately before Nexobrid® application, the wound is thoroughly irrigated to remove blisters, soot, foreign particles, and any loose devitalised tissue. Lavage is performed with sterile isotonic 0.9% sodium-chloride solution and Prontosan® (B. Braun, Germany). Use of Prontosan—both before and after the enzymatic phase—is strongly recommended, because its polyhexanide-based surfactant both cleanses the wound bed and minimises microbial burden without impairing bromelain activity (**Figure 3**).

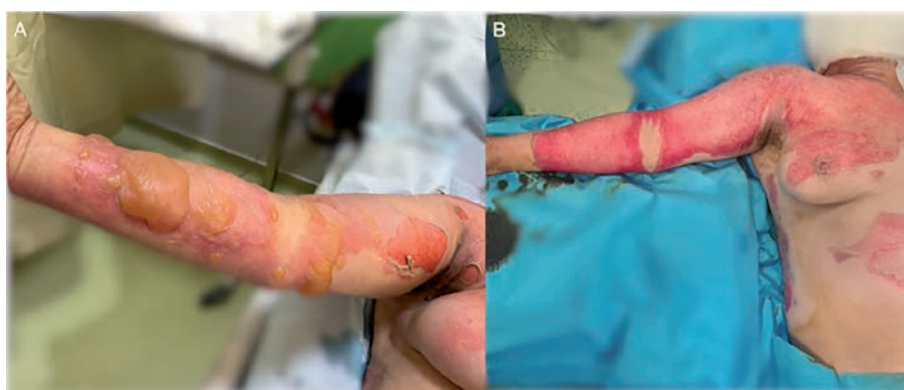


Figure 3.
 Burn of the upper limb. (A) Before wound irrigation and (B) after irrigation with removal of blisters and devitalised tissue.

Hydrogel dressings may also be applied to hydrate and condition the burned integument before enzymatic debridement; a minimum pre-hydration interval of 2 hours is recommended. Adequate analgesia is mandatory both during and after NexoBrid® application. Clinical studies suggest maintaining pain control for at least 48 hours post-debridement, with extension as required according to burn depth, extent, and each patient's individual pain threshold.

With respect to anaesthetic choice for enzymatic debridement in burn patients, loco-regional techniques are preferred whenever the anatomical site permits, thereby avoiding general anaesthesia with endotracheal intubation. When NexoBrid® is applied to the upper limb, an axillary, infraclavicular, supraclavicular, or interscalene block is selected according to the exact level of injury. For lower-extremity burns, femoral or sciatic nerve blocks are favoured. Any of these regional approaches may be supplemented with intravenous sedation. Burns of the head, neck, thorax, or upper abdomen, by contrast, necessitate general anaesthesia with endotracheal intubation. To maintain adequate analgesia for at least 48 hours after NexoBrid® application, a continuous-infusion catheter delivering a long-acting local anaesthetic is recommended.

2. *Isolation of the burn from adjacent healthy skin.* Surrounding intact skin is protected with gauze dressings thoroughly impregnated with petroleum jelly—or a comparable greasy ointment—and firmly anchored in place. Any prior escharotomy incisions are shielded in the same fashion. When NexoBrid® is applied to facial burns, the eyes must be covered with a double-layer compress (**Figure 4**).
3. *Preparation and application of the product.* Reconstitute NexoBrid® by gradually mixing the lyophilised powder into the gel, then spread the resulting suspension with a spatula in a uniform layer 1.5–3 mm thick, exactly as specified by the manufacturer (**Figure 5**).
4. *Cover and seal the treated area with a non-absorbent film*, then add a second layer: Either sterile gauze compresses or an additional hydrofilm sheet: To secure the dressing (**Figure 6**)
5. *The bromelain-based formulation is left in situ for 4 hours*; after this dwell time, the agent is rinsed away with sterile saline and Prontosan®, using gauze pads,

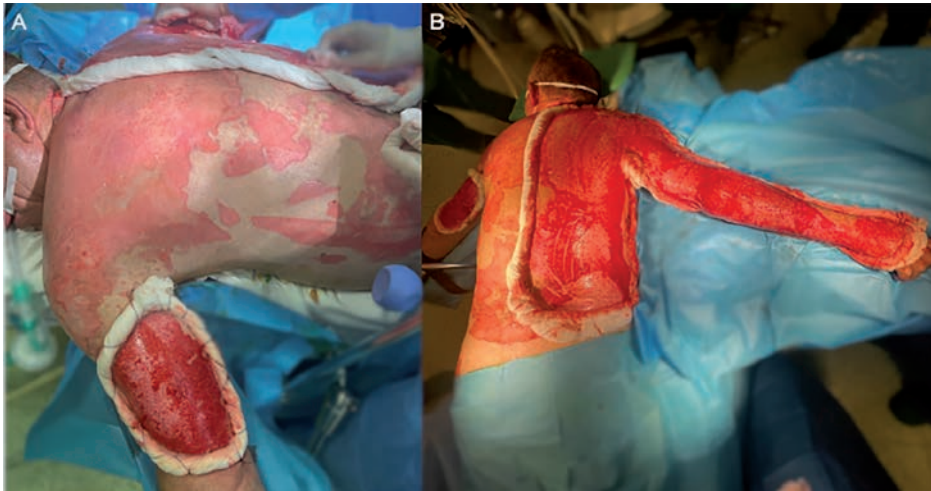


Figure 4.
Barrier isolation of the target debridement field from adjacent uninvolved integument.

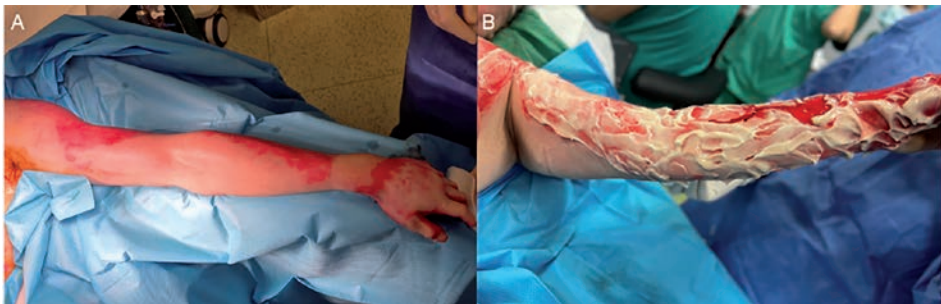


Figure 5.
(A) Circumferential deep-partial (II-B degree) and full-thickness (III-rd degree) burn of the upper limb; (B) topical enzymatic debridement with Nexobrid®.

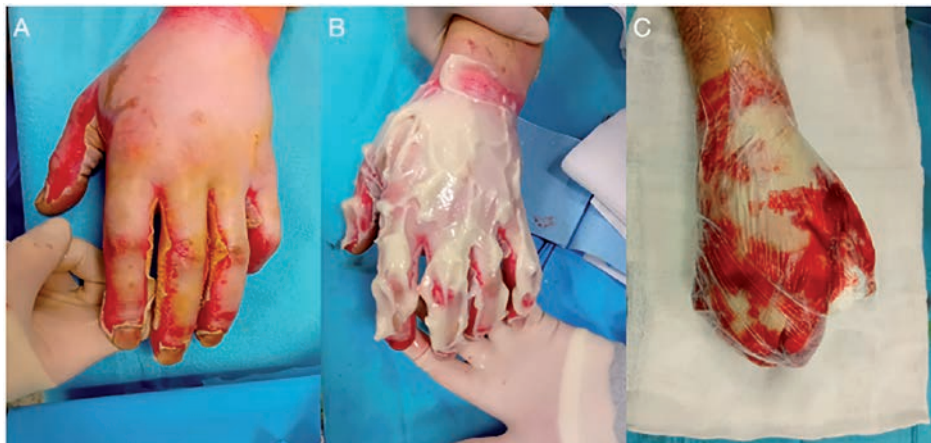


Figure 6.
(A) Deep burn on the dorsal aspect of the hand; (B) application of Nexobrid® to the dorsal hand burn; (C) treated area sealed with an occlusive dressing for 4 hours.

spatulas, or mildly abrasive sponges to remove both the residual preparation and the loosened eschar. A hydrosurgery system can also be employed to complete the debridement (**Figure 7**).

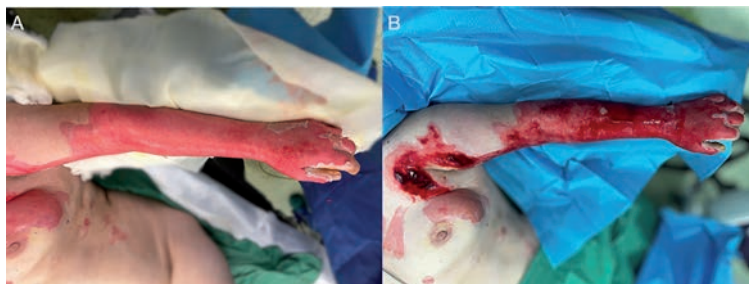


Figure 7.
 (A) Circumferential burn of the left forearm and (B) appearance after removal of the debriding agent and irrigation with Prontosan[®] (B. Braun, Melsungen, Germany).

6. Prontosan[®] (B. Braun, Melsungen, Germany) dressings.

7. The debrided area must be covered to prevent desiccation, the formation of pseudo-eschar, and infection by applying a permanent or temporary skin substitute, such as Suprathel[®], Biobrane[®], or Mepitel[®], or allografts in cases of burn wounds showing vital dermis and good healing potential or autografts in deep burns requiring surgical treatment (**Figures 8 and 9**) [30, 51, 56–58].



Figure 8.
 Enzymatic debridement sequence: (A) burn wound after initial lavage; (B) right leg immediately post-debridement; (C) application of the enzymatic agent to the left leg; (D) wound appearance 3 days post-debridement; (E) wound appearance 6 days post-debridement; (F) spontaneous healing outcome following enzymatic debridement.



Figure 9.

Evolution of a grade II-B burn on the dorsal right hand following enzymatic debridement: (A) immediate post-debridement appearance; (B) wound aspect at 4 days post-debridement; (C) wound aspect at 10 days post-debridement; (D) wound aspect at 14 days post-debridement; (E) complete healing achieved by directed epithelialisation.

8. *Assessment 24: 48 hours after debridement*, the observed effects, and the ensuing therapeutic plan for the residual wound: Either spontaneous healing through directed epithelialisation, subsequently supported by topical agents or skin coverage by one of several grafting methods conventional split-thickness skin grafting harvested with an electric dermatome or meek micrografting (**Figures 10 and 11**)

A schematic outline of the steps for employing NXB is shown in **Figure 12**.



Figure 10.

(A) Post-burn regions enzymatically debrided and covered with Meek micrografts at the shoulder and upper arm; (B) healing in progress; (C, D) spontaneous epithelialisation of the forearm and complete integration with healed burn areas at the shoulder and proximal third of the arm.

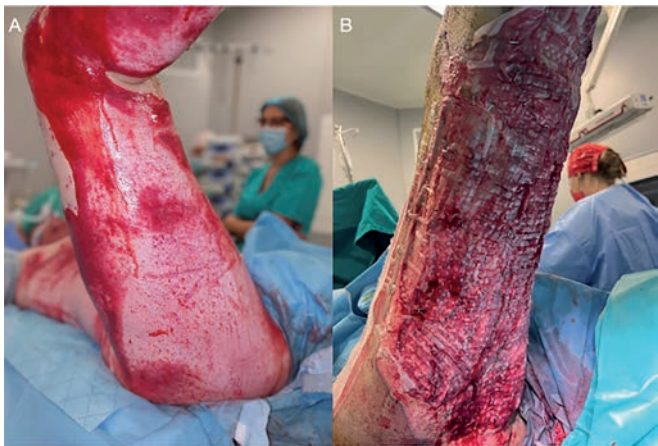


Figure 11.
(A) Post-enzymatic debridement appearance of a circumferential burn on the right lower limb and (B) coverage of the initially enzymatically debrided areas with Meek micrografts.



Figure 12.
The steps for employing NXB.

4. Use of enzymatic debridement in special anatomical regions: The face and the hand

4.1 Use of NexoBrid® on the face

Although initially regarded with caution, enzymatic debridement has progressively gained acceptance for use on the face, as growing clinical evidence has confirmed its safety and efficacy. Facial burns affect up to 5.3% of all burn patients and even small lesions can inflict major aesthetic and psychosocial harm [9]. Beyond visible scarring, functional sequelae involving the eyelids, nasal alae, lips, and oral commissures can profoundly compromise daily activities. Because facial skin is thin and highly vascularised, timely debridement that preserves the maximum amount of viable tissue accelerates healing and improves the final cosmetic outcome [9].

The 2020 update of the European consensus on bromelain-based enzymatic debridement specifically addressed deep facial burns, emphasising that safe application of NexoBrid® hinges on meticulous protection of natural orifices—particularly the eyes—through careful shielding and moisture control [30].

Reports in the literature outline several techniques for protecting the eyes during facial application of NexoBrid®. Schulz et al. describe covering the eyes with Bepanthen® ointment (Bayer, Germany), sealing them beneath an occlusive plaster, and then surrounding the area with a ring of Adapt® paste (Hollister, Germany) [9]. Ferancikova et al. achieved similar protection of the orbital region—and of the external auditory canal—using a generous layer of sterile [59], medical-grade petroleum jelly (**Figures 13 and 14**).

Due to the need for complex and reliable ocular protection methods, enzymatic debridement is difficult to apply in cases of eyelid burns, where there is a significant risk of ocular damage. Given the extreme thinness of the eyelid skin, intermediate and deep burns which are the typical indications for enzymatic debridement often lead to exposure of the tarsal plate. In such situations, the use of enzymatic agents may be of limited benefit, as the risk to the eye outweighs the expected therapeutic advantage.

A similar issue arises with the use of NexoBrid® in burns affecting the auricular pavilion. However, enzymatic debridement may be more feasible in this location, as the external auditory canal can be easily and safely protected during the procedure.



Figure 13.

(A) Full-thickness burn involving the face and anterior thorax; (B) isolation of zones prepared for enzymatic debridement; (C) application of the enzymatic debridement agent; (D) appearance of debrided areas immediately after NXB removal; (E) removal of protective eye and periocular dressings, confirming intact adjacent skin; (F) debrided facial region 24 hours after enzymatic debridement.



Figure 14.
 (A) Full-thickness (grade III) facial burn; (B) enzymatically debrided burn at 5 days post-debridement, showing active epithelialisation; (C) outcome at 3 weeks post-debridement – areas fully or partially re-epithelialised, with cicatricial ectropion of the left eye.

4.2 Use of enzymatic debridement on the hands

Burns of the hand can result in profound aesthetic and functional deficits. Treating such injuries is particularly challenging: the hand is a highly complex organ whose fine motor capabilities and appearance—alongside the face—form our primary interface with the outside world, underpinning interpersonal interaction and carrying powerful symbolic meaning [60–65]. For this reason, every hand-burn case must be managed with the overarching objectives of preserving anatomical integrity and function while minimising scarring, thereby limiting any long-term impact on the patient's social, professional, and personal life [63].

Because the dorsal skin of the hand is exceptionally thin, medium- and deep-depth burns often leave extensor tendons exposed. In these circumstances, simple coverage with a split-thickness skin graft is not feasible, and alternative reconstructive strategies must be pursued [60–65]. Frequently, the lack of healthy adjacent tissue necessitates distant flap techniques, which entail extensive surgery, produce additional scars, and carry the added morbidity of donor sites [65].

Accordingly, the optimal strategy is a highly selective debridement technique that preserves every viable island of intact skin (**Figure 15**).



Figure 15.
 (A, B) Deep burn from prolonged contact with wax and (C, D) appearance after enzymatic debridement.

NexoBrid® is now regarded as the first-line treatment for hand burns, because it removes only necrotic tissue while sparing every viable skin island—sources of epithelial cells that drive directed re-epithelialisation and later wound closure. Although surgical excision followed by grafting is still the classic standard for medium- and full-thickness burns elsewhere, for deep-partial and full-thickness burns of the hand the preferred standard is selective enzymatic debridement, with grafting reserved for cases in which residual dermal cover proves insufficient [60–65].

Selective enzymatic debridement followed by directed epithelialisation permits continuous mobilisation of the hands throughout the healing phase, so that functional sequelae are minimal or altogether absent [64].

By contrast, split-thickness skin grafts on the hand require a postoperative period of immobilisation to secure graft take, with an attendant risk of stiffness and contracture [61–64]. In addition, spontaneous healing after enzymatic debridement consistently delivers superior aesthetic outcomes: the resulting scars are thinner, more pliable, and better colour-matched than those produced by conventional grafting (**Figure 16**) [61–65].



Figure 16.
Burn of dorsal faces of both hands: (A) Day 2 post-debridement, (B, C) complete epithelialisation.

The effectiveness of enzymatic debridement on the hands must also be evaluated in relation to the numerous flexion creases present at the level of the fingers, both dorsally and palmarly, as well as at the wrist.

These anatomical areas are particularly challenging to cover using split-thickness skin grafts, as graft contraction frequently occurs, leading to significant functional impairment. In such cases, outcomes are often inferior to those achieved through directed epithelialisation. This principle applies to all areas with flexion folds—including the elbow, knee, ankle, neck, and others.

In paediatric patients, enzymatic debridement is notably more effective when applied to the hands and other flexural regions compared to adults. This is due to the significant advantage of avoiding skin grafting in children, as skin grafts do not grow proportionally with the child. As a result, repeated grafting procedures may be necessary throughout childhood until growth is complete.

4.3 Use of enzymatic debridement in the prevention and management of compartment syndrome arising from circumferential limb burns

Compartment syndrome occurs when intra-compartmental pressure exceeds the perfusion pressure of the blood vessels within that compartment, ultimately resulting

in tissue ischaemia and necrosis. It is a surgical emergency. Although there are multiple etiologies, the most common triggers of compartment syndrome are traumatic injuries and burns [66].

In burn injuries, compartment syndrome more frequently develops in the limbs when the burns are circumferential and of deep thickness. In these cases, the pathogenesis may involve interstitial fluid accumulation that raises intra-compartmental pressure or the inelastic burned skin acting like a tourniquet, likewise increasing compartmental pressure [66].

To prevent irreversible muscle contracture, nerve damage, and ultimately tissue necrosis with potential limb loss, emergent fasciotomies are indicated [66, 67].

Fasciotomies constitute a surgical intervention associated with inherent risks, including significant blood loss. With the advent of enzymatic debridement, in cases of early circular limb burns—within the first hours post-injury—the onset or even treatment of compartment syndrome can be managed using NexoBrid®. The primary concern, however, is the four-hour action window of NXB's proteolytic enzymes, during which there is effectively no real-time control over the evolution of compartment pressures [67, 68].

Nevertheless, studies have demonstrated that enzymatic debridement is effective in preventing, managing, and treating compartment syndrome in deep circumferential burns (**Figure 17**).



Figure 17.
Deep circumferential burn of the forearm: (A) immediate post-burn aspect and (B) immediate post-debridement aspect.

European consensus guidelines indicate that early eschar removal with NexoBrid® can reliably prevent the need for surgical escharotomy of the upper extremities [30, 53]. By excising the eschar, one averts the development of elevated pressures within the subcutaneous and subfascial compartments; performing this intervention promptly also attenuates local inflammation and oedema, both of which drive burn-related compartment syndrome [30].

Enzymatic debridement with a bromelain-based preparation (NXB) is a safe, feasible, and effective method for performing an “enzymatic escharotomy” to counteract compartment-pressure build-up in deep extremity burns and thereby reduce the need for surgical escharotomy [66, 67].

This enzymatic escharotomy must, of course, be performed early. In cases of very deep or extensive burns (exceeding 50% TBSA), it may still be necessary to combine enzymatic debridement with a conventional surgical escharotomy [67].

The literature reports shorter hospital stays and fewer surgical interventions in patients who underwent enzymatic debridement to prevent burn-induced compartment syndrome. As with other burn wounds, enzymatic debridement is then followed either by spontaneous re-epithelialisation or by coverage of denuded areas using split-thickness skin grafts harvested with an electric dermatome or by Meek micrografting [30, 66, 67].

5. Discussion

The high global incidence of burn injuries—and the resulting annual mortality exceeding 180,000—renders these traumas a critical public health concern [69, 70]. This heightened attention has driven the search for novel therapies, leading to the widespread adoption of bromelain-based enzymatic debridement (NexoBrid®) as a primary modality in burn care worldwide [30].

Bromelain, derived from pineapple, was first described in 1891 by Venezuelan scientist Vicente Marcano, with its extraction process developed 3 years later [71]. It is a mixture of proteolytic enzymes—primarily comosain and ananain—that catalyse the breakdown of proteins into amino acids. Beyond its role in wound debridement, bromelain is employed in the treatment of various ENT, respiratory, cardiovascular, and rheumatologic conditions [72].

Bromelain is extracted as a glycosylated monomeric protein, found in both the stem and the fruit of pineapple. The two isoforms—stem bromelain and fruit bromelain—are highly homologous, differing primarily in their isoelectric points: stem bromelain is alkaline ($\text{pH} > 9.5$), while fruit bromelain is acidic ($\text{pH} \approx 4.6$). Their molecular weights, optimal pH, and temperature ranges are very similar. The key differences lie in their amino-acid sequences, which confer subtle variations in substrate affinity and enzymatic kinetics [71].

In addition to its anti-inflammatory properties, bromelain’s antibacterial activity has been attributed to its constituent phytochemicals—tannins, saponins, and flavonoids. Ali et al. have demonstrated that bromelain inhibits the growth of *Escherichia coli* and *Proteus* species [73, 74].

Potential adverse effects of this enzymatic compound have also been investigated. Animal studies (in rabbits and mice) have shown that bromelain exhibits very low toxicity, even at high doses, without detectable impairment of cardiac, renal, or gastrointestinal function, nor significant alterations in haematologic parameters [51].

The use of the bromelain-based compound—NexoBrid®—for burn debridement has expanded dramatically worldwide in recent years. Consequently, multiple studies

have evaluated NXB in burn therapy, and both national and European consensus guidelines have been developed to standardise its application (**Table 1**).

Countries such as Spain, Italy, Poland and Romania, have issued and published national consensus statements on NXB use, all of which align with and adhere to the two European consensus documents from 2018 and 2020 (**Table 2**) [30, 53, 75–80].

In Spain, in 2017, Martinez Mendez published a national consensus on NXB use that involved seven burn units across the country [75].

In 2023, Serracanta et al. updated this earlier consensus by including not only plastic surgeons but also intensivists and anesthesiologists—16 experts in total. Of the nine certified burn centres in Spain, eight participated in the 2023 consensus.

Region.	Author/ year	Panellists	Patients	Evaluated topics	Key contributions
Europe	Hirche C et al. [53]	Austria, Belgium, Germany, Italy, Slovak Republic, Spain, Switzerland, the United Kingdom	500	• Indications • Pain management • Anaesthesia- Timing and technique of application • Post-intervention wound care • Skin grafting after ED • Blood loss • Cost-effectiveness • Training & learning curve • Research needs	• ED indicated for hands, feet, face • Not for chemical burns • Suitable for thermal, scald, flame, contact burns • Safe up to 15% TBSA/ session (up to 30% off-label) • Regional anaesthesia recommended for limbs • Late application = >72 h • Eschar removal within 7 days • Reapplication not recommended after failure
Europe	Hirche C et al. [30]	Austria, Belgium, Germany, Italy, Norway, Poland, Romania, Spain, Switzerland, the United Kingdom	1232	• Indications • Pain & anaesthesia • Large surface use • Timing • Post-debridement wound care • Grafting • Scar & revision • Cost-efficiency • Patient perspective • Logistics • Training	• Application timing: immediate (<12 h), early (12–72 h), delayed (>72 h) • No use in chemical burns • Suitable for full- thickness burns • Early use may prevent compartment syndrome • Highly recommended for facial, hand, foot, perineal, genital burns • Up to 15% TBSA/session sequentially • Local anaesthesia useful in minor burns

ED – enzymatic debridement, TBSA – total burn surface area, h – hour.

Table 1.
European consensus guidelines on the use of NexoBrid® in burn care.

Country	Author/year	Panellists	Patients	Evaluated topics	Key contributions
Spain	Martinez-Mendez et al. [75]	Burn units of: Madrid, Barcelona, Zaragoza, Valencia, A Coruña, Murcia, Valladolid	350	Indications, recommendations	• ED indicated for deep dermal burns • Limited experience with electrical burns • Use up to 15% TBSA • Limited experience on the face • Reapplication protocol not defined • Avoids escharotomy in circular burns
Spain	Serracanta J. et al. [76]	Burn units of: Barcelona, Madrid, Zaragoza, Valencia, A Coruña, Bizkaia, Seville, Valladolid	>1000 cases	Indications, critical patients, pain, application, post-ED care	• ED indicated for deep dermal burns • Used by experienced professionals only • Off-label for paediatric patients • Effective on face, hands, neck, neckline • Safe on up to 15% TBSA • Not for chemical/high-voltage burns • Avoids surgical escharotomy in circumferential burns
Spain	Gonzalez et al. [77]	Burn units of: Barcelona, Madrid, Zaragoza, Valencia, A Coruña, Vizcaya, Seville, Valladolid, Alicante	Approx. 1500 cases	Admission, pain control, application/removal, post-ED	• Trained nurses manage ED patients • Plastic surgeon provides education • Better scar quality and fewer sequelae • Optimising wound bed for healing or grafting

Country	Author/year	Panellists	Patients	Evaluated topics	Key contributions
Italy	Ranno R et al. [78]	Burn centres of: Catania, Bari, Brindisi, Cesena, Genova, Milano, Napoli, Palermo, Parma, Pisa, Roma, Sassari, Torino, Verona	1068	Indications, pain, timing, technique, post-ED, mass casualty	• Not for epidermal/superficial burns • Requires trained staff • Useful on face, hands, neck, décolleté • Reduces bleeding on the chest/abdomen • Max 15% TBSA per application • Reapplication possible >24 h • Not for chemical/electrical burns • Useful in eschar removal from circumferential burns
Poland	Korzeniowski et al. [79]	Burn centres of: Cracow, Gryfice, Siemianowice Śląskie, Poznań, Łęczna	>500 cases	Indications, pain, anaesthesia, large surfaces, timing, prep, post-ED, outcomes, cost, training	• Recommended for deep dermal/full-thickness burns • Safe with an experienced team • Not for chemical/electrical burns • Effective for hands, face, groin • Max 15% TBSA/session • Indicated for circumferential burns • -Pain management needed • Delayed use (>72 h) still possible

Country	Author/year	Panellists	Patients	Evaluated topics	Key contributions
Romania	Marinescu S. et al. [80]	7 healthcare units	342	Indications, surface, prep, timing, pain, anaesthesia, post-ED, grafting, follow-up, patient view, logistics, training	• Use within 24 h • Face, hands, feet burns (max 15% TBSA) • Indicated for thermal burns (not chemical/electrical) • Reduces need for escharotomy in circumferential burns • Facial/genital/perineal burns highly indicated • Limb burns managed with loco-regional anaesthesia

ED- enzymatic debridement, prep – preparation, TBSA – total burn surface area, h-hour.

Table 2.
National consensus guidelines on the use of NexaBrid® in burn care.

As with other guidelines, this document was aligned with the Summary of Product Characteristics (SPC) [76].

In Italy, Ranno R et al. reported a consensus on NXB use in 2021, led by two principal investigators and encompassing 20 experts from 14 burn centres nationwide [78].

In Poland, a 2022 consensus was developed with input from five burn centres. In Romania, Marinescu et al. published the 2020 consensus, which included experts from four health units [79, 80].

Both national and European consensus guidelines were developed according to the Oxford Level of Evidence Classification System. The inaugural European consensus convened panellists from Austria, Belgium, Germany, Italy, the Slovak Republic, Spain, Switzerland, and the United Kingdom. This consensus examined multiple facets of enzymatic debridement in burn care, including: the indications for enzymatic debridement; pain management and choice of anaesthetic technique; the optimal timing of application; precise application methodology; post-debridement wound care; the timing of skin grafting; dosing and haemorrhage control; and, critically, the economic impact, requisite training protocols, and associated learning curve [53]. Since the 2017 consensus, NexoBrid® has been recognised as both effective and indicated for burns of the hands, feet, and face [53]. The second European consensus on enzymatic debridement included expert panels from Austria, Belgium, Germany, Italy, Norway, Poland, Romania, Spain, Switzerland, and the United Kingdom. While many topics mirrored those of the inaugural consensus, this update also incorporated: rigorous evaluation of clinical outcomes following enzymatic debridement; standardised protocols for scar management and revision; formal cost-effectiveness analyses; the integration of patient-reported perspectives; and detailed considerations of NexoBrid® logistics and supply-chain requirements [30]. In the second European consensus, precise definitions were established for the temporal categories “very early,” “early,” and “late,” corresponding to post-burn intervals of <12 hours, 12–72 hours, and > 72 hours, respectively [30]. A pivotal advancement was the formal introduction of the “enzymatic escharotomy” concept, defined as the application of enzymatic debridement within the first 12 hours after injury in cases of circumferential burns; this approach can both prevent the development of compartment syndrome and treat incipient syndrome without resorting to surgical decompression incisions [66].

Application of enzymatic debridement for burns covering less than 2% TBSA is generally not recommended, primarily for cost-efficiency reasons. Regarding anaesthetic technique, small treatment areas may be managed under local anaesthesia; limb burns typically employ regional blocks; and spinal anaesthesia is also an option. As a broad recommendation, procedural sedation and analgesia are preferred over general anaesthesia with endotracheal intubation [81, 82].

The indications for NexoBrid® encompass both intermediate- and full-thickness burns. Reapplication to the same area—when initial debridement fails to achieve the desired effect—is generally not recommended and is permissible only in exceptional cases. The consensus emphasises enzymatic debridement for burns of the hands, feet, perineal, and genital regions; for facial burns, ED is both indicated and efficacious, provided that meticulous protection of the eyes and natural orifices is maintained. Preparation protocols and timing remain identical to those defined in the first European consensus, including the limit of 15% TBSA per application.

Prior to NXB application, any pre-existing or burn-induced coagulopathies must be corrected to ensure patient safety. If no spontaneous epithelialisation is evident 21 days post-debridement, surgical skin grafting should be considered [83]. Recent updates have extended NXB indications to paediatric patients: children aged

4–18 years may be treated on up to 15% TBSA in a single session, while in those aged 0–3 years the maximum is 10% TBSA.

In light of these advances, Romania is preparing to revise its national consensus on enzymatic debridement, drawing on the collective experience of six medical centres using NXB.

6. Conclusions

Enzymatic debridement offers a valuable alternative to surgical excision, providing advantages in terms of speed, tissue selectivity, and overall safety. Bromelain-based debridement, particularly with NexoBrid[®], has shown superior capacity to preserve viable tissue, minimise blood loss typically associated with surgical excision, and reduce the need for skin graft donor sites. These benefits are linked to lower morbidity, improved functional outcomes, and earlier patient mobilisation. Additionally, scars resulting from enzymatic debridement tend to have a more favourable aesthetic appearance compared to those following surgical treatment.

However, while current findings are promising, further large-scale studies are required to conclusively establish the safety, efficacy, and appropriate clinical indications of bromelain-based therapy. At present, surgical debridement followed by autografting remains the gold standard in burn management. Nonetheless, combining enzymatic and surgical approaches may be beneficial in treating extensive burns of varying depth.

The effectiveness of enzymatic debridement in chemical and electrical burns, as well as its safety in cases involving larger TBSA involvement, remains to be fully clarified. Notably, our observations suggest that early application of NexoBrid[®] in deep, circumferential limb burns may help prevent the onset of compartment syndrome—though this hypothesis warrants further investigation.

Conflict of interest

The authors declare no conflict of interest.

Acronyms and abbreviations

NXB	Nexobrid [®]
ED	enzymatic debridement
TBSA	total burn surface area
SPC	Summary of Product Characteristics

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