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REVIEW ARTICLE

Bromelain-based enzymatic burn debridement: A systematic review of clinical studies on patient safety, efficacy and long-term outcomes

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Abstract

In 2012 the European Medicines Agency approved a pineapple stem-derived Bromelain-based debridement concentrate of proteolytic enzymes (NexoBrid®, MediWound Ltd, Yavne, Israel) for adult deep burns. Over 10 000 patients have been successfully treated with NexoBrid® globally, including in the US. The aim of our study is to perform a systematic review of the current literature on Nexobrid® outcomes. We conducted a literature search in PubMed, Google Scholar, Embase, and other search engines (2013–2023). The online screening process was performed by two independent reviewers with the Covidence tool. The protocol was reported using the Preferred Reporting Items for Systematic Review and Meta-Analyses, and it was registered at the International Prospective Register of Systematic Reviews of the National Institute for Health Research. We identified 103 relevant studies of which 34 were found eligible. The included studies report the positive effects of Nexobrid® on burn debridement, functional and cosmetic outcomes, scarring, and quality of life. Also, they validate the high patient satisfaction thanks to enhanced protocols of analgosedation and/or locoregional anaesthesia during Bromelain-based debridement. Two studies investigate potential risks (coagulopathy, burn wound infection) which concluded there is no strong evidence of these adverse events. NexoBrid® is a safe, selective, non-surgical eschar removal treatment modality. The benefits of Bromelain-based debridement are faster debridement and healing times, reduced operations, length of stay, cases of sepsis, blood transfusions, and prevention of compartment syndrome. Existing evidence suggests that the indications and the role of Bromelain-based debridement are expanding to

cover "off-label" cases with significant benefits to the global healthcare economy.

KEYWORDS

bromelain, enzymatic debridement, learning curve, NexoBrid, review, selective, spontaneous healing

Key Messages

- during the past decade since European approval of Bromelain based burn debridement there has been a growing body of evidence regarding its safety and efficacy
- we conducted a literature search in PubMed, Google Scholar, Embase, and other search engines using the terms "NexoBrid", "bromelain" and "burn enzymatic debridement" published during 2013–2023
- we identified 103 relevant studies of which 34 were eligible, reporting the positive effects of Nexobrid® on burn debridement, functional and cosmetic outcomes, scarring, and quality of life

1 | INTRODUCTION

Over half a century ago, Zora Janzekovic introduced the concept of early tangential excision of deep burns and selective eschar removal followed by skin grafting which allows the preservation of viable dermis.[1] It took many years for this pioneering technique to be accepted as the standard of care (SOC) around the world.[2–11] Despite surgical escharectomy remaining the mainstay of treatment for deep burns, it is often associated with complications, such as bleeding, heat loss, risk of hypothermia, as well as high operating room (OR) costs and utilization of human resources.

On the other hand, bromelain-based debridement (BBD) with NexoBrid® (NXB, MediWound Ltd, Yavne, Israel), a pineapple plant (*Ananas comosus*) stem-derived concentrate of proteolytic enzymes (anacaulase-bcdb, e.g., thiol-endopeptidases, phosphatases, glucosidases, peroxidases, cellulases, glycoproteins, carbohydrates, and other nonprotein components),[12] has become popular for deep partial thickness (DPT) and/or full thickness (FT) burn debridement.[13–15]

The product consists of a powder of enzymes mixed with a hydrating gel. The mixture is applied topically on the burn eschar for 4 h during which, selective debridement is achieved. Bromelain has anti-inflammatory, anti-oedematous, analgesic, anti-thrombotic, and exfoliative properties mediated through the kallikrein-kinin and arachidonic acid pathways, as well as through effects on cell-mediated immunity.[16–18] Unlike surgical debridement, NXB is a more selective eschar removal agent resulting in a wound bed with a sufficient quantity of viable dermis to support spontaneous re-epithelialization. BBD is a bedside procedure with no requirement for OR staff, sophisticated equipment, or expensive resources.

NXB proved valuable during the COVID-19 pandemic which pushed the healthcare system to its limit due to staff shortages, and high Intensive Care Unit (ICU) demands (e.g., ventilators, transfusion of blood products, operating room supplies, etc.). In an attempt to save resources, there was a shift towards non-surgical care of burn patients worldwide.[19–21] For example, several authors reported their successful experiences with the use of NXB during the pandemic. They believed BBD was a suitable alternative to surgery with the highest level of evidence globally.[20,22,23]

Decades of translational research on NXB led to its final approval for clinical use in 2012 by the European Medicines Agency (EMA).[24–37] The centralized European Union approval was based on the results of 7 clinical trials.[38] Since then, approximately 10 000 patients have been successfully treated with NXB for deep thermal burns. European consensus guidelines[39,40] and individual European country guidelines have been published, including Spain,[41,42] Italy,[43] Romania,[44] and Poland.[45] It is currently approved for use in forty-four countries worldwide, most recently in the United States,[46] and in pre-approval stages in Australia.[47]

The aim of our systematic review is to analyse the data of the randomized clinical trials (RCTs) and retrospective studies on patient safety, efficacy and outcomes from BBD, published during the decade since the initial European approval.

2 | METHODS

We conducted a literature search (2013 until April 8, 2023) in PubMed, Google Scholar, Embase, Clinicaltrials.gov, World Health Organization International Clinical Trials Registry Platform (WHO ICTRP), UK Clinical Research Network (UKCRN) Portfolio, International Traditional Medicine Clinical Trial Registry (ISRCTN) using the terms "NexoBrid", "bromelain" and "burn enzymatic debridement" in various combinations (Boolean operators).

The first two authors completed the search. Regarding the PubMed search, 746 papers were identified in the last decade, and screened by two independent reviewers based on title and abstract using the Covidence tool. After exclusion of irrelevant articles ($n = 212$), full-text online screening of 576 articles took place based on predetermined inclusion and exclusion criteria. A similar approach was applied for identifying the relevant clinical trials on www.clinicaltrials.gov and the other search engines **(**Table 1**)**. The screening yielded 103 relevant reports about NXB, of which 34 were found to be eligible. The clinical characteristics of the participants in the publications were not limited by age, sex, location, nationality, race, wound depth and TBSA (%).

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart is shown in Figure 1. The protocol was registered at the International Prospective Register of Systematic Reviews (PROSPERO, CRD42023411458: Bromelain-based Enzymatic Burn Debridement: A Systematic Review on Patient Safety, Efficacy and Long-term Outcomes) of the National Institute for Health Research (NIHR).

Primarily, our focus was articles analysing the outcomes of BBD on burn patients from RCTs and prospective studies, and secondarily from retrospective studies. These outcomes pertain to the following categories: efficacy of selective debridement (i.e., time to complete debridement (TCD), time to wound closure (TWC), wound management), need for surgery, length of stay (LOS), pain management, scar quality (i.e., functional restoration, cosmetic results), quality of life (QoL), application in burn mass casualty events (BMCEs), cost-effectiveness, safety profile (i.e., potential risks), and supporting literature.

TABLE 1 Search strategy, inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Adult and paediatric deep partial/ full thickness burns	Superficial burns
Treatment modality: BBD	Pilot studies
Human subjects	Reviews and commentary articles
Prospective and retrospective clinical trials	Letters to the Editor, Case reports (<10 patients), Correspondence, Viewpoints, low level of evidence
Publication in the English language	In vitro, in vivo, ex vivo studies
Published from 2013 until April 2, 2023	Non-English language
Full text available	
PubMed/ Google Scholar/ Embase Search strategy (((nexobrid[Title/Abstract]) OR (enzymatic[Title/Abstract])) AND (burn debridement[Title/Abstract])) OR (eschar[Title/Abstract])	
Clinicaltrials.gov/ WHO ICTRP/UKCRN/ ISRCTN Search Strategy bromelain OR NEXOBRID	

Abbreviations: BBD, bromelain-based debridement; ISRCTN, International Standard Registered Clinical Trial Number Registry (WHO Registry Network); UKCRN, UK Clinical Research Network Portfolio; WHO ICTRP, World Health Organization International Clinical Trials Registry Platform.

3 | RESULTS

The study designs and treatment methods used were highly variable among the articles. The data retrieved were heterogeneous and could not be combined numerically. Therefore, a systematic review without a meta-analysis was performed. One hundred and three papers were identified as relevant to our study, of which 34 were eligible based on the review criteria. These included four prospective (including 3 RCTs) and 30 retrospective studies. The additional 69 reports published about NXB during the past decade included case reports, letters, reviews, learning curve reports, consensus papers, combined modality studies, non-english language reports and in vitro studies.

3.1 | Treatment efficacy

Four prospectives studies (including 3 RCTs) and 10 retrospective studies on efficacy, and eight studies on "off label" indications were analysed in which the number of participants ranged from 26 to 182, both children and adults. Studies with statistically significant results are shown in Tables 2-4. Suboptimal

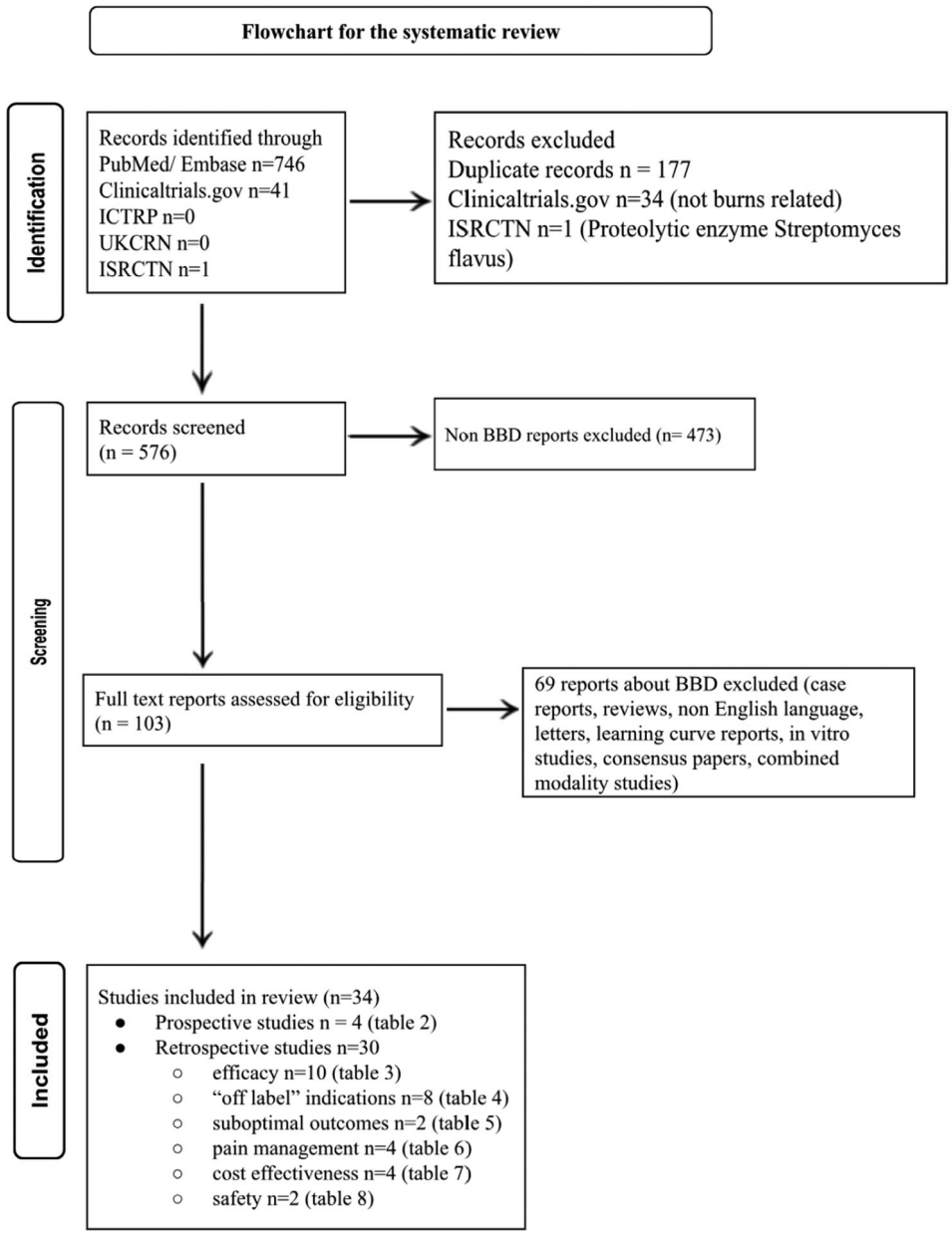

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart.

outcomes were reported in two studies **(**Table 5**)**. These studies report the effects of NXB on burn debridement, the functional and cosmetic outcomes, scar and quality of life, and complications.

3.2 | Pain management

Four studies on different types of pain regimes (i.e., analgosedation, locoregional anaesthesia), their efficacy and safety were analysed for our review. The number of participants ranged from 20 to 491. The age of the participants, TBSA, and outcome measures varied in each study **(**Table 6**).** These reports validate the high patient satisfaction during BBD.

3.3 | Cost-effectiveness

Four cost analysis studies were identified. The data were obtained from the national burn registries of each country, or from the simulation models. BBD may have enormous economic benefits for the healthcare system **(**Table 7**)**.

3.4 | Safety profile

Two studies investigate potential risks (coagulopathy, burn wound infection). The number of participants ranged from 40 to 132. They concluded there is no strong evidence of these adverse events **(**Table 8**)**.

TABLE 2 Prospective clinical trials on NexoBrid® efficacy and outcomes.

Reference	Country	Type of study	No. of Participants	Age Range (yr)	Mean TBSA (%)	Follow-up (mo)	Primary outcomes	Parameters	Results	Conclusion
Hickerson et al., 2021	USA Europe India Israel	Phase III multicenter RCT (DETECT study—NCT #: NCT04040660)	175	Adults	15–30	12	Incidence of complete debridement TCD TWC Scar quality Function and QoL	MVSS POSAS EQ-5D VAS BSHS-B	Complete debridement: BBD vs. Gel placebo cohort (93.3% vs 4%) BBD vs. SOC (4% vs 72%, $p < 0.0001$) TCD: BBD vs. SOC (1 day vs 3.8 days, $p < 0.0001$) TWC: BBD and SOC (27 and 28 days) MVSS 3.70 ± 2.10 NXB vs. 5.08 ± 3.11 SOC POSAS followed similar trends QOL was generally similar among the treatment arms	Safety of BBD treatment, significantly better MVSS
Shoham et al., 2021	Israel Hungary	Multicenter RCT (NCT #: NCT02020746)	73	65.8 ± 16.2	33.6 ± 29.7 cm^2	6	TCD Granulation TWC Safety Pain	LUMT score Adverse events VAS	55.1% vs. 29.2% complete debridement with 10 daily treatments 7.6 ± 4.1 ESX vs. 8.4 ± 4.1 days gel group (NS)	No significant safety issues of ESX for DFU, VLU, post-traumatic/postop wounds
Schulz et al., 2017	Germany	CT	40	18–76	10.1 ± 13.9 (mean hand 1.1 ± 0.5)	3	Hand scar quality, NXB effectiveness	VSS	Similar VSS	Superior outcomes with NXB in burn depth evaluation, tissue preservation, completeness of debridement, and wound closure

(Continues)

TABLE 2 (Continued)

Reference	Country	Type of study	No. of Participants	Age Range (yr)	Mean TBSA (%)	Follow-up (mo)	Primary outcomes	Parameters	Results	Conclusion
Rosenberg et al., 2014	Germany Brazil Romania Israel Slovakia France UK India Australia Poland Netherlands Portugal	Multicenter RCT (NCT #: NCT00324311)	182	4–55	5–30	2–3 yrs	TCD TWC BICS DBL Scar quality QoL Pain	MVSS SF-36 BOQ Photographic analysis	TCD significantly shorter in NXB vs. SOC group (2.2 vs. 8.7 days) NXB decreased % of wounds requiring SD (24.5% vs. 70.0%), burn area surgically excised (13.1% vs. 56.7%) vs. SOC 3.6 days longer TWC in NXB, but shorter in children and hand burns Similar MVSS, QoL, pain scores	BBD reduced need and extent of surgery and escharotomies Better long-term outcomes in children and hand burns cohorts Significantly lower need for autografting No escharotomies for hand burns no significant differences in adverse events

Abbreviations: BICS, burn-induced compartment syndrome; BOQ, Burns Outcome Questionnaire (children); BSHS-B, Burn Specific Health Scale – Brief scale; CIP, compartment interstitial pressure; CRP, C-reactive protein; CT, clinical trial; Cutometer® dual MPA 580 (measures viscoelasticity and pliability); DASH, Disabilities of the Arm, Shoulder and Hand questionnaire; DBL, Debridement-related blood loss, SD; DFU, diabetic foot ulcer; DPT, deep partial thickness burn; EQ-5D, EuroQol 5 Dimensions; ESX, EscharEx (Nexobrid); LUMT score, Leg Ulcer Measurement Tool; MBS, modified Baux score; Mexameter® MX 18 (measures scar erythema and melanin); MHOQ, Michigan Hand Outcomes Questionnaire; MOI, mechanism of injury; MVSS, Modified Vancouver Scar Scale; MYS, modified Yeong scale; NR, not reported; NS, normal saline; NXB, nexobrid; O2C, Oxygen-to-see device (measures Laser tissue oxygen saturation, haemoglobin level and microcirculation); PCT, procalcitonin; POSAS, Patient and Observer Scar Assessment Scale; PRWE-G, Patient-Related Wrist Evaluation Score; QoL, quality of life; RCT, randomized controlled trial; ROM, range of motion; SD, surgical debridement; SF-36, Short Form-36 questionnaire (adults); SOC, standard of care; SSG, split skin graft; standard debridement; TBSA, Total body surface area; TCD, Time to complete debridement; Tewameter TM300 (measures trans-epidermal water loss); TWC, time to wound closure; VAS, Visual Analog Scale; Visioscan® (visualization of skin surface topography); VLU, venous leg ulcer; VSS, Vancouver Scar Scale.

TABLE 3 Retrospective studies on NexoBrid® efficacy and outcomes.

Reference	Country	No. of Participants	Age Range (yr)	Mean TBSA (%)	Follow-up (mo)	Primary outcomes	Parameters	Results	Conclusion
Alekseev et al., 2023	Russia	15	37.3 ± 11.6	9.5 ± 4.1	NR	TWC TCD Scar	VAS	Spontaneous healing in 80%	Rapid, effective, and safe eschar removal, sufficient preservation of viable dermis
Corrales-Benitez et al., 2022	Spain	72	43.6 ± 18.9 (mean)	6 ± 4.8	1 yr	Hand function Scar quality QoL	ROM DASH score MHOQ VSS	Normal and improved DASH and MHOQ	Full restoration of function and QoL
Pertea et al., 2021	Romania	30	20–56	<15	6	Scar quality	VSS	86% effective BBD	Superior scar outcomes
Rivas-Nicolls et al., 2020	Spain	33	47.7	NR	24	Hand burn debridement, scar, spontaneous healing	TWC	100% effectiveness in debridement 50% spontaneous epithelialization at 24.9 days	Superior debridement with NXB, decreased need for SSG, faster healing
Hofmaenner et al., 2021	Switzerland	59	31–59	6–26	NR	Safety	Systemic Inflammatory reaction, bleeding, hemodynamic instability, electrolytes	Catecholamine use was similar in both groups. No differences in leukocyte counts, CRP, PCT, lactate, sodium, potassium, chloride, and phosphate levels	Safe BBD for TBSA>15%
Dadras et al., 2020	Germany	44 (52 hands)	20–90	9	48	TCD Predictors of spontaneous re-epithelialization oh hand burns	MOI TBSA Dressings	Worse healing in hand electrical burns	Spontaneous healing post-BBD of DPT hand burns best in contact burns and less than 15% TBSA
Bernagozzi et al., 2020	Italy	36	51–59	20	48	DBL Autografts LOS (days) Scar quality	Haemoglobin (g/dl) Haematocrit (%) Transfusions MYS	50% of BRM-treated patients spontaneously Healed without a requirement of skin graft No difference in LOS	Excellent aesthetic results in scars

(Continues)

TABLE 3 (Continued)

Reference	Country	No. of Participants	Age Range (yr)	Mean TBSA (%)	Follow-up (mo)	Primary outcomes	Parameters	Results	Conclusion
Cordts et al., 2016	Germany	16	47.8 ± 14.9	20.1	3	Upper extremity post-BBD functional outcomes	DASH PRWE-G VSS	No surgery required in 53.8% 37% reduction in skin-grafted area	Good functional results and pain levels with regional block
Schulz et al., 2017	Germany	26	18–78	2–78	12	Facial scar quality, debridement selectivity, wound closure	POSAS, VSS, Mexameter® MX 18, Cutometer® dual MPA 580, Tewameter TM300, O2C, Visioscan®	Significantly higher percentage burns in the NXB Group were more superficial	Significantly superior functional and cosmetic outcomes compared to SD
Bowers et al., 2022	UK	29	23–74	30	NR	DBL TCD TWC SD Pain protocol	Time from burn injury to commencement BBD Blood transfusion Mortalities MBS	66% debrided within 24 h	Significantly reduced blood loss, need for autografting, SDs Improved dermal preservation, Steep learning curve Potential for treating larger burns (>70% TBSA) 2 deaths (large TBSA, inhalation injury and chest sepsis)

Abbreviations: BBD, bromelain-based debridement; BICS, burn-induced compartment syndrome, ICS, interstitial-compartmental pressure; BICS, burn-induced compartment syndrome; BOQ, Burns Outcome Questionnaire (children); BSHS-B, Burn Specific Health Scale – Brief scale; CIP, compartment interstitial pressure; CRP, C-reactive protein; CRP, C-reactive protein; DASH, Disabilities of the Arm, Shoulder and Hand questionnaire; DASH, Disabilities of the Arm, Shoulder and Hand questionnaire; DBL, Debridement-related blood loss, SD; DFU, diabetic foot ulcer; DPT, deep partial thickness burn; ED, enzymatic debridement; EQ-5D, EuroQol 5 Dimensions; ESX, EscharEx (Nexobrid); Hb, haemoglobin; Leuts, leukocytes; LOS, length of stay; LUMT score, Leg Ulcer Measurement Tool; MBS, modified Baux score; MHOQ, Michigan Hand Outcomes Questionnaire; MOI, mechanism of injury; MVSS, Modified Vancouver Scar Scale; MYS, modified Yeong scale; N/A, not applicable; NR, not reported; NR, not reported; NS, normal saline; NXB, nexobrid; NXB, nexobrid; PCT, procalcitonin; POSAS, Patient and Observer Scar Assessment Scale; POSAS, Patient and Observer Scar Assessment Scale; PRWE-G, Patient-Related Wrist Evaluation Score; QoL, quality of life; RCT, randomized controlled trial; ROM, range of motion; SD, surgical debridement; SE, surgical excision; SF-36, Short Form-36 questionnaire (adults); SOC, standard of care; SSG, split skin graft; standard debridement; TBSA, total body surface area; TCD, Time to complete debridement; TWC, time to wound closure; VAS, Visual Analog Scale; VLU, venous leg ulcer; VSS, Vancouver Scar Scale.

TABLE 4 Retrospective studies on outcomes for "off label" NexoBrid® indications.

Reference	Indications	Country	No. of Participants	Age Range (yr)	TBSA (%)	Follow-up (mo)	Primary outcome	Parameters	Results	Conclusion
Korzeniowski et al., 2022	Children	Poland	24	8.5 ± 4.01 (3–15)	29 ± 21	24	Reconstruction Safety LOS	LOS	3.5 times less risk of the need for reconstructive procedures Shorter LOS (35.25 ± 22.98 vs. 44.75 ± 24.53)	Safe to improve the treatment and QoL of children with severe burns Reduced scar contractures
Fischer et al., 2018	BICS	Germany	13	50.2 ± 17.9	21	11.9	Hand burn outcomes	DASH	Minimal disability	BBD is effective for BICS prevention
Mataro et al., 2020	BICS	Italy	23	47.08 ± 2.12	≤30	NR	Release of ICS	Compartment pressure device (MicroTip/ Ultra©)	60% reduction of BICS within 1 h from NXB application, complete debridement after 4 h	Noninvasive, rapid, and safe method to reduce ICS
Cherubino et al., 2021	BICS	Italy	18	39	3	15	Hand debridement, BICS	POSAS DASH	POSAS 14 (range 6–38) DASH 0 (33.3%) 19.88 days to complete wound closure LOS 2.16 days	Simple, fast, selective debridement, may prevent BICS, early physiotherapy
Harats et al., 2020	Delayed BBD Chemical burns chronic wounds	Israel	33	8 month-99 years	12	NR	Efficacy	LOS	76% successful ED	BBD effective for late-presentation burns, chemical burns, and chronic wounds No adverse effects in children

(Continues)

TABLE 4 (Continued)

Reference	Indications	Country	No. of Participants	Age Range (yr)	TBSA (%)	Follow-up (mo)	Primary outcome	Parameters	Results	Conclusion
Schulz et al., 2018	Genital/perineal burns	Germany	149 ($n = 3$ NXB)	2–92	46	12	Debridement efficacy Aesthetic outcomes	Photographic assessment of burns	Spontaneous healing	BBD allows earlier and more selective debridement, which can improve the aesthetic outcomes for genital/perineal burns
Ojeda-Regidor et al., 2017	Large burns (≥15% TBSA)	Spain	242	46.87	≥15%	NR	Compare BBD vs. SE	N/A	No statistically significant differences in wound bed colonization	BBD reduced number of surgeries/escharotomies, blood transfusions
Waldner et al., 2021	Delayed BBD	Switzerland	32	54.0 ± 19.0	10.6	NR	TWC Safety Comparison between early vs. delayed ED	Hb, CRP, Leuts	Time to complete epithelialization (28.2 days vs. 27.3 days, $p = 0.45$) 18.8% vs. 6.3%, ($p = 0.28$) in the delayed group	Delayed BBD feasible (>72 h) Slightly higher infection rates in delayed ED group

Abbreviations: BBD, bromelain-based debridement; BICS, burn-induced compartment syndrome; CRP, C-reactive protein; DASH, Disabilities of the Arm, Shoulder and Hand questionnaire; ED, enzymatic debridement; Hb, haemoglobin; ICS, interstitial-compartmental pressure; Leuts, leukocytes; LOS, length of stay; N/A, not applicable; NR, not reported; NXB, nexobrid; POSAS, Patient and Observer Scar Assessment Scale; SE, surgical excision; TWC, time to wound closure.

TABLE 5 Studies with suboptimal outcomes of NexoBrid®.

Reference	Country	Type of study	No. of Participants	Age Range (yr)	Mean TBSA (%)	Follow-up (mo)	Primary outcomes	Parameters	Results	Conclusion
Grünherz et al., 2023	Switzerland	Retrospective	62	42.5 ± 17.7	31.3 ± 18.3	N/A	Escharotomy for DPT/ FT circumferential burns (U/LE, torso)	ABSI score, mortality local complications	Number of surgeries: NXB 4.2 ± 2.9 vs. SE 7.7 ± 5.7 LOS NXB 37.2 ± 26.7 vs. SE 74.5 ± 68.8 days Death NXB 10.3% vs. SE 36.4%	Surgical escharotomy more reliable and faster than BBD in critically burned patients Mortality significantly higher with surgical escharotomy Increase in BBD for BICS prevention More complications with SE (SSG loss, delayed healing, wound infections)
Tapking et al., 2022	Germany	Retrospective	54	Scalds 47.5 ± 19.9 Flame 41.8 ± 22.6	Scalds 24.5 ± 20.0 Flame 10.6 ± 9.6	NR	Comparison between BBD of scald vs. flame burns	LOS SE	SE in 88.9% scalds vs. 52.8% flames LOS scald 7.8 ± 9.2 days vs. flame 3.7± 3.8	Increased need for surgical excision and autografting after ED of scald vs. flame burns

Abbreviations: ABSI, abbreviated burn severity index score; DPT, deep partial thickness; ED, enzymatic debridement; FT, full thickness; LOS, length of stay; N/A, not applicable; NR, nor reported; SE, surgical escharectomy; SSG, split skin graft; U/LE, upper/ lower extremity.

TABLE 6 Studies on pain management during BBD.

Reference	Country	Type of study	No. of Participants	Age Range (yr)	TBSA (%)	Primary outcome	Parameters	Results	Conclusion
Claes et al., 2022	Belgium	Retrospective	82	7.5–49.1	10.8–12.5	Pain Safety of anaesthesia	NRS	Low pain levels, significant decrease in time to wound closure	Regional anaesthesia should be the method of choice for bedside BBD
Galeiras et al., 2018	Spain	Retrospective	28	48.0 ± 18.7	7.7 ± 6.3	Pain Safety	VAS	Adequate pain relief	PSA is efficient and safe support strategy for BBD on patients not requiring IMV
Schiefer et al., 2020	Germany	Retrospective	491	53	5.3	Pain Patient satisfaction with anaesthesia	QUIPS	High satisfaction with pain medication ($p < 0.001$), the lowest pain level ($p = 0.001$)	BBD can be performed sufficiently under analgosedation, or locoregional anaesthesia
Arkoulis et al., 2020	UK	Retrospective	20	42.5	20	Pain Effectiveness LOS	N/A	55% successful BBD Inotrope support associated with NXB failure ($p = 0.015$) LOS 29 days	Anaesthetist-led analgesia in all patients, useful adjunct

Abbreviations: BBD, bromelain-based debridement; IMV, invasive mechanical ventilation; LOS, length of stay; N/A, not applicable; NR, not reported; NRS, Numeric Rating Scale for pain; NXB, Nexobrid; PSA, procedural sedation and analgesia; QUIPS, quality improvement in postoperative pain management questionnaire; VAS, Visual Analogue Scale.

TABLE 7 Studies on NexoBrid® cost-effectiveness.

Reference	Country	Type of study	No. of Participants	Age Range (yr)	Mean TBSA (%)	Primary outcome	Parameters	Results	Conclusion
Kern et al., 2018	Germany	Cost simulation model	N/A	N/A	1–15	total treatment costs of burn patients	LOS ICU stay	total cost/ patient can be reduced by 30% if NexoBrid® completely substitutes for SOC	NexoBrid® avoids OR utilization, allowing for increased reimbursements from other surgical cases
Claes et al., 2021	Belgium	Belgian Nexobrid registry data review	41	22–87	11.1 ± 9.2	Burn related costs	Budget impact analysis	NexoBrid will realize yearly savings for the Belgian Healthcare budget of at least 30.000€	NIHDI granted a final reimbursement for BBD in adults
Farahati et al., 2017	USA	ABA NBR 2015 data review	NR	NR	NR	NR	Market size clinical effectiveness and cost-effectiveness, product cost, market adoption rates	No adverse effects 95.1% successful BBD	Potential cumulative spillover benefits of up to $1.8 billion, depending on reduction in hospital LOS, the number of autografts performed, and peak market share in 10 years.
Guidice et al., 2017	Italy	Retrospective	20	18–69	14–22	Cost analysis	Total net savings	ICU stay NXB 31 vs. SOC 37 days NXB 0 vs. SOC 10 escharotomies Blood transfusions NXB 0.12–0.9 vs. SOC 0.7–1.9	53 300€ worth of savings from NXB

Abbreviations: ABA NBR, American Burn Association National Burn Repository; BBD, bromelain-based debridement; ICU, Intensive Care Unit; NIHDI, Belgian National Institute for Health and Disability Insurance; NR, not reported; NXB, Nexobrid; OR, operating room; SOC, standard of care.

TABLE 8 Studies on NexoBrid® safety profile.

Reference	Country	Type of study	No. of Participants	Age Range (yr)	Mean TBSA (%)	Primary outcome	Parameters	Results	Conclusion
Pfister et al., 2022	Switzerland	Retrospective	132	46	17	Coagulopathy	INR aPTT Fibrinogen Factor XIII PLTs	1st week: significantly higher factor-V in NXB group No difference in INR-, aPTT-, fibrinogen-, factor-XIII- and thrombocyte-concentrations	NXB does not increase risk of bleeding
Sharaf et al., 2022	UK	Retrospective	40	45.7	11.78–2.08	Burn wound microbiology	Gram-positive Gram-negative pathogens	Microbial profile of burn wounds treated with NXB is similar to what cases treated without ED	No strong evidence NXB changes bacterial colonization in burn wounds

Abbreviations: aPTT, activated partial thromboplastin time; INR, international normalized ratio; NXB, Nexobrid; PLTs, platelets.

4 | DISCUSSION

4.1 | Controlled trial outcomes on treatment efficacy, safety, scarring, function and quality of life

In 2021, the phase III multicenter RCT from major burn centers in the US, Europe, India, and Israel (DETECT study, NCT #: NCT04040660) showed superior and faster complete debridement with BBD vs. Gel (placebo) and BBD vs. SOC cohorts, respectively (93.3% vs. 4%, and 1 day vs. 3.8 days, $p < 0.0001$), significantly less blood loss vs. SOC, lower incidence of surgical excision vs. SOC (4 vs. 72%) Additionally, it showed that the BBD cohort ($n = 75$) had significantly better Modified Vancouver Scar Scale scores (MVSS) compared to the cohort treated with SOC debridement methods ($n = 75$) in one-year follow-up.[48]

A 2021 multicenter RCT (NCT#: NCT02020746) showed that EscharEx (ESX, NexoBrid) and gel vehicle arms achieved similar reductions in wound area, non-viable tissue area and wound healing scores during the debridement period in 73 patients with diabetic foot ulcers (DFUs), venous leg ulcers (VLUs), and post-traumatic/ postoperative wounds. They found faster healing with ESX (55.1% vs. 29.2% gel group) and complete debridement with 10 daily treatments (7.6 ± 4.1 ESX vs. 8.4 ± 4.1 days gel group). There were no significant safety issues and ESX demonstrated a favourable benefit to risk profile in 6 months follow-up.[49]

Schulz et al. performed a clinical trial including 26 patients with deep facial burns, where they found significantly superior functional and cosmetic outcomes from NXB compared to surgical debridement (SD) based on a series of objective readings, e.g., exameter® MX 180 that measures scar erythema and melanin, and Patient and Observer Scar Assessment Scale (POSAS).[50]

Rosenberg et al. (2014) reported promising results from BBD in a multicenter RCT (NCT #: NCT00324311) with 182 patients. They found that NXB significantly reduced TCD (2.2 vs. 8.7 days in the SOC group), decreased the percentage of wounds requiring SD (24.5% vs. 70.0% in SOC group), decreased the burn area surgically excised (13.1% vs. 56.7% in SOC group), and expedited the TWC in children and hand burns. In addition, they found superior long-term outcomes in the children and hand burn cohorts. They concluded that NXB is a valid minimally invasive modality which significantly reduced the need and extent of surgery including escharotomies and autografting.[51]

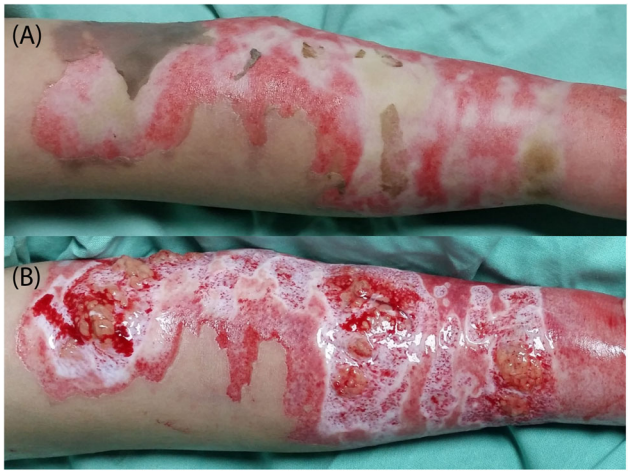

FIGURE 2 Hot oil mixed-depth circumferential burn on the left upper limb. (A) Pre-, (B) post-Nexobrid® enzymatic debridement down to healthy bleeding wound bed, note selective debridement and release of distal constriction.

4.2 | Paradigm shift, selective debridement, and wound management from retroprospective studies

BBD represents a major paradigm shift in the treatment of burns, and as such requires a number of changes from previous standard practice. This includes the following: medical training (a requirement by EMA in order for a burn center to be able to use NXB safely),[52] logistic alterations in the management of burns in the Emergency Department and on the wards (e.g., avoiding the use of Silver Sulfadiazine or Iodine-based ointments before NXB application), the need for several dressing changes necessitating an increased nursing staff workload on treatment day, and adequate pain management on the ward/ ICU. Sequential BBDs for treatment of large burns (up to 15% TBSA per session) requires adequate monitoring and hemodynamic support.[39] Patient compliance is crucial to achieve a sufficient debridement.[53] Even for experienced burn surgeons there is a learning curve to assess the post-enzymatically debrided wound bed and to predict the need for grafting versus spontaneous wound healing and epithelial regeneration.

One of the key benefits of BBD is the selective debridement which preserves viable dermis and allows spontaneous epithelialization, reducing the need for autografting and donor-site morbidity. Although post-BBD of deep burns often require more than 21 days to re-epithelialize, long-term cosmetic outcomes are equivalent, if not better, to surgical excision and grafting.[54] In cases of residual viable dermis that is insufficient to sustain spontaneous healing post-BBD, prolonged pre- (2–24 h) and post- (12–24 h) NXB wet-to-dry soakings to ensure a moist environment, enhance graft take after a few days.[39,41,43,53,55–60] A moist wound environment is achieved with a plethora of dressings that have been used, including Suprathel®, Mepilex Ag®, Biobrane®, Medihoney® and allografts,[39,41,53] SpinCare™, an electrospun polymer nanofibrous temporary epidermal layer,[61] intact fish skin grafts (Kerecis®),[62] and Epiprotect™ (a thin film of biosynthetic cellulose polymer),[63] as well as platelet-rich fibrin (PRF),[64] autologous cell therapy combined with PRF or fibrin glue.[65]

After gaining ample experience with this novel product,[53,55,56] the post-BBD wound bed viability and perfusion are assessed immediately after removal of NXB, thus allowing surgeons to correctly diagnose wound depth, and potentially reduce the need for grafting (-Figure 2).[57,66,67] Schulz et al. in a study with 40 patients with hand burns found superior outcomes post-BBD in burn depth evaluation, tissue preservation, completeness of debridement, and wound closure.[68] Although Laser Doppler Imaging (LDI),[69,70] and ultrasound for assessing skin thickness[71] may be helpful, subjective clinical inspection of the remaining dermal elements is the standard method for assessing the post-enzymatically debrided wound bed.

Despite a learning curve needed to master this technique, researchers agree on the superior functional[72] and aesthetic outcomes post-BBD,[38,73,74] skin preservation,[50,60,75,76] reduced need for skin grafting, decreased hypertrophic scarring,[68,77,78] and faster healing times.[79] These outcomes are based on objective measures of quality of life (QoL), good scarring and functional outcomes (e.g., Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire, the Michigan Hand Outcomes Questionnaire (MHOQ), and Vancouver Scar Scale (VSS), respectively).

Additionally, multiple studies show encouraging outcomes for off-label indications, e.g., burn-induced compartment syndrome (BICS),[74,80,81] paediatric burns, electrical burns,[82] chemical burns,[83] hard to heal chronic wounds,[84] genital burns,[85] >15%TBSA burns,[86,87] and delayed BBD.[88] However, not all off-label reports are unanimous about BICS. While Grünherz et al. reported a steady increase in the use of NXB for preventive decompression in circumferential deep burns in their practice, they concluded that a surgical escharotomy is still to be preferred in severely burned patients.[89]

4.3 | Pain management

Adequate pain management should be considered standard practice during BBD as per the European consensus guidelines.[40] Patients should be appropriately informed as enzymatic debridement with NXB is painful without

adequate analgesia.[39] Pain levels peak shortly after application of NXB and again upon its removal. Thus, analgesia (e.g., non-steroidal anti-inflammatory drugs, opioids), anaesthetic agents (e.g. ketamine), sedation (e.g. midazolam), and/or locoregional blocks should be tailored accordingly.[90,91] Patient satisfaction was reported as high when adequate pain management with analgosedation, or locoregional anaesthesia was utilized.[92]

4.4 | Burn mass casualty events (BMCEs)

The principles of BBD can be applied in BMCEs. Rapid and efficient non-surgical debridement has the potential to raise surgical capacity. The US government via the Biomedical Advanced Research and Development Authority (BARDA) recognized NXB as a potential solution to a radiological or nuclear event, where there may be an overwhelming need to treat radiation and/or thermal burns.[93] In this scenario, traditional burn care methods would prove insufficient. In addition, BARDA invested many public funds for the development of NXB as part of its arsenal of medical countermeasures for potential BMCEs.[93] BBD was used to treat 39 patients in 3 hospitals during the 2015 aftermath of the nightclub fire in Romania.[94] Bowers et al. advocated that BMCEs could be successfully managed with BBD in their experience of a house explosion with five patients.[60] Kiely et al. reported a similar experience in a house explosion with 4 patients.[95]

4.5 | Cost-effectiveness

Several reports confirm that thousands of dollars are saved from hospital budgets thanks to reductions in ICU stays, length of hospitalizations, need for surgical excision and autografting. NXB use reduces OR utilization, allowing for increased reimbursements from other surgical cases.[96] Indeed, a market access consultant calculated that NXB will realize yearly savings for the Belgian Healthcare budget of at least 30.000€, and therefore reimbursement was approved.[97] Farahati et al. projected the economic spillovers of this public investment, assuming integration of BBD into the US burn care system. They calculated potential cumulative spillover benefits of up to $1.8 billion, depending on the extent of reduction in hospital LOS, the number of autografts performed, and peak market share in 10 years.[98] Similarly, a cost analysis was performed by Giuduce et al. who estimated savings worth 53 300€ by using NXB in ten patients.[99] Martinez-Mendez et al. found that hospital length of stay was the main cost determinant and the actual cost of NXB was only 13.9% of the total treatment cost.[100]

4.6 | Safety profile

Despite its success in treating burn patients, there have been a few potential safety issues. The potential risk of bromelain dust inhalation, respiratory sensitization and subsequent allergic reactions were historically questioned as a result of mixing the enzyme powder with the hydrating gel before topical application. Smolle et al. measured the particle concentration in the air during the mixing process and found that very low exposure levels of inhalable particles were present. They concluded that the manufacturer's instructions for safe preparation and use of the product were sufficient.[101]

According to the Summary of Product Characteristics, oral bromelain administration reduced platelet aggregation and plasma fibrinogen concentrations, and moderately increased prothrombin and activated partial thromboplastin times (aPTT). Bromelain is safe, however, according to a 2016 safety and efficacy report. Caution should be exercised by healthcare providers with patients on anticoagulants, with thrombocytopenia, or in other causes of increased risk of bleeding.[18] Pfister et al. found that enzymatic debridement in burn patients ($n = 66$) with a mean TBSA of 17% does not increase the risk of coagulation abnormalities based on the international normalized ratio (INR), aPTT, fibrinogen, factor-XIII and platelet counts compared to the regular surgical approach.[102] The safety profile was confirmed by investigating trends in systemic inflammatory reaction, bleeding, hemodynamic stability, and electrolytes.[87] It is important to remember that coagulopathy is often associated with the burn pathophysiology itself.

Regarding possible alterations in the microbiological pattern of burn wounds post-BBD, Sharaf et al. showed that the microbial profile of 40 burn patients treated with NXB was similar to what is widely reported in cases treated without enzymatic debridement in all stages of wound healing.[103]

4.7 | Strengths and limitations

Additional studies to corroborate the findings of our work include Edmondson et al. They strongly advocated for modern enzymatic approaches for eschar debridement which have the potential to maximize dermal preservation and improve long-term scar outcomes.[104] Others considered debriding enzymes as adjuncts to surgical excision, and concluded that NXB is effective in deep burns by decreasing the percentage of grafting required

without significant adverse effects.[105–107] Kwa et al. found the TCD was the shortest for NXB, while the TWC was the longest compared to tangential excision, hydrosurgery, and shock waves, although this did not lead to decreased scar quality. They hypothesized that this may be due to the earlier eschar removal and its implications on the quality of spontaneous healing.[108]

A 2020 review on the clinical trial experience in children showed that BBD is safe and effective in children.[109] The results of a recent paediatric RCT on 72 children treated with NXB compared to 73 children treated with standard debridement methods, mentioned that all three primary endpoints (shorter TCD, less need for surgical excision, and non-inferior scarring results) were achieved. Also, the safety and efficacy of NXB in the paediatric population were demonstrated.[110] As over two-thirds of NXB treated patients in this RCT suffered from scalds, these results contradict those of a retrospective study by Tapking et al where NXB efficacy in scalds was questioned as compared to its efficacy in flame burns.[111]

Future research should focus on optimizing the protocols for treatment of the paediatric population and burn patients with comorbidities and BICS.

5 | CONCLUSIONS

Through scrutinous review and approval processes from multiple regulatory agencies including the US Food and Drug Administration (FDA), a substantial body of evidence supporting the safety and efficacy of NXB as a valid non-surgical eschar removal agent has accrued over the past decade. The benefits of BBD include faster time to complete eschar removal and faster healing time, reduced operations, LOS, cases of sepsis, blood transfusions, and prevention of BICS of the extremities and escharotomies. Existing evidence suggests that the indications and the role of BBD are expanding to cover "off-label" cases with significant benefits to the global healthcare economy.

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CONFLICT OF INTEREST STATEMENT

YS is a consultant for MediWound Ltd. YS and JG are consultants for Vericel Corp. The other authors have nothing to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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