Review Article

Topical Antimicrobial Agents for the Prevention of Burn-Wound Infection. What Do International Guidelines Recommend? A Systematic Review

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ABSTRACT

Background: Choosing adequate topical antimicrobial agents in burn patients still represents a challenge. Therefore, this systematic review was conducted to compile and evaluate current recommendations in international clinical practice guidelines (CPGs) to develop more consistent clinical guidance.

Methods: A systematic search for CPGs was conducted independently by two reviewers using PubMed, EMBASE, Google Scholar, and external citations. The quality of the selected CPGs was evaluated separately using the AGREE II instrument, and intraclass correlation coefficients were calculated. Statistical analysis was performed using R V 1.4.1 statistical software.

Results: Eleven CPGs were included in the study. Most guidelines tend to recommend silver-containing dressings over antiseptics or antibiotics, regardless of the depth of the burn. Silver sulfadiazine is the most recommended topical antimicrobial in low-resource settings. An overall mean appraisal AGREE II score of 68.2% was obtained. The global intraclass correlation coefficient was 0.62 (95% confidence intervals 0.54-0.69), which corresponds to a substantial global concordance between both appraisers.

Conclusions: Great heterogeneity was found between recommendations and CPGs. The three determining factors considered to issue a recommendation were the clinical scenario, burn-wound depth, and burn severity. There is consensus among the guidelines to use topical antimicrobials as a tool to prevent infection, and most of these recommend the use of silver-containing dressings for most scenarios. However, there is currently no ideal topical antimicrobial agent that can be recommended for all clinical scenarios. The development of more consistent recommendations is warranted to standardize clinical practice.

Keywords: Burn; Infection; Prevention; Antimicrobials; Topical

Please cite this paper as:
Garcia Garcia JA, Gonzalez Chavez AM, Orozco Grados JDJ. Topical Antimicrobial Agents for the Prevention of Burn-Wound Infection. What Do International Guidelines Recommend? A Systematic Review. World J Plast Surg. 2022;11(3):3-12.
doi: 10.52547/wjps.11.3.3

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Received: 19 Oct 2022
Accepted: 19 Sep 2022

INTRODUCTION

Although just decades ago the adoption of topical antimicrobial agents led to a significant reduction in complications such as dissemination and sepsis, burn-wound infection still represents a potential challenge in burn care.

[DOI: 10.52547/wjps.11.3.3]

According to the American Burn Association (ABA), two out of the five most common complications in burn patients are burn-wound infectious conditions (cellulitis in third place and burn-wound infection in the 5th [1,2]. What is more, current infection-related mortality rates still range from 50-75%.[3-6]. These numbers highlight the importance of preventing any type of infectious disease and inherent complications among burn-injured subjects. Furthermore, whereas nowadays solid evidence exists for the treatment of both burn-wound contamination and established infection [7,8] . There is a lack of consensus in the literature [9,10], and international clinical practice guidelines (CPGs) regarding the optimal use of topical antimicrobial agents to prevent burn-wound infection in different settings. Therefore, condensing the currently available recommendations is essential to develop more consistent guidance for practitioners in their clinical decisions.

Clinical practice guidelines represent a systematically developed link between scientific evidence and standardized clinical practice; thus, medical practitioners rely on their recommendations for evidence-based decisions [11]. Nevertheless, the recommendations found in these resources may sometimes be unclear, ambiguous, or may contain gaps. Furthermore, recommendations may vary between international guidelines, making consensus difficult. Such is the case of the recommendations for optimal topical antimicrobial agents to prevent burn-wound infections. The reason for these contrasting recommendations may be that, as various authors conclude, the available studies in the area provide flawed, contradictory data and may be at high risk of bias [10, 12-14]. For the scope of this review, Supplementary table 6 provides a detailed definition and classification of topical antimicrobial agents used in burn care as defined by Cambiasio et al [7].

Given that infection is still one of the leading causes of morbidity and the main cause of mortality in burn patients [1,15] , selecting optimal topical agents for the prevention of burn-wound infection is essential, especially in the imminent era of antimicrobial resistance. While clear recommendations regarding topical antimicrobial agents exist in the therapeutic setting (i.e., established burn-wound infection), international recommendations for their use in infection prevention are contrasting and may be ambiguous. Therefore, we conducted a systematic review to evaluate the methodological quality of different published clinical practice guidelines using the AGREE II critical appraisal approach instrument [16] and compared their key recommendations on the use of topical antimicrobial agents for burn-wound infection prevention in partial-thickness and full-thickness wounds in adult patients. In the absence of a consistent consensus, a comprehensive systematic review that evaluates the variable recommendations for different settings and clinical scenarios in currently available guidelines was warranted. This manuscript condenses these recommendations and sheds light on the preferred topical management to prevent burn-wound infection in different situations.

METHODS

Data resources and search methodology

A detailed description of the search methodology can be found in Supplementary Tables 1 and 2. A systematic search was conducted in duplicate by two independent reviewers between July 24 and 25, 2021. Three databases (PubMed, EMBASE, and Google Scholar) were searched to identify clinical practice guidelines (CPGs) published between January 1, 2010, and July 25, 2021, using the search algorithms described in Supplementary Table 1. The database search results' titles and abstracts were scrutinized for references to additional CPGs, which were also included. In addition, five international guideline repositories [17-21] and six websites of international burn associations and journals [22-27] were searched. Language restriction to English, Spanish, French, and German was applied.

Study selection and data extraction

Inclusion and exclusion criteria are outlined in Supplementary Table 2. CPG selection and data extraction were completed in duplicate. Both reviewers independently screened titles and abstracts of search results and selected guidelines that appeared to meet potentially standards for inclusion. Both reviewers obtained full-text guidelines and screened a second time using the pre-specified inclusion and exclusion criteria. Final inclusion and disagreements were resolved by mutual consensus. Both reviewers undertook guideline scoring independently, using a pre-designed data-pooling worksheet for AGREE II-scores. As for guideline contents, the following data were synthesized and documented: guideline title, author, year of publication, publishing

[DOI: 10.52547/wjps.11.3.3]

society/organization or journal, country of origin, and a summary of topical antimicrobial agent recommendations with infection prevention as an outcome (burn-wound depth, minor/major burn, inpatient/outpatient management, clinical scenario, recommended agents, alternatives). The study selection process was documented using a flow diagram as per the PRISMA 2020 guideline for reporting systematic reviews [28] found in Supplementary Figure 1.

Assessment: Guideline Recommendations

Each guideline's previously outlined key data were retrieved, synthesized, and tabulated by one reviewer. The tabulated results were revised and compared with the corresponding guidelines by

Table 1: Summarized recommendations on topical antimicrobials with burn-wound infection prevention as an outcome

Title, (PMID if available)	Quality assessment % (Mean appraisal score) %	Summary						
		Recommendations on topical antimicrobial agents to prevent burn-wound infection						
		Burn wound depth (thickness)	Minor/ Major	Outpatient/ Inpatient	Clinical scenario	Addresses: AB, AS, ACD*	Recommended agents	Alternatives
Wound, pressure ulcer and burn guidelines – 6: Guidelines for the management of burns, second edition [40] **(PMID:** 32343002)	83.33 (75.79)	**Partial**	Major	Inpatient	Initial treatment	AB	Not specified.	Not specified.
		Partial	Major	Inpatient	Not specified.	ACD	Silver-containing Hydrofiber (1A)	"Silver alginate and silver-containing polyurethane foam/soft silicone. (2A)"
Guidelines for Burn Care Under Austere Conditions- Surgical and Nonsurgical Wound Management [39] **(PMID:** 27355660)	58.33 (60.07)	**Full**	Major	Inpatient	Austere conditions, scarce supply, and delayed excision.	AB	Mafenide acetate 11% cream	Silver sulfadiazine as a sole agent, silver-containing dressings, aqueous 10% mafenide acetate solution, Dakin's solution, cerium-based products, honey.
		Full	Major	Inpatient		AS	Silver sulfadiazine	
		Full and Partial	Minor	Outpatient	Austere conditions	AS, AB	Silver sulfadiazine cream and Mafenide acetate, Silver impregnated dressings	Bacitracin, Polysporin®, and Neosporin®
		Not specified	Minor	Outpatient	Austere conditions, facial burns	AB	Bacitracin, Polysporin®, and Neosporin®	Not specified.
European Practice Guidelines for Burn Care [38]	75 (70.98)	**Not specified**	Not specified	Inpatient	Not specified. General recommendation.	ACD	Dressings containing nanocrystalline silver.	Not specified.
Behandlung thermischer Verletzungen des Erwachsenen (33)	66.66 (69.39)	**Superficial partial**	Not specified	Inpatient	Not specified.	ACD	Silver-containing dressings.	Non-specified antimicrobial ointments, medicinal honey.
		Partial (Unclear depth)	Not specified	Inpatient	Temporally unable to tell burn-wound depth.	ACD	Antiseptic dressings (Non-specific)	Not specified.
Best practice recommendations for the prevention and management of burns. In: Foundations of Best Practice for Skin and Wound Management. (32)	66.66 (61.31)	**Not specified**	Not specified	Not specified	Not specified. General recommendation.	AS and AB	Honey, PMHB, Gentian Violet/Methylene Blue, Silver sulfadiazine (SSD) 1% cream, Mafenide acetate cream 11% or solution 5%	Not specified.
		Not specified	Minor burns	Not specified	Not specified.	ACD	PVP-I dressings (Knitted viscose fabric impregnated with polyethylene glycose containing 1% povidone-iodine)	Not specified.
		Deep-partial and full	Not specified	Inpatient	Burns awaiting surgery	ACD	Silver-containing dressings	Not specified.
Prise en charge du brûlé grave à la phase aiguë chez l'adulte et l'enfant (36)	83.33 (80.90)	**Full and Partial**	Major	Inpatient	Emergency room. The patient cannot be transferred to a Burns Treatment Center within hours of the accident	ACD, AB, AS	Silver or antiseptic-containing dressings (Chlorhexidine, Povidone Iodine)	Not specified.
Clinical Guidelines: Diagnosis and Treatment Manual. Chapter 10: Medical and Minor surgical procedures, Burns. (31)	16.66 (26.19)	**Full and Partial**	Major	Inpatient	Curative care at the dispensary and primary hospital in health care exclusion settings.	AS	Silver sulfadiazine	Not specified.
		Not specified	Minor	Outpatient		AS	Silver sulfadiazine	

[DOI: 10.52547/wjps.11.3.3]

Countinued Table 1: Summarized recommendations on topical antimicrobials with burn-wound infection prevention as an outcome

Title, (PMID if available)	Quality assessment % (Mean appraisal score) %	Summary						
		Recommendations on topical antimicrobial agents to prevent burn-wound infection						
		Burn wound depth (thickness)	Minor/ Major	Outpatient/ Inpatient	Clinical scenario	Addresses: AB, AS, ACD*	Recommended agents	Alternatives
Clinical Guidelines: Burn Patient Management (30)	66.66 (61.31)	**Partial**	Not specified	Not specified	Not specified.	ACD	Ionic silver dressings	Not specified.
		Partial	Not specified	Not specified	Not specified.	ACD	Chlorhexidine impregnated paraffin gauze, Mesh gauze impregnated with 3% Xeroform® (Bismuth tribomophophenate)	
		Full and Partial	Not specified	Not specified	Not specified.	ACD	Nanocrystalline silver dressings	
		Full and Partial	Major	Inpatient	Burn units	AS	Silver sulfadiazine 1% + Cerium nitrate 2.2%	
ISBI Practice Guidelines for Burn Care. (37) **(PMID:** 27542292)	100 (91.17)	**Superficial-partial**	Not specified	Not specified	Fresh burns expected to heal spontaneously.	ACD	Iodine and silver-containing dressings.	Not specified.
		Superficial-partial	Not specified	Not specified	Resource-limited settings with no available modern dressings to cover de-roofed or snipped blisters.	NSTA	Not specified.	Not specified.
		Full and deep-partial	Not specified	Inpatient	Burn wounds awaiting excision. Closed technique.	NSTA	Not specified.	Not specified.
		Full and deep-partial	Not specified	Inpatient	Burn wounds treated with open (after eschar removal) and semi-open techniques in resource-limited settings	NSTA	Not specified.	Not specified.
ISBI Practice Guidelines for Burn Care, Part 2 (35) **(PMID:** 30343831)	100 (91.17)	**Not specified**	Not specified	Not specified	In general, for most burn wounds, weigh the risk of delayed wound healing	NSTA	Not specified	Not specified
		Full and deep-partial	Major	Inpatient	Especially applies to burn wounds prior to surgical debridement	AS, ACD	Silver-based topical agents and dressings.	Not specified
		Superficial-partial thickness	Minor	Outpatient	More superficial burns expected to heal on their own, treated as outpatients.	ACD	Silver-containing dressings (Hydrofiber and activated charcoal dressings)	Not specified
		Full and deep-partial	Minor and major	Inpatient	Deep burns of the ear. Deep burns.	AB	Mafenide acetate 11% cream + *topical nystatin	Mafenide acetate 5% aqueous solution
		Full	Major	Inpatient	It may have a role in for deeper burn wounds (that are not expected to heal spontaneously) prior to surgical excision.	AS	Dakin's solution (0.5% buffered NaOCl)	Not specified
		Superficial-partial	Not specified	Not specified	Resource-limited settings with no available topical antimicrobial ointments or creams	AS	Honey	Not specified
		Full	Major	Inpatient	Early surgical excision and wound closure cannot be performed	AS	Cerium nitrate (2.2% CN with 1% SSD)	Not specified
Guideline and treatment algorithm for burn injuries (34) **(PMID:** 25904267)	41.66 (51.03)	**Superficial-partial**	Minor	Outpatient	Minor burns	ACD	Nitrofurazone 0.2% pomade	Not specified
		Full	Major	Inpatient	Eschar and large burns	ACD	1% silver sulfadiazine (SSD)	Mupirocin, Nitrofurazone

*__Abbreviations:__ AB= Antibiotics, AS= Antiseptics, ACD= Antimicrobial-containing dressings, NSTA= Not specified topical antimicrobials

a second reviewer to check for accuracy. Any discrepancies were resolved through consensus after a third revision. The recommendations and justifications were examined, and we designated the following domains to evaluate similarities and differences between CPG recommendations: burn-wound depth (full or partial-thickness), management according to burn severity (inpatient/

[DOI: 10.52547/wjps.11.3.3]

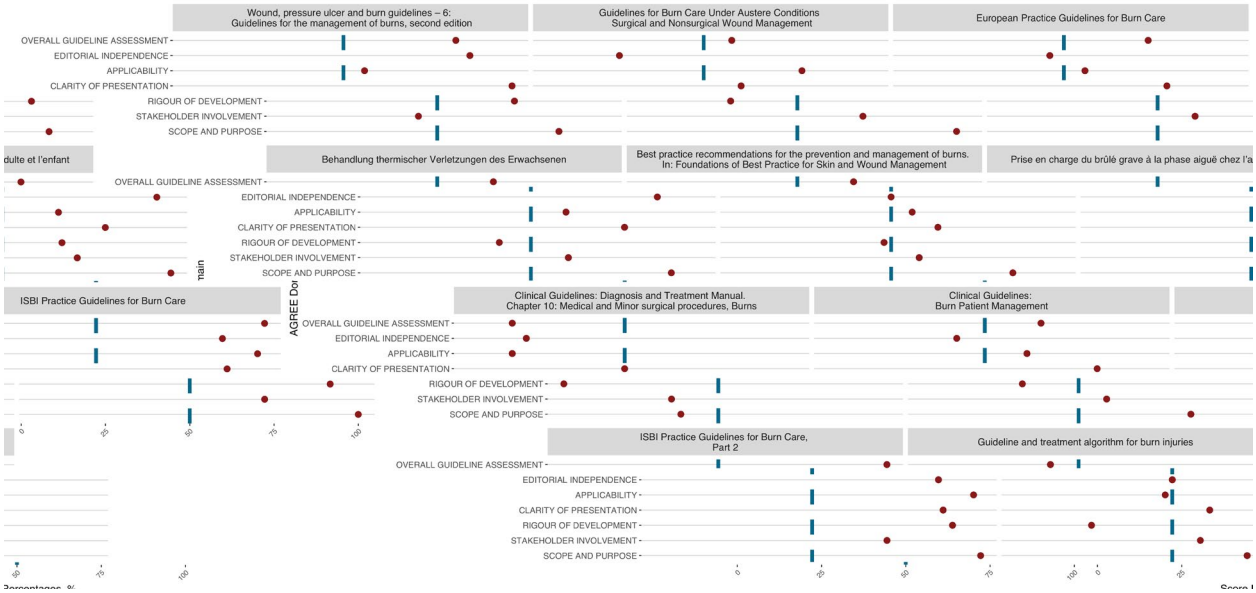

Figure 1: AGREE II domain scores for each CPG

outpatient), clinical scenario, and recommendations (general/specific). Gaps in recommendations in any of these criteria were noted in Table 1.

Assessment: AGREE II

Formal methodological assessment of the guidelines' development process was evaluated using the AGREE II (APPRAISAL OF GUIDELINES FOR RESEARCH & EVALUATION II) tool, which uses a Likert-scale scoring system to evaluate each of its 23 items. Concomitantly, these items are grouped within six main domains: scope and purpose, stakeholder involvement, rigor of development, clarity of presentation, applicability, and editorial independence [16]. As indicated by the AGREE II User's Manual, for each guideline, both evaluators worked independently to assign a score to each of the tool's items, and domain scores were later calculated and tabulated. (Supplementary Table 3) In addition, mean appraisal scores (arithmetic mean for all the domains in one guideline, including overall assessment) were calculated. There is no fixed AGREE II cutoff score at present, so we established a value for mean appraisal scores of >70% as adequate quality, 60-69.99% as intermediate quality, and <60% for low quality.

We used intraclass correlation coefficients (ICC) with a two-way random-effects model [29] and the corresponding 95% confidence intervals to estimate the global inter-rater agreement. Additionally, we calculated ICC values for each AGREE-II domain score and each CPG. Our models were built under the assumption that both evaluators were unbiased now of scoring, both representing a random variable. To test the null hypothesis that the AGREE II appraisal scores were assigned by random chance, we used a two-way random-effects ANOVA model, with *P*-values <0.05 considered statistically significant. The level of agreement of ICC's was classified as poor (ICC < 0.40), moderate (ICC 0.40–0.59), substantial (ICC 0.60–0.79), or excellent (ICC 0.80–1.00). Statistical analyses were performed using R (The R Project for Statistical Computing Version 1.4.1).

RESULTS

Key data and recommendations

Overall, 635 relevant titles were identified through database searches and 14 through Google Scholar and citation searches. After abstract screening and a full-text review of potential titles, 11 CPGs that met the inclusion criteria were selected [11, 30-39]. Table 1 summarizes the key data that was extracted from each CPG. The included CPGs notably originated from a heterogeneous background of countries and geographic regions, with seven different countries identified, one continental CPG [38] and three international CPGs [31,35,37]. It is worth noting that all the selected guidelines were developed by diverse

[DOI: 10.52547/wjps.11.3.3]

medical societies focused on different fields in burn care.

Only two of the selected CPGs provide explicit recommendations in favor of the general use of topical antimicrobial agents in most burn wounds to prevent infection, regardless of other specific factors (burn-wound depth, extension, clinical scenario) [32,35] . Notably, the recommendations vary between most guidelines because they consider these factors for their formulation. In this way, all the included CPGs recommend preferred topical antimicrobial agents to prevent burn-wound infection in specific situations. Nonetheless, only five CPGs suggested alternative agents in the same specific scenarios [33–35,39,40] . In general, the majority of guidelines tend toward recommending antimicrobial-containing modern dressings over conventional antiseptics/ antibiotics [30,32–38,40] . As for more conventional agents, silver sulfadiazine (SSD) is the most commonly reported; however, recommendations tend to favor its use in low-resource settings and in deeper wounds (Full and deep-partial thickness).

Among the most commonly identified clinical scenarios in CPGs were low-resource settings and scenarios with austere conditions [31–33,35,37,39]. Interestingly, among the alternative agents recommended in these scenarios are honey [32,33,35,39] and SSD [31,39] for partial and full-thickness wounds, and Dakin's solution for full-thickness wounds[39] . Other commonly identified clinical scenarios were deeper wounds in settings where early excision is not possible [32,35,37] or prior to excision [32,35,39] . Likewise, these recommendations showed a preference for silver compounds and silver-containing dressings. Other reported scenarios include facial burns[39], deep ear burns[35], uncertainty about wound depth [33], emergency room (inability to transfer the patient to burn unit) [36], and burn unit-specific topical management [30].

Finally, categorizing burn wounds and considering wound depth is paramount in identifying key recommendations for their management. Five CPGs provide at least one recommendation in favor of using topical antimicrobials without explicitly specifying burn-wound depth[31,32,35,38,39]. Contrarywise, in most recommendations, burn-wound depth was clearly identified and addressed. As for superficial-partial thickness wounds, silver-containing dressings were the most recommended [33,35,37], but other preferred agents included iodine-containing dressings [37], honey [35], and nitrofurazone[34]. Of note, recommendations for deeper wounds often incorporate deep-partial and full-thickness burn wounds. For these categories, silver-containing dressings [32,35,36,39], silver sulfadiazine 1% [31,34,35,39], mafenide acetate 11% cream[35,39] were the most recommended agents. Overall, most guidelines have listed silver compounds as the preferred strategy for burn-wound infection prevention in terms of burn-wound depth.

Methodological assessment

The AGREE II domain scores for each CPG are presented in Figure 1. Of the 11 CPGs, only five guidelines reached a mean appraisal score and overall assessment of >70% [35–38,40], while two guidelines obtained mean appraisal scores and overall assessments <60% [31,34]. The overall mean appraisal score (%) of all the included CPGs was 67.20%, and similarly, the mean overall assessment was 68.9%. The domain that obtained the highest mean score for all guidelines was "1. Scope and purpose" with 86% (SD=17.87%), which assesses the guideline's aim, formulation of specific health questions, and target population [16]. On the contrary, the domain with the lowest mean score for all guidelines was "3. Rigor of development" with 53.87% (SD=29.85%), which evaluates the systematic methods for collecting information, formulating recommendations, and updates [16]. The global ICC was 0.62 (95% confidence intervals 0.54-0.69), which corresponds to a substantial global concordance between both appraisers. The *P*-value for the global ICC was <0.001, qualified as statistically significant. A detailed description of the domain scores for each CPG and intraclass correlation (ICC) calculations can be found in Supplementary tables 3, 4, and 5.

DISCUSSION

The key strength of this systematic review is that, to the extent of our knowledge, a study that evaluates the methodological quality of burn-care CPGs and assesses their recommendations on this subject has not been previously conducted. In this way, including AGREE II appraisal scores provides insight into the recommendations included herein and the methodological standards under which they were developed. While other studies have used

[DOI: 10.52547/wjps.11.3.3]

the AGREE II appraisal tool to evaluate CPGs in burn care, they have focused on areas other than burn-wound management.[41–43.] Moreover, we did not restrict our search to English or databases only, broadening the possibilities of finding as many available international CPGs as possible. We also included guidelines from various societies and disciplines that address different clinical scenarios, which further enriches the compilation of recommendations in different settings and allows for comparison and contrast.

Given that there is no apparent consensus on the optimal use of topical antimicrobial agents to prevent burn-wound infection, the objective of the present systematic review was to identify, compare and condense the recommendations that current international CPGs provide in different clinical scenarios. Notably, while all the comprised CPGs provide recommendations in favor of topical antimicrobial agents to prevent burn-wound infection in specific situations, the recommendation on preferred topical agents remains dependent on assessing factors such as clinical scenario, burn-wound depth, and burn severity. Still, it is necessary to emphasize that there is currently no ideal topical antimicrobial agent that can be recommended in all clinical scenarios.

The most noteworthy finding is perhaps that silver compounds and their broad range of alternatives are still the most recommended first-choice agents in partial and full-thickness burn wounds. Remarkably, whereas most guidelines will endorse more modern silver-containing dressings for most clinical scenarios, silver sulfadiazine is typically considered for deeper wounds and burn wounds treated in low-resource settings. Extensive evidence exists in favor of recommending the use of silver compounds as the mainstay in burn wounds. Its bactericidal activity, low incidence of antimicrobial resistance [44] and broad antimicrobial spectrum make it useful against gram-positive and gram-negative organisms [45], particularly the most common pathogens infecting burn wounds (*Staphylococcus aureus* and *Pseudomonas aeuriginosa*) [2,46,47,48]. In contrast, the recommendations for using topical antibiotics are unsurprisingly limited to situations like superficial or facial wounds. This can be explained by the findings of a systematic review conducted by Norman et al., who suggest that "antimicrobial resistance is transmitted even more frequently by topical application of antibiotics" [10]. Additionally, a recent meta-analysis conducted in Iran that compared antibiotic-resistance profiles in Iranian burn patients, linked antibiotic overuse and misuse to higher resistance in pathogenic organisms [48]. Hence, in the imminent era of antimicrobial resistance, achieving burn-wound infection prevention while also counteracting the development of resistant organisms is essential.

As to the methodological quality of the CPGs, we used the AGREE II appraisal tool to evaluate the process of formulating these recommendations. We hypothesized that the scores assigned by each appraiser would not be attributed to random chance. In that matter, our appraisal scores yielded an estimated ICC of 0.62 (95% confidence intervals 0.54-0.69, with a statistically significant *P*-value <0.001). This corresponds to a substantial global concordance between both appraisers, thus, rejecting our null hypothesis. Of note, levels of agreement that qualify as excellent are usually highly suggestive of bias.

The results of this systematic review indicate that there are currently few guidelines to guide wound care that satisfactorily meet this tool's evaluating criteria. Consequently, poor methodology in developing recommendations may favor non-standardized practice. Therefore, methodological development of more consistent recommendations identifying a clear question to address, a specific clinical scenario, and explicit recommended agents and alternatives is essential to better guide practitioners in their clinical decisions.

Despite its strengths, certain caveats should be noted regarding the present systematic review. Firstly, a small number of available CPGs met inclusion criteria (n=11), mostly from developed countries. We were unable to retrieve guidelines from geographic regions like Latin America or Africa using our search methods (which would further broaden our compilation of recommendations). However, some of the included guidelines addressed or were aimed at low-resource settings explicitly. Furthermore, the findings in the methodological appraisal may be somewhat limited by the subjective nature of the evaluating scale and the nonideal number of reviewers (minimum two, preferably four) [16]. Despite well-established evaluations and criteria, Likert scores are prone to subjectivity. Nonetheless, the AGREE II has been widely used as

[DOI: 10.52547/wjps.11.3.3]

an available tool to evaluate CPGs since the creation of its first version, and it has undergone extensive testing, with results showing that it is a valid and reliable instrument[49].

CONCLUSION

Burn-wound infection prevention is a priority issue due to the numerous undesirable consequences in the patient, such as alterations in healing, sepsis, and death. Therefore, the use of topical agents with antimicrobial properties is considered a standard intervention. The present systematic review aimed to compile the available recommendations in international CPGs on topical antimicrobial agents to prevent burn-wound infection. Although there is a trend in CPGs towards recommending antimicrobial-containing dressings (specifically silver compounds) for partial and full-thickness burn wounds, most guidelines fail to issue recommendations with specific agents or for specific, different clinical scenarios. Herein, we have developed an integrative approach that approximates guidance that is more consistent by compiling and evaluating available recommendations. Future development of CPGs that abide by methodological criteria is essential for achieving a more standardized practice.

ACKNOWLEDGMENTS

Systematic review was conducted under the supervision of Harvard Medical School Postgraduate Education's Effective Writing for Healthcare faculty. No financial support was received for this study.

CONFLICT OF INTEREST

None declared.

SUPPLEMENTARY FILES

Supplementary Files are available here.

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