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Recent Progress in Nutrition

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Review

Nutritional Profile and Topic Management for Wound Healing in Children with Epidermolysis Bullosa: What Is the Evidence? A Systematic Review

Maria Lúcia dos Santos, Ana Cristina Monteiro, Andréa Nascimento, Sívia Barbosa, Artur Delgado, Patrícia Zamberlan *

Instituto da Criança e do Adolescente do Hospital das Clínicas - Faculty of Medicine/University of Sao Paulo, Butantã, SP, Brazil; E-Mails: maria.maia@hc.fm.usp.br; ana.csmonteiro@hc.fm.usp.br; andrea.nascimento@hc.fm.usp.br; silvia.barbosa@hc.fm.usp.br; artur.delgado@hc.fm.usp.br; patricia.zamberlan@hc.fm.usp.br

* **Correspondence:** Patrícia Zamberlan; E-Mail: patricia.zamberlan@hc.fm.usp.br

Academic Editor: Amy Anne D. Lassig

Special Issue: Clinical Nutrition: Recent Advances and Remaining Challenges in Aiding Acute Surgical or Traumatic Wound Healing

Recent Progress in Nutrition
2024, volume 4, issue 3
doi:10.21926/rpn.2403010

Received: April 11, 2024
Accepted: July 09, 2024
Published: July 17, 2024

Abstract

Epidermolysis Bullosa (EB) is a rare genetic disorder characterized by fragile skin that blisters and tears easily, leading to significant morbidity and mortality. Depending on the specific genetic mutations and the proteins involved, EB can be classified into several subtypes whose molecular complexity is compounded by the variability in mutation types (missense, nonsense, insertions, deletions), their locations within the genes, and the resultant effects on protein function. This systematic review aimed to identify and synthesize available evidence on wound healing interventions and the nutritional profile of children diagnosed with EB. A comprehensive search yielded 28 articles, including 21 clinical trials and seven observational studies, encompassing 994 patients with various EB subtypes. The majority of studies described subtypes such as Simplex EB (EBS), Junctional EB (JEB), Dystrophic EB (DEB), and EB Kindler. The primary interventions for wound healing included dressings with collagen, biocellulose, and various topical creams. Nutritional assessment was limited, with only six

studies examining nutritional status, predominantly through anthropometry and dietary intake analysis. Subgroup analyses indicated higher malnutrition rates among patients with DEB compared to JEB. The review underscores the importance of addressing wound healing and nutritional challenges in EB management. Further research is needed to explore effective interventions and optimize care for this vulnerable population.

Keywords
Nutrition; pediatrics; wound healing; epidermolysis bullosa

1. Introduction

Wounds acquired as a result of genetic diseases such as EB are challenging to treat, as the drugs used, whether topical or not, tend to stabilize them momentarily. They often reappear whenever there is a care failure and can occur spontaneously during daily tasks [1].

Epidermolysis bullosa (EB) is a group of rare, inherited skin disorders characterized by extreme fragility of the skin and mucous membranes, leading to blisters and erosions in response to minor mechanical trauma or friction. Mutations in genes responsible for the structural integrity and adhesion of the skin layers cause this condition. Depending on the specific genetic mutations and the proteins involved, EB can be classified into several subtypes, varying in severity and clinical presentation. Despite the passing years and several emerging researches, there is still no cure; topical therapies may help alleviate some symptoms and discomfort, improving patients' quality of life [1, 2].

This class of skin disease is comprehensive and can be divided according to the degree of phenotypic manifestations and the level of tissue separation within the cutaneous basement membrane zone [3]. The molecular complexity of these subtypes is compounded by the variability in mutation types (missense, nonsense, insertions, deletions), their locations within the genes, and the resultant effects on protein function. This complexity leads to a wide range of clinical manifestations, from mild blistering to severe, life-threatening conditions, and necessitates tailored approaches to diagnosis, management, and potential therapeutic interventions. The four main types are EBS, JEB, DEB, and EB Kindler, which are differentiated by the level of blister cleavage and subdivided according to the pattern of genetic inheritance, lesion morphology, and involved genetic mutation [1-4]:

- EBS: This subtype is typically caused by mutations in the KRT5 and KRT14 genes, which encode keratin proteins K5 and K14. These proteins are crucial for the structural stability of the epidermal keratinocytes;
- JEB: This subtype is associated with mutations in genes such as LAMA3, LAMB3, LAMC2, and COL17A1, which encode components of the hemidesmosomes and anchoring filaments, such as laminin-332 and type XVII collagen. These mutations disrupt the adhesion between the epidermis and the dermis, causing blistering at the level of the lamina lucida within the basement membrane zone;
- (DEB): This subtype is caused by mutations in the COL7A1 gene, which encodes type VII collagen, a critical component of anchoring fibrils that secure the epidermis to the dermis.

DEB can further be divided into two subtypes: recessive and dominant. Recessive DEB (RDEB) is the most severe type, transmitted when both parents carry the defective gene, and Dominant DEB (DDEB) can be transmitted if only one parent carries the faulty gene, and it typically presents with milder clinical symptoms,

- EB Klinder: This rare subtype involves mutations in the FERMT1 gene, which encodes kindlin-1, a protein essential for cell adhesion, signaling, and cytoskeletal organization.

The most important aspects for children with EB are care-related, including proper wound management and dressing changes. Skin protection measures are also vital to decrease tissue rupture. Children are usually active and engage in constant movement inherent to their age, which results in more skin lesions and thus should be avoided, as friction and shear forces can exacerbate blister formation.

Nutrition plays a vital role in symptom control and proper wound healing, which may be compromised by malnutrition, itching, and pain. A balanced diet rich in proteins, vitamins, and minerals aids in wound healing and improves the immune system's performance. Children with EB have an increased risk of developing infections, anemia, and growth deficits, and therefore, nutrition seems promising in treatment [5]. Personalized nutritional interventions are necessary for patients with EB and monitoring by specialists, given the importance of managing the nutritional alterations and deficiencies the patient faces, thus ensuring well-being and quality of life.

The involvement of various specialists is necessary for maintaining care, as well as close monitoring by a multidisciplinary team including physicians, nutritionists, nurses, psychologists, therapists, pharmacists, and physiotherapists, who should work closely together to ensure that the patient's needs are met and that the care plan is adjusted as necessary. For effective wound management associated with EB, professionals must understand the underlying causes and contributing factors to its development [3, 5, 6].

Advances in research and treatment options offer hope that children with EB may have a better quality of life, with minimized symptoms and maximized comfort and well-being.

1.1 Review Question

What is the nutritional status of children with EB, and what are the available and effective treatments for wound healing?

1.2 Objectives

- To identify and synthesize the available evidence on wound healing in patients with EB;
- To describe the nutritional profile of children diagnosed with EB.

2. Material and Methods

This systematic review was conducted following the guidelines of the Joanna Briggs Institute and The PRISMA [7, 8].

2.1 Eligibility Criteria

2.1.1 Participants

Patients up to 19 years old, with no gender, race, and/or socioeconomic status restrictions, were diagnosed with EB undergoing wound treatment.

2.1.2 Interventions

This review considered studies that used dressings, bandages, and/or ointments with pharmacological or non-pharmacological principles to heal wounds and evaluated the nutritional status, wound area, presence of wound infection, and time to wound healing in patients with EB. The interventions were used independently and/or in combination. All interventions used for wound healing in patients with EB were included.

2.1.3 Comparators

The usual care described in the primary studies, such as saline solution, placebo, and non-adherent gauze, were considered comparators.

2.1.4 Outcomes

This review considered studies that assessed the nutritional status, types of topical wound treatments, time to wound healing, wound area, and presence of wound infection.

2.1.5 Types of Studies

Included were studies with a multicenter randomized clinical trial design, single-center randomized clinical trial design, retrospective observational study, longitudinal study, and cross-sectional study.

2.2 Search Strategy

The search strategy was conducted in three stages to identify published and unpublished studies. The search was limited to 1 January 1984 to 31 January 2024. The same search strategy was used for all databases included in the survey (considering the controlled language of each). These databases included Web of Science, LILACS, EMBASE, CINAHL, Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, and the Brazilian Registry of Clinical Trials. ProQuest and the Brazilian CAPES Thesis Database were searched to identify unpublished studies. The following descriptors were used: Epidermolysis Bullosa, Wound Healing, Nutritional Status, Malnutrition, Nutritional Support, and Children.

2.2.1 Study Selection

The searches identified during the search were uploaded to the reference manager myendnoteweb.com (Clarivate Analytics, PA, USA), and duplicates were removed. Titles and abstracts were screened by two independent reviewers, guided by inclusion and exclusion criteria.

Two independent reviewers reviewed full texts. There was no disagreement at this stage, and the search and selection process is described in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [7] flow diagram.

2.2.2 Quality Assessment

Two independent reviewers conducted the methodological quality assessment. For studies with a randomized controlled trial design, the Risk of Bias 2 (RoB 2) tool from Cochrane [8] was used, comprising five questions that assess bias related to the randomization process, deviation from planned interventions, missing outcome data, outcome measurement bias, and bias in the selection of reported results. For studies with a quasi-experimental design, the checklist for quasi-experimental studies (non-randomized experimental studies [9]) was utilized, consisting of nine questions that evaluate the clarity of cause and effect relationships, similarity between treatment groups, and variation in outcome measures. The certainty of evidence was assessed using GRADEPro [10].

2.2.3 Data Extraction

Data were extracted from the studies by two independent reviewers using the standardized data extraction tool in Joanna Briggs [11]. The extracted data included specific details about the participants (age, gender, subtype of EB, type of intervention, measured outcomes, country and year of publication, wound size, time to wound healing, and nutritional status). There were no disagreements between the reviewers at this stage. The results of the extraction of the studies were reported in the form of narrative synthesis and tables and odds ratio.

2.2.4 Data Synthesis

The data were combined using the standardized mean difference (SMD) and the random-effects model [12], a meta-analysis approach to standardize and combine the results of studies that assessed the same outcome but measured it differently [13]. For the combination of dichotomous data, the odds ratio (OR) and the fixed-effects model were used in the absence of significant heterogeneity ($I^2 \leq 50\%$). In contrast, the random-effects model was chosen despite considerable heterogeneity [14].

Heterogeneity among studies was assessed using the I^2 test, with statistical significance at $p < 0.05$. I^2 values ranging from 0% to 25% indicate low heterogeneity, 25% to 75% moderate heterogeneity, and greater than 75% high heterogeneity.

Studies were included in the meta-analysis if the measured results were sufficiently similar to be combined and contained sufficient data.

The meta-analysis results were presented using forest plots, and the potential publication bias of included studies was assessed using funnel plots. Statistical calculations were performed using Review Manager software version 5.4.1 from Cochrane [15].

The certainty of evidence was assessed using the GRADEPro [10] system, as summarized in Table 1.

Table 1 Recommendation grades for the certainty of evidence from studied outcomes in the review.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Topical treatment**	**usual care**	**Relative (95% CI)**	**Absolute (95% CI)**		
Topical treatment for wound healing												
4	RCTs	serious	not serious	serious	serious	none	240	242	-	SMD **0.82 SD lower** (1.26 lower to 0.38 lower)	⨁◯◯◯ Very low	IMPORTANTE
Proportion of wounds healed within 30 days												
3	RCTs	serious	very serious	not serious	not serious	publication bias strongly suspected	140/219 (63.9%)	174/234 (74.4%)	**OR 0.57** (0.29 to 1.12)	**121 fewer per 1.000** (from 287 fewer to 21 more)	⨁◯◯◯ Very low	IMPORTANTE
Proportion of wounds healed in 60 days												
4	RCTs	serious	very serious	not serious	not serious	publication bias strongly suspected	125/233 (53.6%)	147/242 (60.7%)	OR 0.75 (0.52 to 1.08)	70 fewer per 1.000 (from 162 fewer to 18 more)	⨁◯◯◯ Very low	IMPORTANTE
Proportion of wounds healed in 90 days												

4	RCTs	serious	very serious	not serious	not serious	publication bias strongly suspected	119/234 (50.9%)	121/230 (52.6%)	OR 0.95 (0.66 to 1.39)	13 fewer per 1.000 (from 103 fewer to 81 more)	⊕◯◯◯ Very low	IMPORTANTE
Effect of topical treatment on itchiness control												
4	RCTs	serious	very serious	not serious	not serious	publication bias strongly suspected	14/227 (6.2%)	16/234 (6.8%)	OR 0.92 (0.41 to 2.06)	5 fewer per 1.000 (from 39 fewer to 63 more)	⊕◯◯◯ Very low	IMPORTANTE
Effect of topical treatment on infection control												
4	RCTs	serious	very serious	serious	serious	publication bias is strongly suspected	14/227 (6.2%)	46/234 (19.7%)	OR 0.36 (0.13 to 1.02)	116 fewer per 1.000 (from 166 fewer to 3 more)	⊕◯◯◯ Very low	IMPORTANTE
Malnutrition by subtype of EB												
5	RCTs	serious	very serious	serious	not serious	publication bias is strongly suspected	12/37 (32.4%)	108/183 (59.0%)	OR 0.40 (0.20 to 0.82)	225 fewer per 1.000 (from 367 fewer to 49 fewer)	⊕◯◯◯ Very low	IMPORTANTE

CI: confidence interval; OR: odds ratio; SMD: standardized mean difference

Results were presented descriptively in tables and figures for studies not included in the meta-analysis.

3. Results

3.1 Search and Selection of Studies

Through a database search, 1044 articles were identified. After examining titles and abstracts, 994 articles were considered out of this review's scope and were excluded. Further screening was performed by reading the full text, and 16 articles were found to be non-eligible. After a second evaluation, 5 articles were excluded due to: participants over 19 years old (n =2) and articles just about the pharmacodynamic profile of the medicine used in the treatment (n = 4). Finally, 28 articles met the inclusion criteria and were finally considered in the present systematic review.

Figure 1 displays the flowchart for the assessment and eligibility of the studies included in the review.

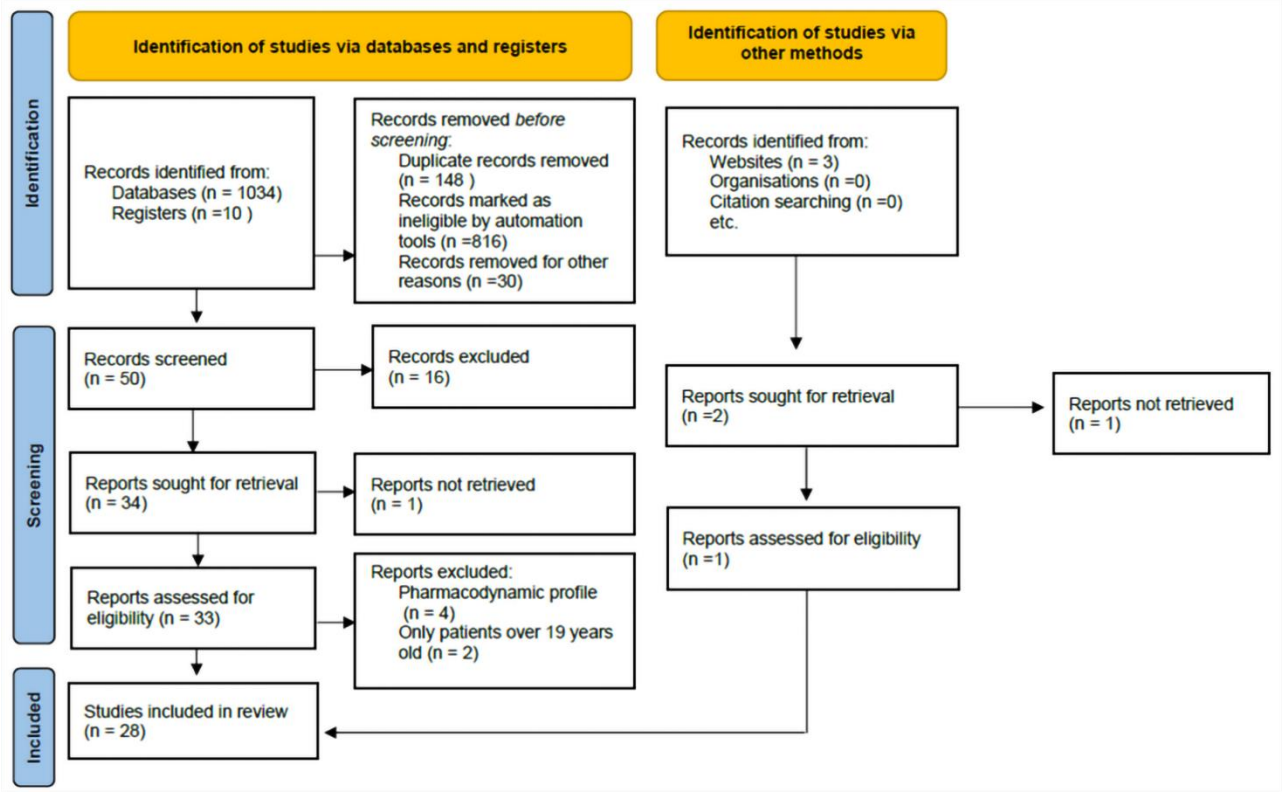

Figure 1 Flow diagram of studies assessed for eligibility per screening stage. (From Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ. 2021; 372: n71. doi: 10.1136/bmj.n71. [7].

3.2 Characteristics of Included Studies

The selected studies for the review are described in Table 2.

Table 2 Characteristics of the studies included in the review.

Author, Year, Journal	Study design	Sample	Intervention	Assessment nutritional status?	Mains results
Dwiyana et al., [16] 2019 J Wound Care	Blind, randomized, and controlled clinical trial	36 wounds from 4 patients, all male. The median age was 10.25 (1 - 23) years	Group 1. Biocellulose dressing Group 2. Carboxymethylcellulose dressing Group 3. Saline solution dressing (control)	NO	Mean healing time in group 1 was seven days, eight days in group 2 and 14 days in group 3. There were significant differences in healing times between group 1 and group 3 (p = 0.0001) and between group 2 and 3 (p = 0.001). The results showed a significant reduction in the percentage of wounds area on day three for each group: 51.7% in group 1, 51.9% in group 2, and 26% for group 3. All wounds in groups 1 and 2 had healed at day 12 (100%) and at day 24 (100%) in group 3. There were significant differences in the reduction of percentage wound area between group I and group 3 at day 3 (p = 0.044) and day 6 (p = 0.000), and between group 2 and 3 at day 6 (p = 0.003).
Dwiyana et al., [17] 2019 Dermatol Ther	Single-blind controlled trial	14 infected EB wounds of 5 patients (4 male and 1 female patients), clinically diagnosed as EB.	Group 1. Coated cotton acetate dressing (CCAD)(Cutimed Sorbact®) Group 2. a combination of normal saline dressing and 2% mupirocin ointment.	NO	The average time required for complete wound closure was 8.6 and 11.1 days in Groups 1 and 2, respectively (p = 0.014), which was statistically significant. Both groups showed complete bacterial elimination on day 3 based on negative Gram stain results and on day 6 based on clearance of clinical manifestations (p = 1.000).
Blanchet-Bardon et al., [18] 2005 J Wound Care	Open-label uncontrolled clinical trial	20 patients (11 adults and 9 children) with EB simplex or DDEB, if they presented with at least one skin lesion requiring management with a	Urgotul dressing size 10 × 10	NO	All patients completed the trial. 19 out of 20 wounds healed within 8.7 ± 8.5 days. Overall, 11 patients (55%) considered that their quality of life had improved following use of the dressing, which was also reported to be pain free and 'very easy' or 'easy' to remove at most dressing changes. 19 out of 20 patients stated

		non-adherent wound dressing.			that they would use the study dressing to manage their lesions in future.
Schwieger-Briel A et al., [19] 2017 Dermatol Res Pract	Open, blindly evaluated, controlled, prospective phase II pilot trial	10 patients with diagnosis of hereditary EB and at least 1 wound between 10 cm^2 and 200 cm^2 (alternatively 2 comparable lesions of at least 5 cm^2 each). The median age of patients was 20 years (range: 6–48 years).	Group 1. Oleogel-S10 + non-adhesive dressing. Group 2. Non-adhesive dressing alone	NO	20 wound pairs of 10 patients with DDEB were evaluated. In 5 of 12 cases, both blinded reviewers considered epithelialization of the intervention wounds as superior. In 3 cases, only one reviewer considered Oleogel-S10 as superior and the other one as equal to control. Measurements of wound size showed a trend towards accelerated wound healing with the intervention but without reaching statistical significance.
Kern et al., [20] 2023 Br J Dermatol	Double-blind, randomized, vehicle-controlled, phase III study	223 patients with DD EB, JEB or Kindler EB and a target partial-thickness wound lasting ≥21 days and <9 months that was 10-50 cm^2	Oleogel-S10 or control gel - both with standard-of-care dressings. Study gel was applied to all wounds at least every 4 days.	NO	109 treated with Oleogel-S10, 114 with control gel. The primary endpoint was met; Oleogel-S10 resulted in 41.3% of patients with first complete target wound closure within 45 days, compared with 28.9% in the control gel arm (relative risk 1.44, 95% confidence interval (CI) 1.01-2.05; P = 0.013).
Kern et al., [21] 2019 Trials	Double-blind, randomized, placebo-controlled	96 patients Aged ≥4 to 11 years	Group 1: Oleogel-S10 (10% birch bark triterpenes) Group 2: Placebo	NO	No results. Only study protocol information.
Torres et al., [22] 2024. Adv Ther	Observational retrospective study	13 patients diagnosed with EB. Most subjects were female (69.2%), and the mean age	Oleogel-S10	NO	Reduction in percentage of body surface area percentage (BSA) affected, from a mean of 27.3% at baseline to 10.4% at 24-month follow-up, despite treatment interruptions. A reduction in total body wound burden (BDASI) skin activity score of - 16.2 (24 months) together with a reduced skin damage index score of - 15.4 (18 months) was also observed.

		was 19 years (ranging from 3 to 53).			
Murrell et al., [23] 2020 Orphanet J Rare Dis	Multicenter, randomized, double-blind, vehicle-controlled, phase 3 trial	87 pacients, mean age 13.9 years	Group 1. SD-101 6% is a topical cream containing 6% allantoin in an oil-in-water emulsion. Group 2. SD101 6% or vehicle	NO	Mean time to target wound closure within 3 months was 53.6 days, with a range of 14 to 142 days. The proportion of patients with target wound closure increased over time from 7.1% at day 14 to 53.6% at month 3. Mean (SD) changes from baseline in body surface area percentage (BSA) of total wound burden and BSA of lesional skin at month 3 were −2.3% (6.3) and −5.0% (13.5) of total body coverage, respectively.
Gorell et al., [24] 2015 Pediatr Dermatol	Clinical trial	10 patients (7 completed the study). The age ranged from 8 to 24 years.	Natural purified type I collagen skin substitute	NO	6 subjects showed a positive response to the type I collagen skin substitute. 3 subjects demonstrated full wound reepithelialization. Woundstreated using the collagen skin substitute showed statistically significantly greater improvement. Average scores for pruritus and pain decreased significantly.
Paller et al., [25] 2020 Orphanet J Rare Dis	Phase 3, multicenter, randomized, double-blind, vehicle-controlled study	169 patients were enrolled and randomly assigned to SD-101 6% (n = 82) or vehicle (n = 87). Mean age 13.8 years.	SD-101 6% (allantoin) or vehicle	NO	There were no statistically significant differences between treatment groups in time to target wound closure (hazard ratio, 1.004; 95% confidence interval [CI] 0.651, 1.549; P = 0.985) or proportion of patients with complete target wound closure within 3 months (odds ratio [95% CI], 0.733 [0.365, 1.474]; nominal P = 0.390). A positive trend toward faster wound closure with SD-101 6% versus vehicle was observed in patients aged 2 to <12 years and those with total body wound burden ≥5% at baseline.
Teng et al., [26] 2023 J Drugs Dermatol	Clinical trial	Follow-up for 12 weeks. 8 patients, 4 in the placebo group and 4 in the intervention group.	Group 1: Sirolimus 2% Group 2: Placebo	NO	The EBDASI index increased from 2.6 to 2.9 after 12 weeks in the Sirolimus treatment group and decreased from 3.5 to 2.5 in the placebo group. The itching scale varied from 12.8 to 12.5 and

		5 females and 3 males.			from 11.5 to 11.8 in the Sirolimus and placebo groups, respectively.
Niazi et al., [27] 2022 Dermatol Pract Concept	Single-arm, uncontrolled clinical trial	7 patients (3 boys and 4 girls). The age range of the patients was 5-32 years.	1% henna ointment once daily for 4 weeks	NO	There was a significant improvement in the skin symptoms of EB including skin redness, itching, burning, and local warmness ($P < 0.05$).
Guttmann-Gruber et al., [28] 2021 Orphanet J Rare Dis	Two-armed, double blind, randomized, cross-over phase II study.	6 patients, aged ≥6 years and with a known mutation in the COL7A1 gene	0.05 µg/g calcipotriol ointment or placebo for 4 weeks	NO	Topical low-dose calcipotriol treatment led to a signifcant reduction in wound area at day 14 compared to placebo (88.4% vs. 65.5%, $P < 0.05$). Patients also reported a signifcant reduction of pruritus with calcipotriol ointment compared to placebo over the entire course of the treatment as shown by itch scores of 3.16 vs 4.83 ($P < 0.05$) and 1.83 vs 5.52 ($P < 0.0001$) at days 14 and 28, respectively.
Heo et al., [29] 2023 Drugs	Double-blind clinical trial	Subtypes of EB: DDEB, JEB and Kindler. Mean age: 12 years.	Group 1. 10% Birch Bark Extract (Oleogel-S10) Group 2. Control gel	NO	There was a higher proportion of wound closure in the Oleogel-S10 group compared to the control group at 45 days.
Petrof et al., [30] Br J Dermatol 2013	Prospective, double-blind, randomized, vehicle-controlled phase II trial.	26 erosions in 11 subjects with RDEB	Single treatment of 5×10^6 fibroblasts per linear cm of erosion margin or vehicle.	NO	Treatment difference between fibroblasts and vehicle was -23.5% [95% confidence interval (CI) -3.5 to -43.5, $P = 0.025$] at day 7, -19.15% (95% CI 3.36 to -41.66, $P = 0.089$) at day 14 and -28.83% (95% CI 7.97 to -65.63, $P = 0.11$) at day 28. Beyond day 28, however, changes in mean erosion area did not differ significantly between the two groups.
Therapeuticsl., [31] 2020 Clinicaltrial	Phase 2b, multi-center, randomized, double-blind, vehicle-controlled study	Ages 9 to 15 years. 2 female and 26 male. EBS, JEB and DDEB.	Group 1. 6% Allantoin Cream Group 2. 3% Allantoin Cream Group 3. Vehicle without allantoin 0%	NO	After 3 months, complete wound closure was observed in 60%, 56.3%, and 52.9% in groups 1, 2, and 3 respectively. The change in BSAI was -28.02 in group 1, -42.52 in group 2, and -5.75 in group 3. The pain score was 0.91, -0.7, and 1.08 in groups 1, 2, and 3 respectively.

Tsaqilah et a., [32] 2023 Clin Cosmet Investig Dermatol	Retrospective descriptive study	12 patients (6 girls and 6 boys) - mean of 3.8 ± 4.7 years old	N/A	YES	12 pediatric EB patients consisting of 7 DDEB (4 RDEB patients and 3 DDEB, 3 JEB and 2 EBS. The most extensive EB wounds was found affecting 10–20% of the body surface area with a <10% infected wound area. Pain was found in all patients. The most frequent abnormalities in laboratory examination were anemia and low zinc levels. Severe malnutrition was found in almost half of the patients.
Haynes [33] 2006 BrJ Nurs		Paper that describes some of the issues involved in optimizing the nutritional status of children with EB.	N/A	NO	Nutritional support is an important aspect of the multi-faceted care that children with EB need. Successful nutritional support relies on close cooperation with fellow members of specialist teams who can formulate workable management strategies that can help families
Marchili et al., [34] 2022 Orphanet J Rare Dis	Retrospective	160 pediatric EB patients (76 male and 84 female): 31 patients afected by EBS (mean age ± SD: 4.37 ± 7.14), 21 patients afected by JEB (mean age ± SD: 9.26 ± 17.30) and 108 with DDEB (mean age ± SD: 11.61 ± 13.48).	N/A	YES	Malnutrition was detected in a percentage of 50% of the total sample. A defcit of total protein and serum albumin was also detected. Vitamin D defciency was mostly observed in patients older than 10 years old afected by DDEB. Anemia was detected in 66 patients (41.3%), 51 of whom were afected by 148 DDEB (77.2%). Te most afected patients were aged less than 1 years (46.9%), followed by those older than 20 years (31.8%).
Manjunath et al., [35] 2021 Sci Rep	Single center, prospective longitudinal study	57 patients. Median age was 3 years.	N/A	YES	Malnutrition was seen in 40.35% patients (22.81%-moderate and 17.54%-severe), and signifcantly correlated with iscorEB ($r = 0.45$, $p < 0.0001$). On bivariate regression analysis, iscorEB was independently associated with moderate-to-severe malnutrition

					(p = 0.047; OR 1.038, CI 1.011–1.066). iscorEB enabled the identifcation of patients with moderate-to-severe malnutrition with an Area Under Receiver Operating Curve (AUROC) of 0.72 (95%CI 0.58–0.85; p < 0.005). In phase 2, there was signifcant improvement in nutritional status in children with RDEB and DDEB subtype (p < 0.0001). The severity of malnutrition in EB children signifcantly correlates with disease severity, and is an independent predictor of moderate-to-severe malnutrition.
Yavuz et al., [36] 2023 Medicina	Prospective study	26 patients (11 female and 15 male). The age ranged from 0.2 to 30 years.	N/A	YES	100% of the cases had a history of consanguinity to varying degrees, and 50% of the cases had a sibling with EB. Malnutrition was observed in 80.7%, and anemia in 46%
Morales-Olvera et al., [37] 2022 Nutr Clín Diet Hosp	Cross-sectional retrospective study	17 patients with a mean age of 8.4 years (SD 4.6)	N/A	YES	82.3% had malnutrition. Those with more severe subtypes,junctional and recessive dystrophic EB, had acute superim-posed on chronic malnutrition (100% and 63.4% respec-tively), wasting (100% and 72.6%), and stunting (0% and 54.4%) more frequently. Most patients required supplemen-tation (caloric 76.4% and vitamin/mineral 100%)
Zidório et al., [38] 2023 Nutr Hosp	Cross-sectional, analytical study	7 patients (5 female and 2 male) aged up to 18 years.	N/A	YES	All patients showed undernutrition and presented at least three clinical symptoms that affect food consumption: pseudosyndactyly, microstomy, and blisters in the oral cavity. Sip feed constituted between 20% and 50% of the patients' energy intake. Intake of iron and zinc was adequate for most patients (confidence of adequacy ≥0.85), while fiber intake was below the reference value.
Fine et al., [39] 2008	Cross-sectional and longitudinal	450 patients with EB	N/A	NO	Esophageal strictures and growth retardation werecommonly seen among the more severe EB subtypes, mostnotably Hallopeau-Siemens recessive dystrophic EB, andoccurred as

J Pediatr Gastroenterol Nutr					early as within the first year of life. EB subtype-specific differences were also observed in the frequency ofoccurrence of other GI complications.
Wally et al., [40] 2018 J Am Acad Dermatol	Randomized, placebo-controlled, phase 2/3 trial	15 patients. The age ranged from 4 to 12 years	Placebo or the Diacerein 1% (2g/day) for a 4-week treatment and a 3-month follow-up in period 1	NO	The wound area was 4257 cm^2 in the intervention group and 5045 cm^2 in the control group. Diacerein reduced blisters by 70% when used for six weeks. One patient experienced blister recurrence in the 1% diacerein group.
Wally et al., [41] 2013 Orphanet J Rare Dis	Pilot study, open-label, withdrawal, controlled, randomized, and double-blind	5 patients with EBS	An open-label phase of six weeks with the application of 1% diacerein in the armpits in all patients. The second phase was randomized and placebo-controlled.	NO	Significant reduction in blisters during the first two weeks of Phase 1, which remained stable until the end of the study. In Phase 2, no loss of efficacy was observed.
Falabella et al., [42] 2000 Arch Dermatol	Open-label uncontrolled study	69 different acute wounds from 15 patients	Tissue-engineered skin	NO	69 different acute wounds received tissue-engineered skin at the day-1 (24 wounds), week-6 (23 wounds), and week-12 (22 wounds) visits. Overall, 63 wounds (79%) were found healed at the day-7 visit. Of the acute wounds, 82% (51/62) were healed 6 weeks after being treated, 75% (27/36) after 12 weeks, and 79% (11/14) after 18 weeks. Nine chronic wounds were also treated. Four were healed at 6 weeks; however, 7 were still open at the last clinic visit (week 18).
Gurevich et al., [43] 2022 Nat Med	Clinical trial	Safety - Phase 1, 2a, 2b, 2c (n = 9 individual subjects) Efficacy - Phase 1, 2a, 2b wound-based n = 28 wounds B-VEC-treated, n = 18	Gene therapy treatment - Beremagene geperpavec (B-VEC) or placebo for 12 weeks	NO	HSV-1 (herpes simplex virus type 1 vector) and C7 (collagen VII) antibodies sometimes presented at baseline or increased after B-VEC treatment without an apparent impact on safety or efficacy. Primary and secondary objectives of C7 expression, anchoring fibril assembly, wound surface area reduction, duration of wound closure, and time to wound closure following B-VEC treatment were met. A patient-reported pain–severity

		Placebo-treated, n = 10			secondary outcome was not assessed given the small proportion of wounds treated.
Spellman et al., [44] 2019	International, Multicenter, Randomized, Double-Blind, Parallel-Group Phase 2 Study	54 patients 30 females and 24 males	Group 1. Diacerein 1% cream Group 2. Placebo	NO	57.1% of patients in group 1 experienced a reduction of ≥60% in wounds at 8 weeks compared to 53.8% of patients in group 2.
Eisenberg et al., [45] 1986 J Pediatr Surg	Clinical trial	3 patients 1 female and 2 male Aged between 5 and 13 years DDEB	Group 1. An adhesive 1.5 mm tan opaque occlusive oxygen-impermeable hydrocolloid dressing. Group 2. Perforated, non-adhesive, oxygen-permeable plastic film covered by an absorbent layer. Group 3. Paraffin gauze, covered by an absorbent dressing.	NO	The hydrocolloid dressing adhered easily to the surrounding normal skin, and within 24 hours, the dressing portion over the wound was darker and softer than the adjacent areas.

DDEB: Dominant Dystrophic Epidermolysis Bullosa; EB: Epidermolysis Bullosa; SD: Standard deviation; N/A: Not applicable; EBS: Epidermolysis Bullosa Simplex; RDEB: Recessive Dystrophic Epidermolysis Bullosa

The 30 articles included in the review examined 994 patients with Epidermolysis Bullosa, with 21 conducted as clinical trials [16, 24-31, 40-45] and seven conducted as observational studies [22, 32, 34-38]. The majority of them described the disease subtypes as Simplex EB (EBS) [17, 18, 20, 23, 25, 32, 34, 36, 39, 41, 42], Junctional EB (JEB) [17, 20, 21, 23, 25, 29, 32, 34-37, 41, 42], Dystrophic EB (DDEB) [17-22, 24, 25, 29, 31, 32, 34, 35, 37, 38, 42, 45] and Kindler [21, 29, 31]. Of the studies that contained information on gender, 415 (41.7%) patients were female, and 450 (45.3%) were male.

The central interventions studied in the primary research for wound healing varied from dressings and coverings with collagen [24], cellulose [16], carboxymethylcellulose [16], cotton acetate [17], 1% mupirocin creams [17], 10% birch triterpenes [20, 22, 25, 29], 3% and 6% allantoin [23, 25, 31], diacerein [26, 40, 41, 44], 1% henna [27], calcitriol [30], fibroblasts [30], hydrocolloid (HCD) [45], tissue-engineered skin [42].

Of the studies included in the review, only 6 assessed the nutritional status [32, 34-38], with 5 demonstrating the nutritional condition by subtypes of the disease [32, 34, 35, 37, 38]: 6 used anthropometry [32, 34-38], 2 analyzed patients' dietary intake and adequacy [37, 38], hemoglobin was collected in 4 studies (to assess the presence of anemia) [32, 34-36], 2 studies had values of albumin [32, 35], zinc [32, 35], and vitamin D [34, 35], 1 study assessed ferritin [32], and 1 assessed vitamin B12 [35].

Figure 2 summarizes the main clinical factors related to alterations in the nutritional status of patients with EB among the selected studies for the review that evaluated the patients' nutritional condition.

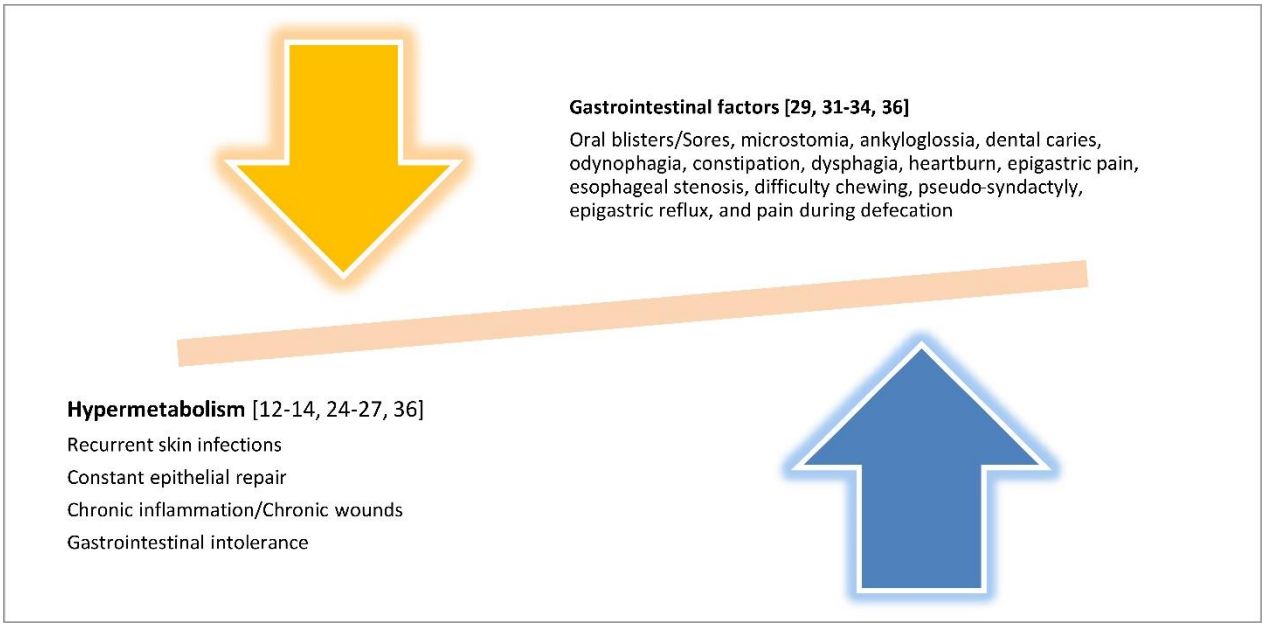

Figure 2 Clinical factors related to alterations in the nutritional status of patients with EB among the selected studies for the review. Source: Adapted from Morales-Olvera D, Gris-Calvo JI, García-Romero MT. Nutritional status of pediatric patients with epidermolysis bullosa. A cross-sectional study. Nutr Clín Diet Hosp. 2022; 42: 146-151. [37]

EB is a rare genetic disease without racial or color preference. Figure 3 illustrates the countries of origin of the patients included in this review, demonstrating that EB affects patients worldwide.

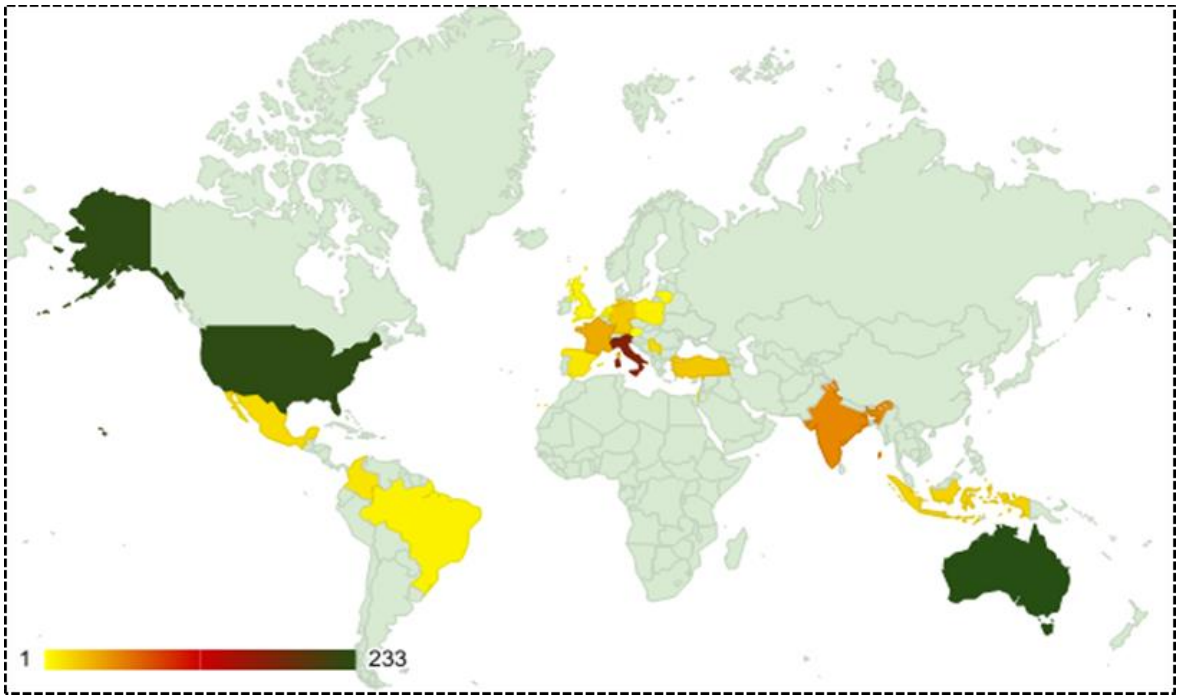

Figure 3 Countries of origin of the patients included in the review.

3.3 Quantitative Synthesis

In a combined estimate from four studies [17, 20, 25, 43] measuring the effect of topical treatment for wound healing in EB patients, the outcome favored topical treatment compared to control (SMD -0.82; 95% CI -1.26 – 0.38, N = 482, I^2 = 71%), as shown in Figure 4. The most effective topical treatments, according to the review, were 6% allantoin cream, 10% birch bark extract in gel, cotton acetate dressing coated with dialkylcarbamoylchloride chloride, biocellulose and carboxymethylcellulose dressing.

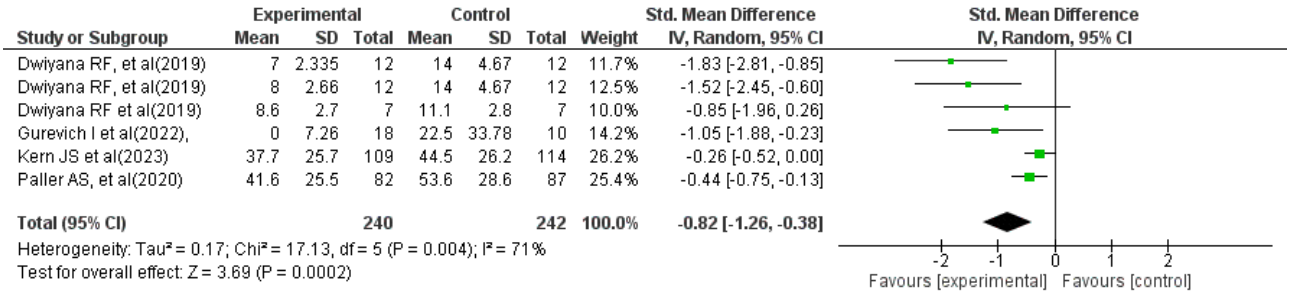

Figure 4 The effectiveness of topical treatment in wound healing among patients with EB.

After the combined analysis, a subgroup analysis was conducted to assess the effectiveness of topical treatment in wound healing among patients with EB at 30, 60, and 90-day follow-ups, and the effect of topical treatment on wound and itch control was examined. These results are described in Figure 5.

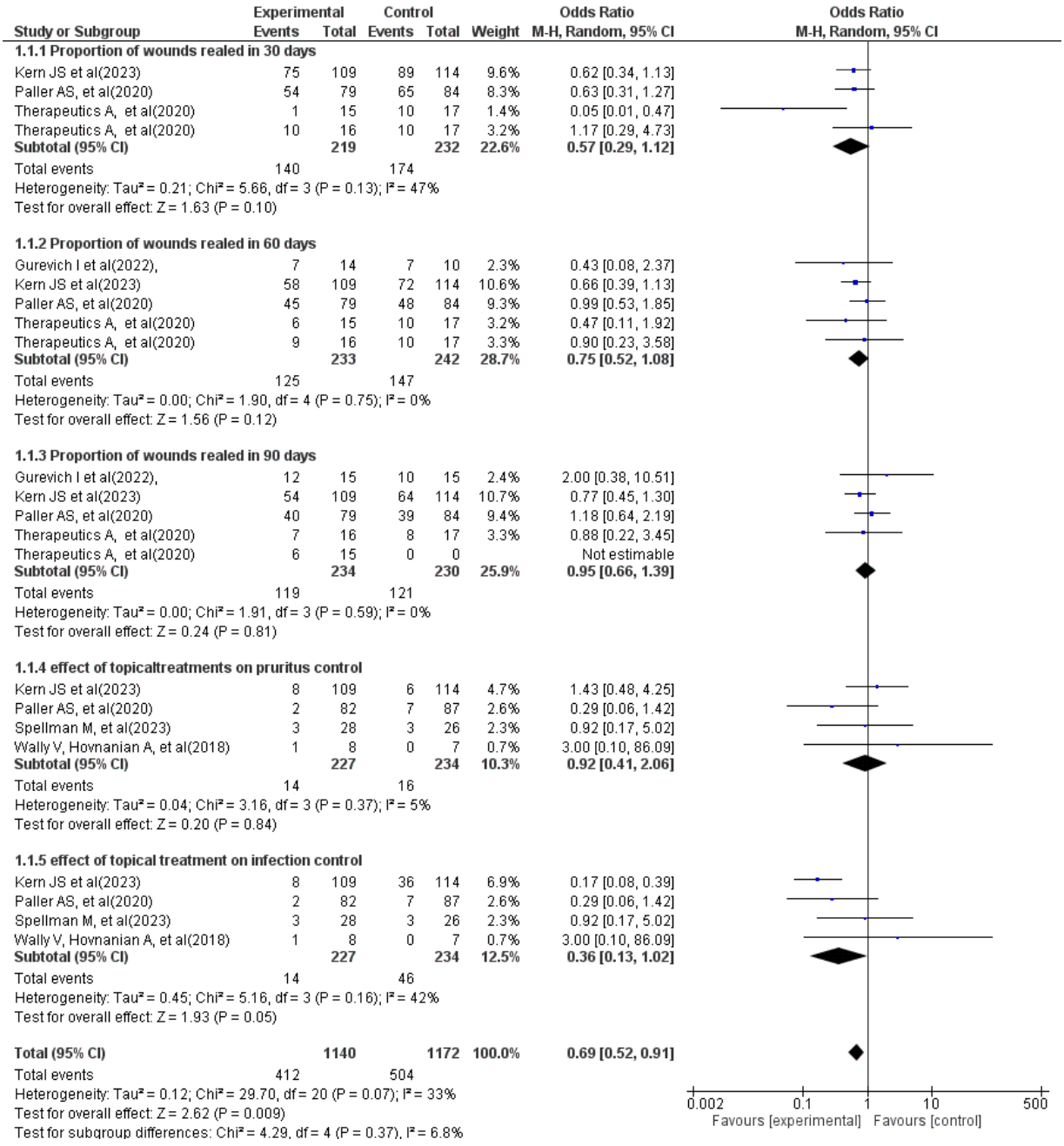

Figure 5 Effectiveness of topical treatment in wound healing among patients with EB at 30, 60, and 90-day follow-ups, and the effect of topical treatment on wound and itch control.

It is possible to observe differences in wound healing between the subgroups that received the topical treatment compared to the group that did not receive it (control) at 30 and 60 days. The same did not occur at 90 days. There were differences in infection control but not in itching.

After analyzing 5 studies [32, 34-37] that evaluated patients with EB and malnutrition, it was possible to observe that patients with DEB have a 2.5 times higher chance of presenting the condition when compared to patients with JEB, as seen in Figure 6. However, it is essential to remember that the small number of studies in the review makes it impossible to generalize such results. It is known that DEB can be more severe due to the formation of blisters below the dense lamina of the basal layer of the skin, leading to more incredible difficulty in healing, as well as other

complications, including malnutrition. Difficulty feeding is also present due to blisters in the oral cavity (mouth), throat, and esophagus, which are sometimes very painful. Pain associated with chewing and swallowing can lead to food refusal and insufficient intake of nutrients.

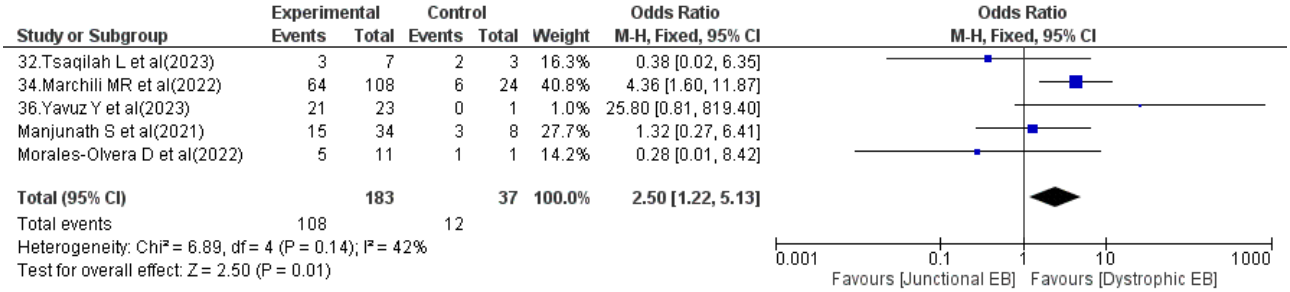

Figure 6 Prevalence of malnutrition by EB subtype (DEB and JEB).

Additionally, more significant protein loss is associated with insufficient protein intake since the blisters on the skin can result in loss of fluids and proteins, leading to malnutrition. This loss can be significant, leading to protein malnutrition, characterized by inadequate protein intake. Scars resulting from blisters can lead to contractures and limitations in joint movement, affecting the patient's ability to eat correctly. Some patients with EB may require dietary alterations, sometimes making it difficult to ingest nutrients, increasing the risk of undernutrition.

3.4 Risk of Bias Assessment

The Critical Appraisal Tool for Quasi-Experimental Studies [9] checklist was used to evaluate the studies with quasi-experimental design. The result indicated a low risk of bias. Table 3 shows the utilization of the checklist for assessing the experimental studies included in the review and the total score of each study.

Table 3 Evaluation of methodological quality of quasi-experimental studies included in the review.

Artigo	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	total
Tores Pradilla M et al [22]	Y	Y	Y	N/A	Y	Y	Y	Y	Y	8/9
Tsaqilah L et al [32]	Y	Y	Y	N/A	N/A	Y	Y	Y	Y	7/9
Marchili MR et al [34]	Y	Y	Y	N/A	N/A	Y	Y	Y	Y	7/9
Manjunath S et al [35]	Y	Y	Y	N/A	Y	Y	Y	Y	Y	8/9
Yavuz Y, et al [36]	Y	Y	Y	N/A	N/A	Y	Y	Y	Y	7/9
Morales-Olvera D et al [37]	Y	Y	Y	N/A	N/A	Y	Y	Y	Y	7/9
Zidório APC et al [38]	Y	Y	Y	N/A	N/A	Y	Y	Y	Y	7/9

Y - Yes, N - No, U - Unclear, N/A - not applicable

1. Is it clear in the study what is the 'cause' and what is the 'effect' (i.e. there is no confusion about which variable comes first)?, 2. Were the participants included in any comparisons similar?, 3. Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?, 4. Was there a control group?, 5. Were there multiple measurements of the outcome both pre and post the intervention/exposure?, 6. Was follow up

complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?, 7. Were the outcomes of participants included in any comparisons measured in the same way?, 8. Were outcomes measured in a reliable way?, 9. Was appropriate statistical analysis used?.

The experimental studies included in the review met the JBI critical appraisal criteria, whose checklist is composed of 9 questions. Positive evaluations were found for 7 out of 9 questions in 5 studies and for 8 questions in 2 studies, denoting a low risk of bias and high methodological rigor. Two questions did not apply to the majority of the studies.

Two independent reviewers conducted the assessment of studies with a clinical trial design. The evaluation result indicates a low risk of bias, as demonstrated in Figure 7.

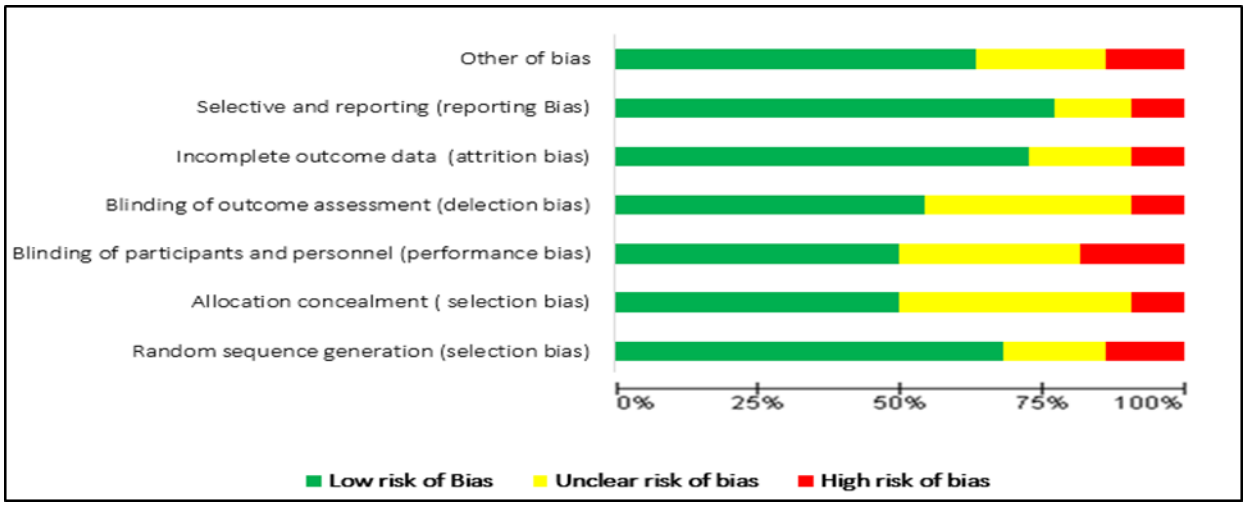

Figure 7 The percentage of risk of bias (high, low, or unclear) of the studies with a clinical trial design is included in the review.

Figure 8 summarizes the bias of the clinical trial studies assessed using the Rob2 scale. The main biases are related to allocation concealment (selection bias), blinding of participants and personnel (performance bias), and blinding of outcome assessment (detection bias), observed in 6 out of the 21 studies included in the review.

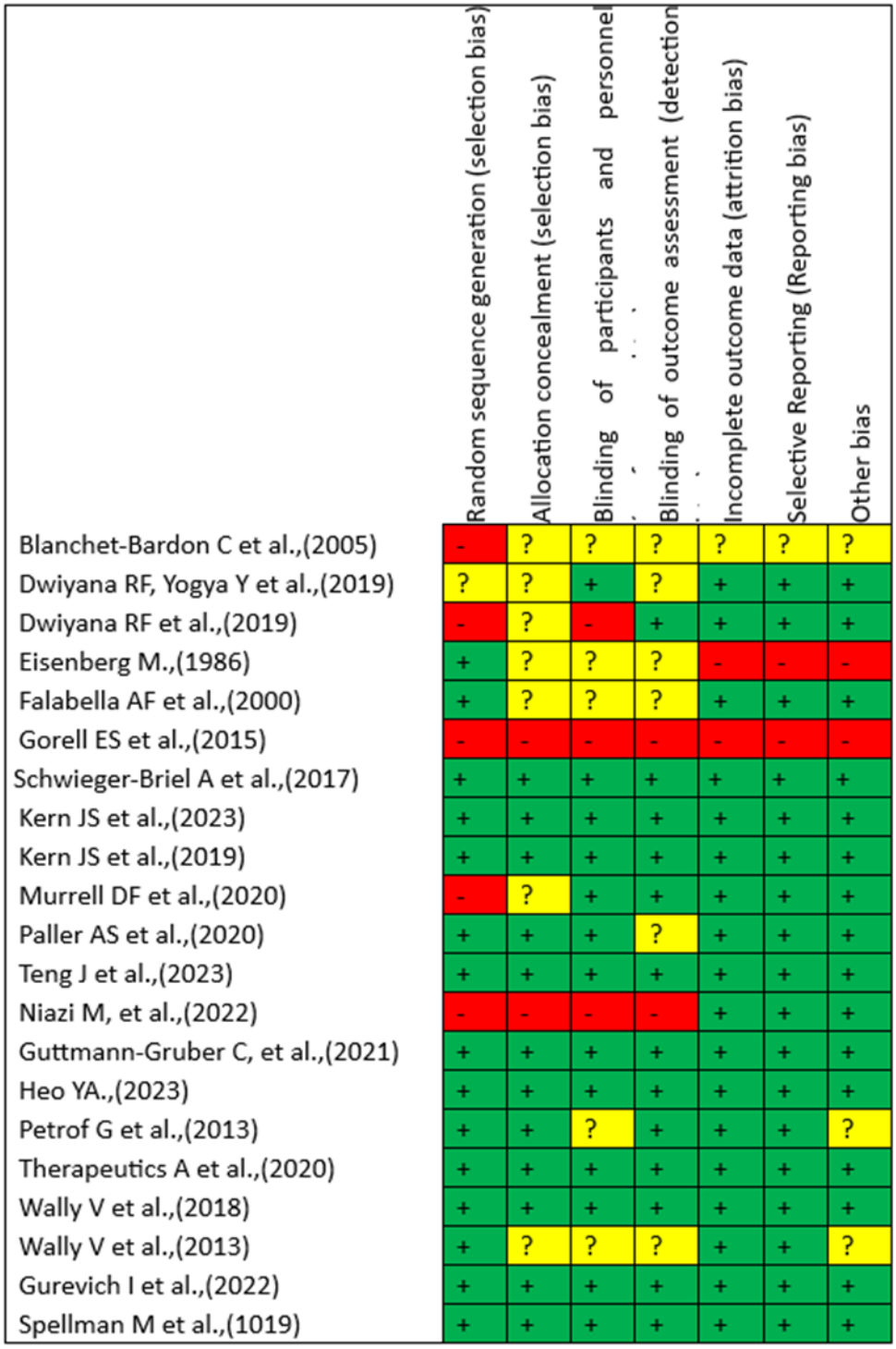

Figure 8 Summary of bias risk of the studies with a clinical trial design included in the review.

Figure 9 depicts the publication bias of the quantitative analyses. The graphs show that there is a certain asymmetry in the qualitative analysis, which may indicate publication bias, with a variety of accuracies among the studies.

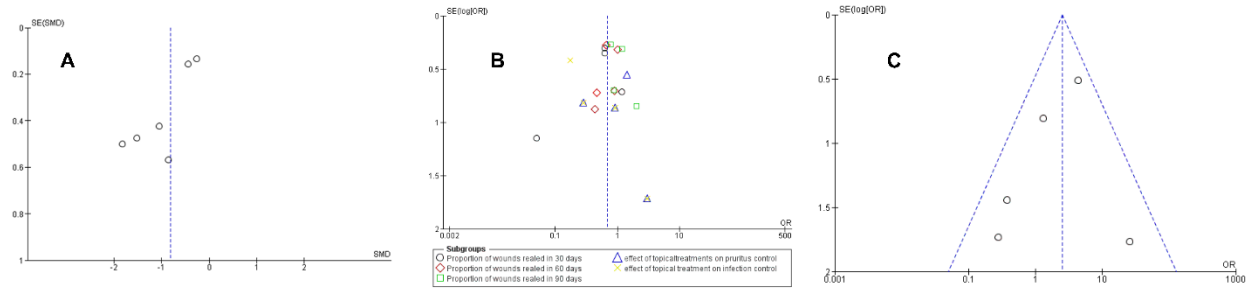

Figure 9 Funnel plot showing publication bias of the quantitative analyses: A) in the effect of topical treatment on wound healing in patients with EB; B) in the subgroup analysis of the effect of topical treatment on wound healing in patients with EB; C) in the analysis of malnutrition presence by disease subtype.

3.5 Assessment of Evidence Certainty

Evidence certainty was evaluated using the GRADEPro [10] software. Table 1 compiles the Recommendation Grades for the certainty of evidence related to the outcomes studied in the review. Following the analysis, a very low recommendation grade was observed for all evaluated outcomes.

4. Discussion

The review provides a comprehensive synthesis of available evidence on wound healing and nutritional profiles in patients with EB. A total of 28 articles were included, encompassing both clinical trials and observational studies involving 994 patients with various subtypes of EB.

It is well acknowledged that malnutrition poses a significant challenge for children with EB, as noted in this review and supported by numerous studies. Malnutrition in EB patients is often attributed to both inadequate intake of essential macro and micronutrients and the body's inability to effectively process and utilize nutrients, which stems from the inherent difficulties faced by children with EB [36]. These difficulties are further compounded by issues such as blistering and open wounds in the mouth and gastrointestinal tract, leading to reduced food intake due to pain and discomfort [46, 47].

The dietary challenges children with EB encounter result in poor nutritional intake, particularly in essential nutrients such as protein, vitamin D, calcium, and iron. High carbohydrate intake is emphasized as crucial for EB patients due to the impaired wound healing process resulting from frequent damage to the skin's basal membrane zone, which requires significant carbohydrate resources for repair. Additionally, protein and its constituent amino acids are highlighted as crucial building blocks not only for skin but also for other tissues, making adequate protein intake vital for EB patients who have numerous wounds and frequent blistering, necessitating a higher protein requirement compared to the average individual [47, 48].

Regarding nutritional profiles, the review indicates a relative lack of focus on this aspect, with only six studies assessing the nutritional status of patients [32, 34-38]. These studies employed various methods, including anthropometry, dietary intake analysis, and measurement of specific nutritional markers such as hemoglobin, albumin, zinc, vitamin D, ferritin, and vitamin B12, and only

two analyzed patients' dietary intake and adequacy [37, 38]. Despite limited attention, the findings suggest that malnutrition may be more prevalent in some subtypes of EB, such as JEB and DEB, than in other subtypes [35, 37-40].

One notable finding from the review is the identification of an odds ratio indicating a higher prevalence of malnutrition among patients with DEB than JEB. Studies have demonstrated that this subtype presents a higher involvement of oral and gastric mucosa, thereby interfering with absorption and predisposing to malnutrition and other complications such as anemia, dental caries, constipation, and bacterial infection. Indirectly, these complications also contribute to malnutrition [49]. This underscores the importance of considering nutritional support as an integral part of the management strategy for patients with EB, particularly those with more severe clinical alterations.

In the management of individuals with EB, nursing intervention plays a paramount role. Nursing support extends beyond wound care to include crucial educational roles for patients and their families regarding the disorder and its effective management. Preventive measures against complications such as infections and pain management are also essential, alongside efforts to facilitate psychosocial balance. Well-trained nurses providing appropriate care can significantly enhance the quality of life for those affected by EB, ensuring support across both emotional and physical domains [48, 50].

In terms of wound healing interventions, the primary research explored a diverse range of approaches, including dressings with collagen, cellulose, carboxymethylcellulose, and various topical creams such as mupirocin, birch triterpenes, allantoin, diacerein, henna, and calcitriol. Additionally, some studies investigated the use of fibroblasts and tissue-engineered skin [16, 17, 20, 22, 23, 25, 26, 29-31, 40-42, 44, 45]. This diversity highlights the ongoing efforts to find effective strategies for managing wound healing in EB patients once the molecular complexity of the subtypes leads to a wide range of clinical manifestations, from mild blistering to severe, life-threatening conditions, and necessitates tailored approaches to diagnosis, management, and potential therapeutic interventions. Subgroup analyses were conducted to assess the effectiveness of topical treatments in wound healing at different follow-up periods, as well as their impact on wound infection and itch control. Such analyses provide valuable insights into the efficacy of interventions over time and their broader effects on patient outcomes.

The results of this review are supported by the findings of a recent systematic review with meta-analysis [51], which evaluated topical treatment for wound healing in patients with EB. The meta-analysis revealed a shorter time for wound healing at 14 and 30 days with topical treatment compared to standard care. However, it is essential to note that the heterogeneous nature of the topical therapies assessed may limit the generalizability of these results, as they vary in administration method and treatment mechanism. Furthermore, the review identified differences in infection control with topical treatments but found no significant differences in itch control. This may suggest that topical measures may not effectively control itching, or it could be attributed to the limited number of studies assessing and measuring this effect, highlighting the need for further research to evaluate and quantify this effect on wound healing in EB patients.

Overall, the review highlights the complexity of managing EB, with many interventions being explored for wound healing, and underscores the need for further research into the nutritional aspects of the disease. By synthesizing existing evidence, the review provides valuable insights that can inform clinical practice and guide future research directions in EB management.

5. Conclusion

This review revealed a diverse range of interventions for wound healing, including dressings, creams, and tissue-engineered skin for patients with EB. However, there remains a limited understanding of the nutritional status of EB patients. The analyses suggested a higher prevalence of malnutrition among patients with the severe subtypes of EB, particularly Dystrophic EB (DDEB), compared to Junctional EB (JEB). This underscores the importance of addressing nutritional needs in comprehensive EB management.

Thus, this review provides valuable insights into the current research landscape on wound healing and nutrition in EB, laying the groundwork for future studies to advance our understanding and improve clinical management strategies for this complex and debilitating condition.

Author Contributions

All authors contributed to the study design. MLS collected and analyzed data. ACM, AN and SB wrote the original draft of the manuscript. PZ and AD reviewed and edited the manuscript.

Competing Interests

The authors have declared that no competing interests exist.

References

1. Machado BR. Gravidade clínica e estado nutricional de pessoas com epidermólise bolhosa. Brasília: Universidade de Brasília; 2019.
2. Gonzalez ME. Evaluation and treatment of the newborn with epidermolysis bullosa. Semin Perinatol. 2013; 37: 32-39.
3. Sheriff A, Jacków-Malinowska J. Advanced gene-editing strategy for epidermolysis bullosa simplex. Mol Ther. 2024; 32: 271-272.
4. Saad R, Duipmans J, Yerlett N, Plevey K, McCuaig C, Woolfe W, et al. Neonatal epidermolysis bullosa: A clinical practice guideline. Br J Dermatol. 2024; 190: 636-656.
5. Jeffs E, Pillay E, Ledwaba-Chapman L, Bisquera A, Robertson S, McGrath J, et al. Costs of UK community care for individuals with recessive dystrophic epidermolysis bullosa: Findings of the prospective epidermolysis bullosa longitudinal evaluation study. Skin Health Dis. 2024; 4: e314.
6. Liy-Wong C, Tarango C, Pope E, Coates T, Bruckner AL, Feinstein JA, et al. Consensus guidelines for diagnosis and management of anemia in epidermolysis bullosa. Orphanet J Rare Dis. 2023; 18: 38.
7. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ. 2021; 372: n71.
8. Higgins JP, Sterne JA, Savovic J, Page MJ, Hróbjartsson A, Boutron I, et al. A revised tool for assessing risk of bias in randomized trials. Cochrane Database Syst Rev. 2016; 10: 29-31.
9. Barker TH, Habibi N, Aromataris E, Stone JC, Leonardi-Bee J, Sears K, et al. The revised JBI critical appraisal tool for the assessment of risk of bias quasi-experimental studies. JBI Evid Synth. 2024; 22: 378-388.
10. GRADEpro. Guideline development tool. McMaster University and Evidence Prime; 2022.

11. Aromataris E, Lockwood C, Porritt K, Pilla B, Jordan Z. JBI Manual for Evidence Synthesis [Internet]. Adelaide: JBI; 2024 [cited date 2024 April 2]. Available from: https://synthesismanual.jbi.global.
12. Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. Res Synth Methods. 2010; 1: 97-111.
13. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003; 327: 557-560.
14. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002; 21: 1539-1558.
15. The Cochrane Collaboration. Computer Program. Version 5.4. Review Manager (RevMan). London: The Cochrane Collaboration; 2020.
16. Dwiyana RF, Yogya Y, Gondokaryono SP, Diana IA, Suwarsa O, Ramali LM, et al. Clinical efficacy of biocellulose, carboxymethyl cellulose and normal saline dressing in epidermolysis bullosa. J Wound Care. 2019; 28: S4-S9.
17. Dwiyana RF, Gondokaryono SP, Rahardja JI, Arline Diana I, Yogya Y, Gunawan H. Clinical efficacy of dialkylcarbamoylchloride-coated cotton acetate dressing versus combination of normal saline dressing and 2% mupirocin ointment in infected wounds of epidermolysis bullosa. Dermatol Ther. 2019; 32: e13047.
18. Blanchet-Bardon C, Bohbot S. Using Urgotul dressing for the management of epidermolysis bullosa skin lesions. J Wound Care. 2005; 14: 490-496.
19. Schwieger-Briel A, Kiritsi D, Schempp C, Has C, Schumann H. Betulin-based Oleogel to improve wound healing in dystrophic epidermolysis bullosa: A prospective controlled proof-of-concept study. Dermatol Res Pract. 2017; 2017: 5068969.
20. Kern JS, Sprecher E, Fernandez MF, Schauer F, Bodemer C, Cunningham T, et al. Efficacy and safety of Oleogel-S10 (birch triterpenes) for epidermolysis bullosa: Results from the phase III randomized double-blind phase of the EASE study. Br J Dermatol. 2023; 188: 12-21.
21. Kern JS, Schwieger-Briel A, Löwe S, Sumeray M, Davis C, Martinez AE. Oleogel-S10 Phase 3 study "EASE" for epidermolysis bullosa: Study design and rationale. Trials. 2019; 20: 350.
22. Torres Pradilla M, Álvarez E, Novoa M, Lozano I, Trujillo M. Oleogel-S10 in dystrophic epidermolysis bullosa: A case series evaluating the impact on wound burden over two years. Adv Ther. 2024; 41: 867-877.
23. Murrell DF, Paller AS, Bodemer C, Browning J, Nikolic M, Barth JA, et al. Wound closure in epidermolysis bullosa: Data from the vehicle arm of the phase 3 ESSENCE Study. Orphanet J Rare Dis. 2020; 15: 190.
24. Gorell ES, Leung TH, Khuu P, Lane AT. Purified type I collagen wound matrix improves chronic wound healing in patients with recessive dystrophic epidermolysis bullosa. Pediatr Dermatol. 2015; 32: 220-225.
25. Paller AS, Browning J, Nikolic M, Bodemer C, Murrell DF, Lenon W, et al. Efficacy and tolerability of the investigational topical cream SD-101 (6% allantoin) in patients with epidermolysis bullosa: A phase 3, randomized, double-blind, vehicle-controlled trial (ESSENCE study). Orphanet J Rare Dis. 2020; 15: 158.
26. Teng J, Paller AS, Bruckner AL. Diacerein 1% ointment for the treatment of epidermolysis bullosa simplex: A randomized, controlled trial. J Drugs Dermatol. 2023; 22: 599-604.

27. Niazi M, Parvizi MM, Saki N, Parvizi Z, Mehrbani M, Heydari M. Efficacy of a topical formulation of henna (Lawsonia inermis Linnaeus) on the itch and wound healing in patients with epidermolysis bullosa: A pilot single-arm clinical trial. Dermatol Pract Concept. 2022; 12: e2022115.
28. Guttmann-Gruber C, Piñón Hofbauer J, Tockner B, Reichl V, Klausegger A, Hofbauer P, et al. Impact of low-dose calcipotriol ointment on wound healing, pruritus and pain in patients with dystrophic epidermolysis bullosa: A randomized, double-blind, placebo-controlled trial. Orphanet J Rare Dis. 2021; 16: 473.
29. Heo YA. Birch bark extract: A review in epidermolysis bullosa. Drugs. 2023; 83: 1309-1314.
30. Petrof G, Martinez-Queipo M, Mellerio JE, Kemp P, McGrath JA. Fibroblast cell therapy enhances initial healing in recessive dystrophic epidermolysis bullosa wounds: Results of a randomized, vehicle-controlled trial. Br J Dermatol. 2013; 169: 1025-1033.
31. Scioderm, Inc. Study of effectiveness and safety of SD-101 in participants with epidermolysis bullosa [Internet]. Bethesda, MD: Clinicaltrials.gov.; 2020 [cited date 2024 April 2]. Available from: https://beta.clinicaltrials.gov/study/NCT02014376.
32. Tsaqilah L, Diana IA, Gondokaryono SP, Effendi RM, Suwarsa O, Gunawan H, et al. A retrospective study on the clinical, laboratory, and nutritional status of pediatric epidermolysis bullosa in a tertiary referral hospital in west java, Indonesia. Clin Cosmet Investig Dermatol. 2023; 16: 1615-1621.
33. Haynes L. Nutritional support for children with epidermolysis bullosa. Br J Nurs. 2006; 15: 1097-1101.
34. Marchili MR, Spina G, Roversi M, Mascolo C, Pentimalli E, Corbeddu M, et al. Epidermolysis bullosa in children: The central role of the pediatrician. Orphanet J Rare Dis. 2022; 17: 147.
35. Manjunath S, Mahajan R, De D, Handa S, Attri S, Behera BN, et al. The severity of malnutrition in children with epidermolysis bullosa correlates with disease severity. Sci Rep. 2021; 11: 16827.
36. Yavuz Y, An I, Yazmaci B, Akkus Z, Ortac H. Evaluation of clinical and oral findings in patients with epidermolysis bullosa. Medicina. 2023; 59: 1185.
37. Morales-Olvera D, Gris-Calvo JI, García-Romero MT. Nutritional status of pediatric patients with epidermolysis bullosa. A cross-sectional study. Nutr Clín Diet Hosp. 2022; 42: 146-151.
38. Zidório A, Carvalho K, Dutra ES. Evaluación de la ingesta de nutrientes de niños y adolescentes con epidermólisis bullosa distrófica recessiva, subtipo severo. Nutr Hosp. 2023; 40: 286-294.
39. Fine JD, Johnson LB, Weiner M, Suchindran C. Gastrointestinal complications of inherited epidermolysis bullosa: Cumulative experience of the National Epidermolysis Bullosa Registry. J Pediatr Gastroenterol Nutr. 2008; 46: 147-158.
40. Wally V, Hovnanian A, Ly J, Buckova H, Brunner V, Lettner T, et al. Diacerein orphan drug development for epidermolysis bullosa simplex: A phase 2/3 randomized, placebo-controlled, double-blind clinical trial. J Am Acad Dermatol. 2018; 78: 892-901.e7.
41. Wally V, Kitzmueller S, Lagler F, Moder A, Hitzl W, Wolkersdorfer M, et al. Topical diacerein for epidermolysis bullosa: A randomized controlled pilot study. Orphanet J Rare Dis. 2013; 8: 69.
42. Falabella AF, Valencia IC, Eaglstein WH, Schachner LA. Tissue-engineered skin (Apligraf) in the healing of patients with epidermolysis bullosa wounds. Arch Dermatol. 2000; 136: 1225-1230.
43. Gurevich I, Agarwal P, Zhang P, Dolorito JA, Oliver S, Liu H, et al. In vivo topical gene therapy for recessive dystrophic epidermolysis bullosa: A phase 1 and 2 trial. Nat Med. 2022; 28: 780-788.

44. Castle Creek Pharmaceuticals, LLC. Safety and efficacy of diacerein 1% ointment for subjects with epidermolysis bullosa simplex (EBS) [Internet]. Bethesda, MD: Clinicaltrials.gov.; 2019 [cited date2024 April 2]. Available from: https://beta.clinicaltrials.gov/study/NCT03154333?tab=results.
45. Eisenberg M. The effect of occlusive dressings on re-epithelializations of wounds in children with epidermolysis bullosa. J Pediatr Surg. 1986; 21: 892-894.
46. Pope E, Lara-Corrales I, Mellerio J. A consensus approach to wound care in epidermolysis bullosa. J Am Acad Dermatol. 2012; 67: 904-917.
47. Piña AR, Romero CS, Díaz KP, González LM, Rocha MG, González SC. Oral health and nutrition: A bidirectional relationship. In: The role of nutrition in integral health and quality of life. Apple Academic Press; 2024. pp. 455-470.
48. Minervini G, Franco R, Marrapodi MM, Giudice AL, Cicciù M, Ronsivalle V. Dental implant survival in epidermolysis bullosa patients: A systematic review conducted according to PRISMA guidelines and the Cochrane handbook for systematic reviews of interventions. Heliyon. 2024; 10: E24208.
49. Pabón-Carrasco M, Caceres-Matos R, Roche-Campos M. Management of skin lesions in patients with epidermolysis bullosa by topical treatment: Systematic review and meta-analysis. Healthcare. 2024; 12: 261.
50. Wu C, Chu X, Tang K, Cheng D, Ren L. Caregiving experiences of caregivers of children with rare diseases: A qualitative meta-synthesis. J Pediatr Nurs. 2023; 75: 31-40.
51. Feinstein JA, Bruckner AL, Chastek B, Anderson A, Roman J. Clinical characteristics, healthcare use, and annual costs among patients with dystrophic epidermolysis bullosa. Orphanet J Rare Dis. 2022; 17: 367.