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Enzymatic debridement with bromelain and development of bacteremia in burn injuries: A retrospective cohort study

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ABSTRACT

Background: Debridement is crucial for effective wound management in patients with severe burn injuries, and bromelain, a proteolytic enzyme from pineapple stems, has emerged as a promising alternative for surgery. However, potential links of bromelain use to fever and sepsis have raised some concerns. Given the uncertainty as to whether this was caused by infection or other inflammatory sources, we aimed to investigate if the use of topical bromelain was associated with bacteremia.

Methods: This single-centre retrospective cohort study included critically ill adult patients with severe burn injuries hospitalised at the Burn Center of the University Hospital Zurich between January 2017 and December 2021. Data were collected from two in-hospital electronic medical records databases. Our primary outcome, the association between topical bromelain treatment and the development of bacteremia, was investigated using a competing risk regression model, taking into account the competing risk of death. As a secondary outcome, the relationship between bromelain treatment and overall ICU mortality was examined using a Cox proportional hazards model.

Results: The study included 269 patients with a median age of 50 years and median burnt total body surface area of 19%. A first bacteremia occurred in 61 patients (23%) after a median time of 6 days. Bromelain treatment was given to 83 (31%) of patients, with 22

Abbreviations: ABSI, Abbreviated Burn Severity Index; BMI, Body Mass Index; CI, Confidence Interval; HR, Hazard Ratio; ICU, Intensive Care Unit; IQR, Interquartile Range; MDR, Multidrug-Resistant; SHR, Subhazard Ratio; TBSA, Total Body Surface Area

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(27%) of these developing bacteremia. In the fully adjusted competing risk regression model, no evidence for an association between bromelain treatment and bacteremia was found (SHR 0.79, 95%CI 0.42–1.48, p = 0.47). During hospital stay, 40 (15%) of patients died. There was no significant difference in mortality between patients treated with bromelain and those who were not (HR 0.55, 95%CI 0.26–1.20, p = 0.14). Among the five multidrug-resistant (MDR) pathogens identified, three were found in patients with bromelain treatment.

Conclusion: Our study did not confirm an association between topical bromelain and bacteremia in patients with severe burn injuries. This finding can inform evidence-based practices by addressing concerns about potential risks of bromelain use, contributing to the development of more effective and safe burn wound management strategies.

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1. Introduction

Patients with severe burn injuries are at a significant risk of increased mortality and prolonged morbidity worldwide, as burn injuries often result in extensive tissue damage, pain, and increased risk of infections [1,2].

Proper wound management is essential in the treatment of burn injuries, and the removal of necrotic tissue (debridement) is a critical step in the healing process [3,4]. Traditional methods of debridement, such as surgical excision or mechanical removal, can be painful and traumatic for patients. Moreover, when performing tangential excision of burn eschars, it has been suggested that on average ~40% of the tissue excised may be viable tissue inadvertently damaged in the process [5].

With the use of bromelain for enzymatic debridement, a promising alternative to complement the traditional methods of debridement in the treatment of severe burn injuries has emerged. Bromelain is a proteolytic enzyme extracted from pineapple stems. It has been shown to have anti-inflammatory and analgesic properties, as well as the ability to selectively digest necrotic tissue while leaving healthy tissue intact, resulting in faster and less painful wound healing [6–9].

However, given the increased risk of bacterial colonisation in burn wounds [10], coupled with the potential for enzymatic proteolysis to further disrupt the skin barrier, there remains a legitimate concern regarding the possibility of bacteremia (i.e., bacterial bloodstream infection) associated with the use of bromelain. On the other hand, it is also possible that the use of topical bromelain for enzymatic debridement could decrease the risk of bacteremia by providing more efficient and continuous debridement of necrotic tissue to reduce bacterial colonisation in wounds. A recent study investigating the profile of bacteria colonising burn wounds did not find evidence of a difference in wounds treated with enzymatic debridement [11].

Several studies have investigated the use of bromelain in the treatment of burn wounds, but mainly focused on efficacy or more general safety and did not explicitly study a potential risk of bacteremia [6,12,13]. While it is widely accepted that enzymatic debridement leads to a lower overall incidence of infections [13], available literature as to whether enzymatic debridement might on the other hand lead to increased susceptibility to invasiveness of colonising bacteria is scarce. This highlights the need for a clinical real-life application study in a high-resource setting with high hospital hygiene standards to reduce the influence on bacteremia from other nosocomial sources. Thus, we aimed to investigate the association of topical bromelain use and the risk of bacteremia in critically ill patients with severe burn injuries in a specialised tertiary intensive care unit. We hypothesised that the use of bromelain would decrease the risk of bacteremia.

2. Methods

2.1. *Study design and population*

This single-centre retrospective cohort study included critically ill adult patients hospitalised with severe burn injuries at a specialised burns intensive care unit (ICU), the Burn Center of the University Hospital Zurich, between January 2017 and December 2021.

All patients with severe burn injury, as assessed by the referring clinicians and confirmed by the treating physician or plastic surgeon of our Burn Center ICU, were included. Patients hospitalised on the adult ICU aged < 18 years were excluded. Severe burn injuries were commonly diagnosed in the presence of one or more of the following: burn injury complicated by major trauma or inhalation injury, a chemical burn, high-voltage (> 1 kV) electrical burn, burns encompassing > 20% of the total body surface area (TBSA).

Patients were considered as having received enzymatic eschar removal with bromelain treatment, if at least one topical application of NexoBrid® (manufactured by MediWound™, Rüsselheim, Germany) was documented in patient charts during ICU stay. For burn wound treatment, NexoBrid® is mixed with an inert carrier gel to form a wound management dressing. NexoBrid® consists of a lyophilized, partially purified proteolytic protein mixture with increased specific enzymatic activity derived from bromelain raw material extracted from pineapple plant stems [6]. The initial administration of NexoBrid® at our centre is typically applied during the early phase of the first week after injury, generally within 2 to 3 days. In cases involving circumferential burns, NexoBrid® is applied on the first day after the burn injury. The duration of NexoBrid® exposure is consistently maintained at 4 h, in accordance with our established standard of care [12].

2.2. Data collection

Data were collected through the use of two in-hospital electronic medical records databases, which included KISIM Version 5.0 (Cistec AG, Zurich, Switzerland) and Patient Data Management System (PDMS) MetaVision Version 6.1 (iMDsoft, Dusseldorf, Germany). Microbiological samples were collected by the ICU healthcare workers as ordered by the treating physicians. Samples were processed at the Institute for Medical Microbiology of the University of Zurich. Standard clinical microbiology analytic techniques were used for culturing, isolation and identification of microorganisms as previously described [14].

2.3. Study outcomes

The primary study outcome was the association between bromelain treatment and the occurrence of a first episode of bacteremia. Secondary outcomes were the occurrence of multidrug resistant bacteria and the association of bromelain treatment and overall ICU mortality.

2.4. Assessment of bacteremia

Bacteremia was defined to be present if at least one positive blood culture was documented that was not considered a contamination. To account for a bacteremia episode to span over midnight, we also included additional pathogens identified in blood cultures taken on the date after the first occurrence. To differentiate between real bacteremia and contamination for common species colonising the skin, like coagulase-negative Staphylococci or *Cutibacterium* spp., at least two aerobic or anaerobic blood cultures with that same species from the same sampling episode had to be positive in order to qualify as true bacteremia.

2.5. Statistical analysis

To investigate the association between bromelain treatment and development of a first bacteremia during ICU stay, a competing risk regression model according to Fine and Gray was used, accounting for the competing risk of death [15]. For the assessment of bromelain treatment and mortality, a Cox proportional hazards model was applied. Variables for adjustment of both the Cox and the competing risk regression models were selected according to their availability and presumed clinical relevance, and included age, sex, body mass index (BMI), abbreviated burn severity index (ABSI) score, treatment on modernised ICU (from 9 July 2019 onward), the presence of additional trauma, affected body surface area, Baux Score and total number of surgical operations during ICU stay. Total number of surgical operations during ICU stay was exempt from adjustment in mortality analysis due to potential for immortal time bias. To address the considerable possibility of unmeasured and residual confounding, and the limited availability of data for adjustments in our study, we employed several strategies. We categorised potential nonlinear confounding by age into five groups: < 35, 35–49, 50–64, 65–79, and ≥ 80 years, in order to minimise residual confounding [16]. Additionally, we adjusted for the number of operations during ICU stay as a post-exposure proxy for injury severity or other unmeasured confounders of initial complications not reflected in the available baseline information [17]. For all analyses we considered a p-value < 0.05 to be statistically significant. All analyses were performed using Stata 16 & 18 (Stata Corporation, College Station, TX, USA).

3. Results

3.1. Cohort characteristics

We included 269 patients between January 2017 and December 2021. The median age of the patients in our cohort was 50 years (interquartile range [IQR] 33–65 years) and only 69 (26%) of the included patients were female. The median proportion of burnt total body surface area (TBSA) was 19% (IQR 11–30%; Table 1). Of all included patients, 44 (18%) also had an inhalation trauma and 30 (11%) an additional physical

Table 1 – Patient demographics and clinical characteristics of burns patients.

	Overall n = 269 (100%)	Bromelain treatment n = 83 (31%)	No bromelain treatment n = 186 (69%)
Age at admission in years, median (IQR)	50 (33-65)	49 (34-60)	50 (33-68)
Female sex, n (%)	69 (26)	25 (30)	44 (24)
BMI, median (IQR)	25 (23-28)	26 (23-28)	25 (23-29)
Modernised ICU[a], n (%)	75 (28)	14 (17)	61 (33)
TBSA %, median (IQR)	19 (11-30)	18 (12-35)	19 (11-28)
Additional trauma, n (%)	30 (11)	12 (14)	18 (10)
Inhalation trauma, n (%)	44 (18)	10 (12)	34 (20)
Total of operations, median (IQR)	2 (2-3)	3 (2-4)	2 (1-3)
ABSI Score, median (IQR)	6 (5-8)	6 (5-8)	6 (5-8)
Baux Score, median (IQR)	70 (52-93)	75 (49-95)	69 (53-93)
Patients with a first bacteremia (%)	68 (25)	29 (35)	39 (21)
Death, n (%)	40 (15)	9 (11)	31 (17)

Abbreviations: BMI = body mass index (kg/m2); TBSA = total body surface area; ABSI = abbreviated burn severity index

[a] Treatment before or after 9 July 2019

trauma. The median of total surgical operations performed was 2 (IQR 2–3), with a maximum of 19 operations in one patient (Table 1). For all patients the ABSI and Baux Scores were calculated, resulting in a median of 6 (IQR 5–8) for the ABSI, and 70 (IQR 52–93) for the Baux Score, respectively (Table 1). The median time between the accident and the initial surgical intervention was 2 (IQR 1–4) days among the 174 (65%) patients for whom surgery dates were available. Overall, the demographics and severity scores between patients with or without bromelain treatment were similar.

3.2. Description of Bacteremia and Causing Pathogens

A total of 61 (23%) of the patients experienced a first bacteremia, resulting in a total of 85 identified pathogens. In 14 (23%) of patients with a first bacteremia, more than one pathogen was identified in the blood cultures. The median time to a first bacteremia was 6 (IQR 5–11) days, and within all first episodes we detected 51 (60%) Gram-positive pathogens and 34 (40%) Gram-negative pathogens (Table 2).

Overall, the most frequent species identified was *Staphylococcus aureus* (n = 16, 19%), followed by *Klebsiella pneumoniae* (n = 7, 8%), *Streptococcus mitis/oralis* (n = 7, 8%), *Pseudomonas aeruginosa (n = 6, 7%)*, *Enterobacter cloacae* (n = 5, 6%) and *Escherichia coli* (n = 5, 7%). The above microorganisms accounted for 54% of total species from blood cultures (Table 2). The bacterial species did not differ substantially between patients with or without bromelain treatment (Table 2, Fisher's exact test p = 0.55). Certain bacteria (*Klebsiella pneumoniae*, Streptococci) appeared to have slightly earlier median onsets of infections than others (*Enterobacter cloacae*, *Escherichia coli*, *Enterococcus faecalis*), but overall we did not observe relevant differences in median time of onset between species (Fig. 1).

In the course of our study, 20 (33%) of our patients with a first bacteremia also experienced subsequent episodes. These later episodes revealed a total of 34 different species of pathogens, including now Candida spp., which were not previously identified in the first bacteremia episodes (Supplementary Figure 1).

3.3. Association of bromelain treatment and bacteremia

Of all patients, 83 (31%) received topical bromelain treatment. Among them, 22 (27%) developed bacteremia, while 39 (21%)

Table 2 – Pathogen table of bloodstream infections.

	Overall n = 85 (100%)	Bromelain treatment n = 39 (46%)	No bromelain treatment n = 46 (54%)
Gram-positive bacteria, no. of bacteria (%)	**51 (60)**	**23 (50)**	**28 (61)**
Staphylococcus aureus	16 (19)	5 (13)	11 (24)
Streptococcus mitis/oralis	7 (8)	3 (8)	4 (9)
Other streptococci[1]	5 (6)	3 (8)	2 (4)
Enterococcus faecalis	4 (5)	2 (5)	2 (4)
Staphylococcus epidermidis	4 (5)	2 (5)	2 (4)
Streptococcus pneumoniae	4 (5)	1 (3)	3 (7)
Gemella sp.morbillorum	2 (2)	2 (5)	0
Lactobacillus fermentum	2 (2)	2 (5)	0
Staphylococcus hominis	2 (2)	1 (3)	1 (2)
Clostridium sordellii	1 (1)	0	1 (2)
Cutibacterium acnes	1 (1)	0	1 (2)
Dialister pneumosintes	1 (1)	1 (3)	0
Parvimonas micra	1 (1)	1 (3)	0
Staphylococcus lugdunensis	1 (1)	0	1 (2)
Gram-negative bacteria, no. of bacteria (%)	**34 (40)**	**16 (35)**	**18 (39)**
Klebsiella pneumoniae	7 (8)	2 (5)	5 (11)
Pseudomonas aeruginosa	6 (7)	5 (13)	1 (2)
Enterobacter cloacae	5 (6)	2 (5)	3 (7)
Escherichia coli	5 (8)	3 (8)	2 (4)
Klebsiella aerogenes	2 (4)	0	2(4)
Serratia marcescens	2 (2)	1 (3)	1 (2)
Acinetobacter baumannii	1 (1)	0	1 (2)
Citrobacter freundii	1 (1)	0	1 (2)
Haemophilus influenzae	1 (1)	0	1 (2)
Klebsiella oxytoca	1 (1)	0	1 (2)
Pantoea sp.	1 (1)	1 (3)	0
Pasteurella multocida	1 (1)	1 (3)	0
Proteus mirabilis	1 (1)	1 (3)	0
Multidrug resistant bacteria, no. of bacteria (%)	5 (6)	3 (8%)	2 (4%)

1 Other streptococci: Streptococcus bovis, Streptococcus agalactiae, Streptococcus anginosus, Streptococcus salivarius

Pathogen species of bloodstream infections stratified according to presence or absence of bromelain treatment and stratified in Gram-positive and Gram-negative, as well as a multidrug resistant column. The data are presented in the number of specific bacteria of a kind and the percentage of the particular column.

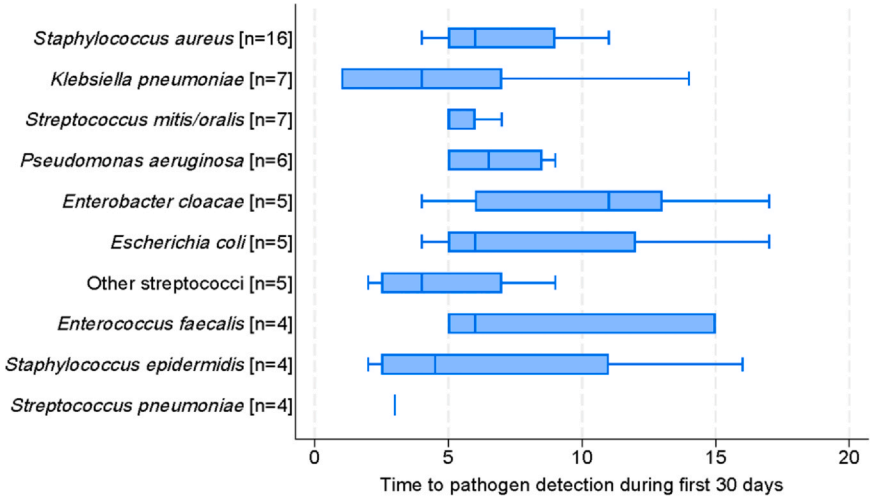

Fig. 1 – *Species of a first bacteremia and time to first pathogen detection*. Time to first bacteremia stratified by species given as horizontal box plots. The median time to first bacteremia did not differ substantially between species, with overall median 6 (interquartile range 5 to 12) days.

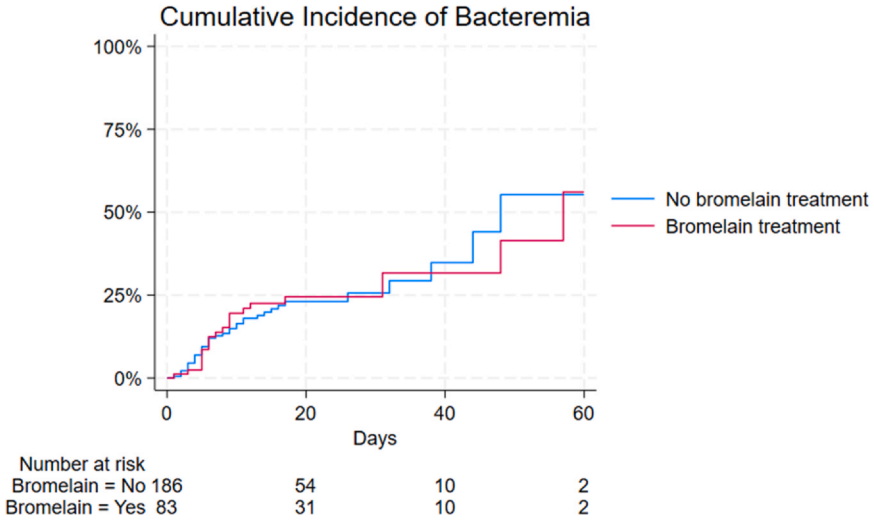

Fig. 2 – *Kaplan-Meier estimates of bacteremia*. Kaplan-Meier estimates (unadjusted) for 60 days cumulative incidence of a first bacteremia, stratified by bromelain treatment.

of patients who did not undergo bromelain treatment experienced a first bacteremia (Fig. 2). In the unadjusted competing risk regression model, where the competing risk of death was taken into account, no evidence was observed for a difference in the rate of bacteremia between patients with and without bromelain treatment (SHR 1.09, 95%CI 0.65–1.83, p = 0.74). In the fully adjusted model, a slight reduction in the subhazard ratio was noted after the number of operations was included as a post-exposure variable (SHR 0.79, 95%CI 0.42–1.48, p = 0.47, Table 3).

3.4. *Bromelain treatment and mortality*

A total of 40 (15%) patients died during their ICU stay. Although mortality seemed somewhat lower in patients treated with bromelain, this difference was likely observed by chance in both the unadjusted (HR 0.56, 95%CI 0.27–1.18, p = 0.13) as well as the fully adjusted model (HR 0.55, 95%CI 0.26–1.20, p = 0.14).

3.5. *Bromelain and bacteremia with a multidrug-resistant pathogen*

Five (7%) of all pathogens exhibited multidrug-resistance (MDR), of which two showed extended spectrum beta-lactamases (ESBL), and one was a Methicillin-resistant *Staphylococcus aureus* (MRSA). Of these five MDR pathogens, three were found in patients with bromelain treatment, which was likely to be observed by chance. Due to the low number of MDR pathogens, further analysis in a statistical model was omitted.

Table 3 – Unadjusted and Adjusted Models for association between Bromelain treatment and bloodstream infections.

Measure	Unadjusted Model	Partially adjusted Model[a]	Fully adjusted Model[b]
SHR	1.09	1.11	0.79
95% CI	0.65-1.83	0.63-1.95	0.42-1.48
p-value	0.74	0.73	0.47

Abbreviations: SHR = subhazard ratio (from competing risk regression model, taking the risk of death into account); 95% CI = 95% confidence interval; ICU = intensive care unit; BMI = body mass index; ABSI = abbreviated burn severity index; TBSA = total body surface area

[a] Adjusting for age, sex, BMI, ABSI score, additional physical trauma, total body surface area affected, Baux Score, modernisation of ICU (before or after 9 July 2019); due to missing values in TBSA (n = 10) and BMI (n = 28), only 241 patients could be included in this analysis.

[b] Adjusting for all variables included in the partially adjusted model plus the total number of operations during ICU stay as a post-exposure proxy for otherwise unmeasured severity or other unmeasured confounders (N = 241). A post-hoc sensitivity analysis excluding missing variables (i.e., BMI and TBSA) on all 269 patients showed similar results (SHR 0.78, 95%-CI 0.43–1.46, p = 0.46).

4. Discussion

In this retrospective cohort study including 269 adult patients admitted to a specialised tertiary intensive care unit (ICU) with severe burn injuries, we found no association of enzymatic debridement with topical bromelain and the subsequent development of bacteremia. While our unadjusted and partially adjusted competing risk regression models appeared to suggest a slight increased risk of bacteremia in a potentially underpowered study, this apparent effect diminished as we added the number of operations as a post-exposure proxy adjustment for potentially unmeasured confounders like severity of injury. Considering that we also observed a statistically non-significant effect suggesting a benefit of bromelain on mortality, we regarded a potentially observed negative effect of topical bromelain on bacteremia as most likely to be caused by unmeasured confounders.

To our knowledge, our study is the first to specifically explore the relationship between topical bromelain use and bacteremia in patients with severe burns. Given the lack of data for comparisons, it is uncertain how our findings relate to other contexts or populations. Nevertheless, we identified similar pathogens as reported in other studies, including *Staphylococcus aureus*, *Staphylococcus epidermidis*, Enterobacterales, *Streptococcus mitis*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*. A previous study investigating the microbial profile of burn wounds managed with enzymatic debridement did not find substantial differences between wounds treated with NexoBrid® in comparison to those with surgical debridement alone [11], which is consistent with our findings focusing on invasive bacterial disease. Both pieces of research reinforce the notion that NexoBrid® can be used without the concern of changing the underlying bacterial landscape of burn wounds. The median time to a first bacteremia in our study was 6 days, closely resembling the reported medians of 7 to 8 days in other research [18,19].

In light of our findings, a previously reported increased incidence of fever and sepsis associated with the use of topical bromelain [20], may warrant reevaluation. The absence of a clear link between bromelain application and increased bacteremia risk in our cohort suggests that the occurrence of fever and sepsis might not primarily be due to increased bacterial invasion. Instead, these systemic reactions might have resulted from a non-infectious inflammatory response to the bromelain treatment or the extracellular matrix fragments resulting from its enzymatic activity.

Our study has several strengths. First, our study was conducted at the largest specialised burn ICU in Switzerland, ensuring better standardisation of treatments and documentation within our cohort due to the centre's expertise and focus on burn care. Second, the high-resource setting with very high hygienic standards limited the influence of other nosocomial sources on bacteremia, providing a more controlled environment to study the association between topical bromelain and bacteremia. Third, we employed a competing risk regression model to account for the high mortality rate in severely burned patients, which allowed for a more accurate analysis of the relationship between topical bromelain and bacteremia in this population. Finally, to our knowledge, our study is the first to investigate the association between topical bromelain and bacteremia in patients with severe burn injuries, contributing fresh insights into the safety profile of topical bromelain use.

Our study also has several limitations. First, the retrospective observational design inherently limits the ability to infer causality and likely introduced biases due to reliance on previously collected data. Second, there is likely unmeasured confounding due to the limited number of variables available for adjustment, which may impact the accuracy of our findings. Third, we did not examine a dose-effect relationship and timing of bromelain application, which could provide additional insights into the association between topical bromelain and bacteremia. Fourth, the absence of evidence for an association between bromelain and bacteremia should not be considered strong evidence of absence for such an association, implying that further research may still reveal a relationship. Fifth, the retrospective nature of our study precluded the collection of specific data on the bromelain treatment timing and treatment areas, nor could we ascertain the extent of surgical necrosectomy in individual patients, which restricts our ability to fully understand individual treatment variations and their potential impacts on patient outcomes. Finally, our study did not include microbiologic samples of burned skin related to bacteremia in the same patient, which could provide a more direct and potentially causal link between the use of topical bromelain and the development of bacteremia.

5. Conclusion

In conclusion, the results of our study provide evidence that enzymatic debridement using topical bromelain is unlikely to be associated with an increased risk of bacteremia in

critically ill patients with severe burn injuries. This finding can help inform clinical decision-making and contribute to the development of evidence-based practices for burn wound management. Future research should prospectively gather more information on potential risk factors for bacteremia that could serve as confounders in an association with bromelain use. Additionally, further studies should focus on identifying colonising bacteria in burnt skin and their connection to bacteremia, in order to establish a potentially causal link.

Given the minimal likelihood that enzymatic debridement by bromelain truly causes bacteremia, the implementation of a randomised controlled trial to further investigate this association may not be deemed practical. Nonetheless, in the event of a more extensive randomised clinical trial designed to further elucidate the benefits of topical bromelain, it would be crucial to integrate the evaluation of a potential causal risk of bacteremia within such a study's safety assessment.

Ethics Approval and Consent to Participate

The ethics committee of the Canton Zurich approved the study protocol (Kantonale Ethikkommission Zurich BASEC ID 2017–01681). All patients (or their legal representatives in case of incapability of judgement) agreed to participate. All research was carried out in accordance with Good Clinical Practice (GCP) standards. The data required for this study were anonymized before their use.

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Declaration of Competing Interest

All authors declare to have no conflict of interest.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used ChatGPT (GPT-4) by OpenAI for text editing and language clarification, and Google Documents for real-time collaboration during the drafting process. It's important to note that ChatGPT was not used for analysis, intellectual content or literature review. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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Consent for publication

Not applicable.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.burns.2023.12.005.

REFERENCES

[1] Greenhalgh DG, Saffle JR, Holmes JH, Gamelli RL, Palmieri TL, Horton JW, et al. American burn association consensus conference to define sepsis and infection in burns. J Burn Care Res 2007;28(6):776–90.
[2] Jeschke MG, Pinto R, Kraft R, Nathens AB, Finnerty CC, Gamelli RL, et al. Morbidity and survival probability in burn patients in modern burn care*. Crit Care Med 2015;43(4):808–15.
[3] Greenhalgh DG. Management of burns. New Engl J Med 2019;380(24):2349–59.
[4] Datta PK, Chowdhury SR, Aravindan A, Saha S, Rapaka S. Medical and surgical care of critical burn patients: a comprehensive review of current evidence and practice. Cureus 2022;14(11):e31550.
[5] Gurfinkel R, Rosenberg L, Cohen S, Cohen A, Barezovsky A, Cagnano E, et al. Histological assessment of tangentially excised burn eschars. Can J Plast Surg J Can Chir Plast 2010;18(3):e33–6.
[6] Rosenberg L, Krieger Y, Bogdanov-Berezovski A, Silberstein E, Shoham Y, Singer AJ. A novel rapid and selective enzymatic debridement agent for burn wound management: a multicenter RCT. Burns 2014;40(3):466–74.
[7] Bernagozzi F, Orlandi C, Purpura V, Morselli PG, Melandri D. The enzymatic debridement for the treatment of burns of indeterminate depth. J Burn Care Res 2020;41(5):1084–91.
[8] Hirche C, Almeland SK, Dheansa B, Fuchs P, Governa M, Hoeksema H, et al. Eschar removal by bromelain based enzymatic debridement (Nexobrid®) in burns: European consensus guidelines update. Burns 2020;46(4):782–96.
[9] Loo YL, Goh BKL, Jeffery S. An overview of the use of bromelain-based enzymatic debridement (Nexobrid®) in deep partial and full thickness burns: appraising the evidence. J Burn Care Res 2018;39(6):932–8.
[10] Park HS, Pham C, Paul E, Padiglione A, Lo C, Cleland H. Early pathogenic colonisers of acute burn wounds: A retrospective review. Burns 2017;43(8):1757–65.
[11] Sharaf A, Muthayya P. Microbial profile of burn wounds managed with enzymatic debridement using bromelain-based agent, NexoBrid®. Burns 2022;48(7):1618–25.
[12] Hofmaenner DA, Steiger P, Schuepbach RA, Klinzing S, Waldner M, Klein H, et al. Safety of enzymatic debridement in extensive burns larger than 15% total body surface area. Burns 2021;47(4):796–804.
[13] Hirche C, Citterio A, Hoeksema H, Koller J, Lehner M, Martinez JR, et al. Eschar removal by bromelain based enzymatic debridement (Nexobrid®) in burns: An European consensus. Burns 2017;43(8):1640–53.
[14] Frey PM, Marti GR, Droz S, Arx M, de R, von, Suter-Riniker F, et al. Bacterial colonization of handheld devices in a tertiary care setting: a hygiene intervention study. Antimicrob Resist Infect Control 2019;8(1):97.
[15] Fine J, Gray R. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 1999;94(446):496–509.

[16] Groenwold RHH, Klungel OH, Altman DG, Graaf Y van der, Hoes AW, Moons KGM. Adjustment for continuous confounders: an example of how to prevent residual confounding studies]) PW (Pharmacoepidemiological R on O of T by a EC Work Programme 2 [Framework for pharmacoepidemiology. Can Med Assoc J 2013;185(5):401–6.

[17] Groenwold RHH, Palmer TM, Tilling K. To adjust or not to adjust? When a "confounder" is only measured after exposure. Epidemiol Camb Mass 2021;32(2):194–201.

[18] Patel BM, Paratz JD, Mallet A, Lipman J, Rudd M, Muller MJ, et al. Characteristics of bloodstream infections in burn patients: an 11-year retrospective study. Burns 2012;38(5):685–90.

[19] Hu Y, Li D, Xu L, Hu Y, Sang Y, Zhang G, et al. Epidemiology and outcomes of bloodstream infections in severe burn patients: a six-year retrospective study. Antimicrob Resist Infect Control 2021;10(1):98.

[20] Leelakanok N, Petchsomrit A, Janurai T, Saechan C, Sunsandee N. Efficacy and safety of bromelain: a systematic review and meta-analysis. Nutr Heal 2023. 026010602311737.