MASCC clinical practice guidelines for the prevention and management of acute radiation dermatitis: part 1) systematic review

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Summary

Acute radiation dermatitis (ARD) commonly develops in cancer patients undergoing radiotherapy and is often characterized by erythema, desquamation, and pain. A systematic review was conducted to summarize the current evidence on interventions for the prevention and management of ARD. Databases were searched from 1946 to September 2020 to identify all original studies that evaluated an intervention for the prevention or management of ARD, with an updated search conducted in January 2023. A total of 235 original studies were included in this review, including 149 randomized controlled trials (RCTs). Most interventions could not be recommended due to a low quality of evidence, lack of supporting evidence, or conflicting findings across multiple trials. Photobiomodulation therapy, Mepitel® film, mometasone furoate, betamethasone, olive oil, and oral enzyme mixtures showed promising results across multiple RCTs. Recommendations could not be made solely based on the published evidence due to limited high-quality evidence. As such, Delphi consensus recommendations will be reported in a separate publication.

Keywords: Radiation dermatitis; Clinical practice guidelines; Systematic review; Radiotherapy; Skin toxicity; Prevention; Management

eClinicalMedicine 2023;58: 101886

Published Online 27 March 2023
https://doi.org/10.1016/j.eclinm.2023.101886

See Article The Lancet Oncology 2023; published online March 27th: DOI: 10.1016/S1470-2045(23)00067-0

This is the first in a Series of two papers on MASCC Clinical Practice Guidelines. (papers 2 appears in The Lancet Oncology)

Introduction

Acute radiation dermatitis (ARD) has long been recognized as a common adverse effect of external beam radiotherapy (RT), developing in up to 95% of cancer patients.[1] The pathophysiology of ARD is complex and involves radiation-induced damage to both the epidermis and dermis, altered proliferation and differentiation of basal and epidermal keratinocytes, barrier disruption, and a trigger of proinflammatory markers that contribute to ARD-associated symptoms.[1,2] ARD, arising within 90 days from the initiation of treatment, is often characterized by changes in skin pigmentation, pain, pruritus, edema, and desquamation (dry and/or moist), with ulceration in severe cases.[1–3] The severity of ARD varies depending on treatment-related factors (e.g., radiation dose, irradiated volume, bolus, concurrent chemotherapy, treatment positioning, etc.) and intrinsic factors (e.g., body mass

DOI of original article: https://doi.org/10.1016/S1470-2045(23)00067-0
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MASCC does not endorse any brand names of therapeutics identified in this document or in any other documents.

index, irradiation site, smoking status, and skin pigmentation).[1–4] Approximately 36% of patients develop moderate to severe acute reactions characterized by moist desquamation, which are postulated to be associated with an increased risk of irreversible late side effects developing in the months to years following RT, such as telangiectasia and fibrosis.[5]

Despite technological advancements to improve skin dose homogeneity and reduce reaction severity, such as intensity modulated RT (IMRT) and skin-sparing techniques, ARD remains a prominent adverse reaction that can negatively impact patient quality of life (QoL), diminish cosmesis, cause infection or sepsis, and treatment interruptions.[1–3,6] Common QoL issues reported in patients with ARD include decreased self-esteem, embarrassment, increased financial burden associated with treatment, pain, and an impaired ability to complete daily activities.[6–8]

Currently, clinical care for ARD is highly variable due to a lack of standardization in approaches to prevent and manage skin reactions, which hampers the homogeneity of clinical practice recommendations worldwide.[9] In 2013, the Skin Toxicity Group of the Multinational Association of Supportive Care in Cancer (MASCC) released a clinical practice guideline in attempt to standardize the care of ARD.[10] While this guideline was valuable to care-providers at the time, it lacked definitive recommendations on ARD care due to a lack of high-quality evidence and therefore received limited uptake in clinical settings. Other guidelines have also been published by institutions, but suffer from similar issues.[9] Therapeutic interventions recommended by these guidelines for both prevention and management include aqueous creams, corticosteroids, and dressings, but a recent narrative review comparing ARD guidelines across cancer institutions revealed significant discrepancies across recommendations, revealing the need for up-to-date, evidence-based guidelines on ARD care.[9] An update to the MASCC ARD guidelines is therefore warranted due to publication of numerous high-quality studies since 2013.

MASCC is an international, non-profit, multidisciplinary organization that is dedicated to research into and education of supportive care for cancer patients. The Oncodermatology Study Group comprises experts in dermatology, medical, radiation, dental/oral surgery, and supportive oncology, nursing, health-related QoL, and pharmacovigilance, with a focus on the research and the development of evidence-based guideline recommendations for the care of cancer-related dermatologic (skin, hair, nail) toxicities. Within this MASCC study group, a working group was formed to compile the current literature on interventions for the care of ARD. We present Part One of a two-part publication series on the MASCC Clinical Practice Guidelines for the Prevention and Management of ARD, which aims to perform an extensive systematic review to highlight the available evidence on the prevention and management of ARD. Part Two, involving Delphi-based expert consensus recommendations, will be reported in a separate publication.

Methods

Search strategy and selection criteria

A systematic review of the literature was conducted in consultation with a medical librarian through Ovid MEDLINE®, Embase, and Cochrane Central Register of Controlled Trials databases. This systematic review aimed to update the findings of the 2013 MASCC skin care guidelines on ARD, with a new expanded search to include all study types from 1946 to September 2020. All original studies from the 2013 guidelines were included in this analysis, in addition to any non-randomized studies and relevant publications identified during the search time frame. The search strategy is summarized in Appendix A. In January 2023, an updated search was conducted from September 22nd, 2020 to January 21st, 2023 to identify any new articles.

All works published in the English-language (either full-text articles or abstracts) were included in the analysis if they answered the research question defined according to the Population, Intervention, Comparison, Outcome (PICO) method[11]: P) patients undergoing external beam RT for cancer; I) any intervention; C) standard of care, placebo, any other intervention, or no intervention; and O) prevention or management of ARD and ARD-associated symptoms. The research question was kept broad to capture all existing literature that included a study population who received RT and were treated with a therapeutic intervention to either prevent or manage ARD. By definition, preventative modalities were considered those administered prior to the start of RT or the onset of any grade ARD and continued throughout the course of RT, while management modalities were those administered during treatment or upon onset of any grade ARD. All randomized and non-randomized studies were included. Works published in a non-English language and/or conducted in animal or in vitro models were excluded.

In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement,[12] two authors (T.B. & S.F.) screened all titles and abstracts independently for eligibility. A third party was consulted for the inclusion of articles in the event of discrepancies (D.G.). Following screening by titles and abstracts, all studies were screened by full-texts; information was extracted from those that met the inclusion criteria, and the extraction was cross-referenced by three reviewers (T.B., S.F., & D.G.) to ensure accuracy.

Data collection and analysis

Among studies included, the following relevant study characteristics were collected: sample size, publication year, patient population and treatment characteristics,

outcomes assessed, types of interventions investigated, and key findings. A formal quality of evidence (QoE) assessment was conducted in accordance with the Hadorn criteria for clinical trials (Appendix B)[13]; any studies identified as having none or minor flaws according to the Hadorn criteria were designated an "adequate" quality of evidence, while those with major flaws were designated a "doubtful" quality of evidence.

Role of funding
No funding was received to complete this study.

Results

Search results
Through the initial database searches, a total of 6478 articles were identified (Fig. 1). After duplicates were removed, 5173 articles remained. After screening by abstracts/titles and full-texts, a total of 235 articles were identified for inclusion in the analysis, with 149 randomized controlled trials (RCTs) and 87 non-randomized studies. The majority of studies evaluated an intervention for the prevention of ARD but had methodological challenges resulting in a doubtful quality of evidence. Interventions were categorized according to the following treatment types: topical non-steroidal agents, topical corticosteroids, barrier films and dressings, laser therapy, natural and miscellaneous agents, growth factors and oral agents, and alternative and multi-component therapies. A summary of key findings according to treatment category has been included in Tables 1 (for prevention modalities) and 2 (for management modalities). Individual characteristics and primary findings of all RCTs have been described in Appendix C (Tables 1–12).

ARD prevention methods
Topical non-steroidal agents
A total of 42 studies assessed topical non-steroidal agents for the prevention of ARD, including 12 and 28 non-randomized studies and RCTs, respectively[14–55] (Appendix C, Table 1). The majority of RCTs assessed trolamine-based products (including Biafine ®),[14–18,21,33] hyaluronic acid/hyaluronan-based products,[22–26] and heparinoid (Hirudoid ®).[30,31,197] A few RCTs demonstrated promising results in the use of trolamine emulsion,[14,21] hyaluronic acid/hyaluronan,[22,24,25] 3M™ Cavilon™ Durable Barrier Cream,[34,35] heparinoid (Hirudoid),[30,31] boron-based gel,[37] and other emulsions[38,47,50,52]; however, evidence supporting the use of these interventions was either conflicting or insufficient to produce recommendations for clinical practice.

Topical corticosteroids
A total of 18 studies assessed topical corticosteroids for the prevention of ARD, including three non-randomized

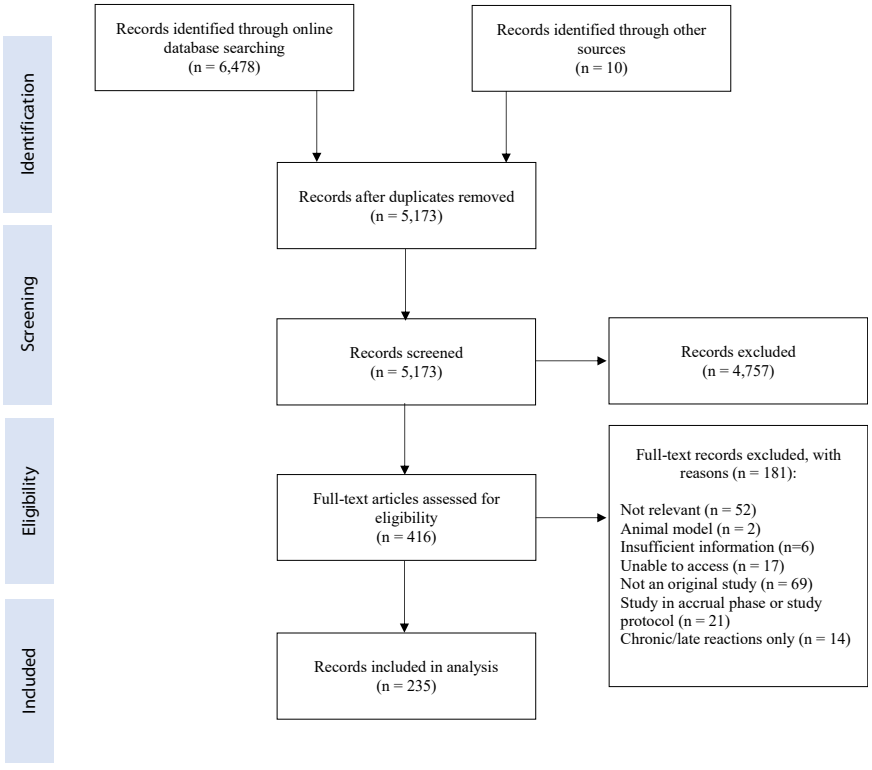

Fig. 1: **Literature search results from 1946 to September 2020.**

Intervention category	Total studies (RCTs)	Total number of patients (Median sample size; range)	Interventions identified (n)	Cancer site included (n)	Key findings	Reference
Topical non-steroidal agents	42 (29)	4364 (64; 1–547)	Trolamine emulsions (8); Hyaluronic acid/hyaluronan (5); Urea (2); Heparinoid (Hirudoid ®) (3); Other (27)	Breast (25); Head and neck (10); Anus (1); Multiple (6)	There was inconsistent evidence supporting the use of trolamine emulsions, hyaluronic acid, and heparinoid for the prevention of ARD. Insufficient evidence was reported to support the use of urea, Xonrid, hydroactive colloid gel, and other interventions.	14–55
Topical corticosteroids	18 (15)	1715 (81; 12–219)	Mometasone furoate (8); Betamethasone (6); Other (4)	Breast (14); Head and neck (3); Multiple (1)	Mometasone furoate and betamethasone were both generally found to be effective in ARD prevention. There is insufficient evidence supporting the use of other corticosteroids, such as hydrocortisone and beclomethasone.	56–73
Barrier films and dressings	25 (18)	1856 (39; 2–333)	Mepitel® film (9); 3M™ Cavilon™ No-Sting Barrier Film (4); StrataXRT® (topical film-forming gel) (3); Silver nylon dressing (3); Other (6)	Breast (15); Head and neck (6); Prostate (2); Other (2)	Mepitel film and Hydrofilm were both generally found to be effective in ARD prevention. There was inconsistent evidence supporting the use of StrataXRT, silver nylon dressings, Cavilon No-Sting barrier film, and other interventions in ARD prevention.	35,62,74–96
Laser therapy	10 (5)	576 (43.5; 25–120)	Photobiomodulation (low-level laser) therapy (9); Photomagnetic therapy (1)	Breast (7); Head and neck (3)	Photobiomodulation (low-level laser) therapy was generally found to be effective in ARD prevention.	97–106
Natural and miscellaneous agents	51 (39)	5290 (62; 1–686)	*Aloe vera* (6); Curcumin (turmeric) (6); Calendula (marigold) (4); Chamomilla recutita (3); Other (38)	Breast (32); Head and neck (12); Multiple (5); NS (2)	Topical olive oil was generally found to be effective in ARD prevention. Honey-based products were generally ineffective in ARD prevention. There was inconsistent evidence supporting the use of aloe vera, oral and topical curcumin, topical calendula (marigold)-based products, topical NS-21 skin repair treatment, topical chamomilla recutita, Holoil, topical silymarin, and other interventions for the prevention of ARD. Insufficient evidence was reported to support the use of urea, Xonrid, hydroactive colloid gel, and other interventions.	21,107–120,121–131,132–156
Growth factors and oral agents	9 (7)	1721 (78; 40-1142)	Enzyme mixture (3); Other (6)	Head and neck (5); Breast (2); Multiple (1); Cervical (1)	Mixed enzyme tablets were generally found to be effective in ARD prevention. Insufficient evidence was reported to support the use of other interventions.	157–165
Alternative and multi-component therapies	31 (17)	4963 (90; 1–1358)	Lactokine-based two-step care system (R1 & R2) (3); Lotion (3% urea, polidocanol and hyaluronic acid) (3); Therapeutic touch (1); Other (25)	Breast (20); Head and neck (5); Multiple (4); Other (2)	Antiperspirant/deodorant use and general skin washing were found to have minimal effects on ARD severity. Insufficient evidence was reported to support the use of any interventions for ARD prevention.	166–196

"n" indicates the number of studies. NS, not specified; RCT, randomized controlled trial; ARD, radiation dermatitis.

Table 1: **Characteristics of studies assessing prevention methods for radiation dermatitis.**

studies and 15 RCTs[56–73] (Appendix C, Table 2). Topical mometasone furoate (most commonly 0.1% potency) was evaluated in eight RCTs[56–62,72] and demonstrated efficacy across trials of both doubtful and adequate QoE in preventing overall ARD and erythema. Betamethasone further demonstrated prophylactic efficacy in ARD

Intervention category	Total studies (RCTs)	Total number of patients (Median sample size; range)	Interventions identified (n)	Cancer site included (n)	Key findings	Reference
Topical non-steroidal agents	18 (9)	2800 (61; 1–573)	Heparinoid (Hirudoid ®) (4); Hydroactive colloid gel (Flamigel ®) (3); Other (11)	Breast (10); Head and neck (2); Multiple (5); Other (1)	There was inconsistent evidence supporting the use of heparinoid (Hirudoid) for the management of ARD. Insufficient evidence was reported to support the use of other interventions.	15,29,30,39,197–210
Topical corticosteroids	2 (2)	230 (115; 19–211)	Hydrocortisone (1); NS (1)	Head and neck (1); Multiple (1)	Insufficient evidence was reported to support the use of any interventions for ARD management.	211,212
Barrier films and dressings	13 (7)	1216 (39; 12–357)	Mepilex ® Lite dressings (3); Other (10)	Head and neck (4); Breast (3); Multiple (5); Skin (1)	Mepilex Lite dressings were generally found to be effective in ARD management. Insufficient evidence was reported to support the use of all other interventions for ARD management.	84,213–224
Laser therapy	5 (0)	96 (4; 1–79)	Photobiomodulation (low-level laser) therapy (3); High level laser therapy (1); NS (1)	Breast (2); Head and neck (1); Skeletal (1); Anal (1)	Insufficient evidence was reported to support the use of any interventions for ARD management.	225–229
Natural and miscellaneous agents	9 (4)	528 (60; 24–126)	Honey (2); Holoil® (containing Hypericum Perforatum/St. John's-wort and Neem Oil) (2); Other (6)	Breast (4); Head and neck (2); Multiple (3)	Insufficient evidence was reported to support the use of any interventions for ARD management.	145,230–237
Alternative and multi-component therapies	11 (4)	422 (30; 1–90)	Hydrotherapy (1); Acupuncture (1); Mixed emulsion (1); Other (11)	Breast (4); Head and neck (1); Multiple (6)	Insufficient evidence was reported to support the use of any interventions for ARD management.	179,186,189,200,238–244

"n" indicates the number of studies. RCT, randomized controlled trial; ARD, radiation dermatitis.

Table 2: **Characteristics of studies assessing management methods for radiation dermatitis.**

prevention,[65–69,73] suggesting that the current evidence supports the use of both mometasone furoate and betamethasone in preventing ARD and associated symptoms.

Barrier films and dressings

Among studies investigating barrier films and dressings, seven non-randomized studies and 18 RCTs were identified, for a total of 25 studies[35,62,74–96] (Appendix C, Table 3). Promising results were found in studies on polyurethane film (Hydrofilm ®),[74,96] topical film-forming gel (StrataXRT ®),[75–77] silicone-based polyurethane (Mepitel ® film),[78,79,84–86] 3M Cavilon No Sting barrier film,[87] and others.[90,93] Despite positive findings in some studies, particularly on Hydrofilm and Mepitel film, there were often conflicting findings or a small sample size supporting film and dressing use, suggesting that future research may be needed to support these interventions.

Laser therapy

Photobiomodulation (PBM) (low-level laser) therapy was investigated in ten studies, including four non-randomized and five RCTs[97–106] (Appendix C, Table 4). The majority of studies found PBM to be beneficial in preventing ARD when compared to standard of care and/or placebo in breast cancer patients. Only one RCT was conducted in head and neck patients, which reported similar benefit in the prevention of ARD and associated pain.[104]

Natural and miscellaneous agents

Natural and miscellaneous agents were assessed in 51 studies, of which 39 were RCTs[21,107–120,121-131,132-156] (Appendix C, Table 5). The majority of interventions showed minimal or no benefit protecting against ARD in a randomized setting, including honey-based products,[125,126] vitamins,[129,130] chamomile-based cream,[141] calendula (marigold)-based products,[113,116] and products containing glutamine.[123,124] Olive oil and a combined olive oil and calcium hydroxide product demonstrated efficacy in two RCTs against placebo[143] and standard of care,[142] respectively. Across multiple RCTs, support for aloe vera,[107,109–112] oral and topical curcumin,[117–122] topical NS-21 cortisone-free skin repair treatment,[131,132] and other interventions was conflicting. While benefits were seen in silymarin,[128] adlay bran extract,[133] zinc,[135] cucumis sativus,[139] Boswellia cream (Bosexil®),[140] lianbai,[145] and other products, a single RCT was considered insufficient to confirm efficacy. The current evidence on

natural and miscellaneous agents is insufficient to provide recommendations for ARD prevention.

Growth factors and oral agents

Two studies evaluated topical epidermal growth factors,[211,212] while seven evaluated oral agents, such as celecoxib,[157] sucralfate,[158] pentoxifylline,[159] histamines,[160] and enzyme mixtures[161–163] (Appendix C, Table 6). Three RCTs consistently supported the use of an oral enzyme mixture containing 100 mg of papain, 40 mg of trypsin, and 40 mg chymotrypsin in ARD prevention, suggesting potential use for oral enzyme compounds in clinical practice. Despite promising findings in epidermal growth factor use in one RCT,[164] further research is needed to discern prophylactic benefit. No benefit was found in the use of all other oral agents.

Alternative and multi-component therapies

Alternative and multi-component therapies were assessed in 17 RCTs and 16 non-randomized studies[166–196] (Appendix C, Table 7). Minimal difference was found between patients who used deodorant or antiperspirant and those who washed regularly,[167,168] did not use any intervention,[169] or used standard of care,[170] suggesting that antiperspirant/deodorant use should not be encouraged with the intent of preventing ARD. Similarly, most other interventions had no preventative benefit across RCTs, such as alkaline water,[172] or minimal benefit confined to one RCT, such as repalysyal[180] or other emulsions.[179,182] Based on evidence from multiple RCTs, aluminum/deodorant use and washing with water and soap do not worsen ARD, but there is insufficient evidence to support their use in the prevention of ARD. Overall, evidence supporting the majority of alternative and multi-component therapies is lacking.

ARD management methods

Topical non-steroidal agents and corticosteroids

Non-steroidal and steroidal agents were evaluated in 18 and two studies, respectively, with a total of 11 RCTs (Appendix C, Tables 8 and 9). Conflicting evidence was reported supporting heparinoid (Hirudoid) use in four RCTs.[29–31,197] All other non-steroidal agents, such as trolamine emulsion,[15] doxepin,[198] and sucralfate[199] had insufficient evidence and/or demonstrated minimal benefit. Topical corticosteroids (hydrocortisone[211] and an unknown steroid[245]) were further shown to have no benefit in managing ARD.

Barrier films and dressings

Across seven randomized and six non-randomized studies, Mepilex® Lite dressings,[213–215] Hydrosorb® (hydrogel polyurethane film),[216] hydrocolloid dressings,[217] and other barrier films and dressings were evaluated for ARD management (Appendix C, Table 10). Mepilex Lite dressings was favoured over aqueous creams[213,215] and standard wound care[214] in three RCTs. Dry dressings (Tricotex[218] and Mepitel film[84]) showed positive results through single RCTs to manage ARD.

Natural, miscellaneous, alternative, and multi-component therapies

A total of 25 studies evaluated interventions in the natural and miscellaneous[145,230–237] and alternative and multi-component categories[179,186,189,200,238–244] (Appendix C, Tables 11 and 12). Among all interventions, insufficient evidence was available to confirm efficacy. Henna-containing ointment,[232] lianbai liquid,[145] hydrotherapy,[246] acupuncture,[244] and an emulsion[179] were effective in managing symptoms once ARD developed, but evidence was only shown through a single RCT, highlighting the need for further research confirming efficacy.

Discussion

To our knowledge, this is the most comprehensive and up-to-date systematic review to compile all published clinical trials investigating methods for ARD care. A systematic review was conducted in 2013 by Wong et al.[10] in the development of previous MASCC clinical practice guidelines for ARD, identifying 56 relevant RCTs. To develop clinically relevant recommendations on the use of various interventions for ARD, we aimed to include all study types through a systematic approach and identified dozens of different interventions evaluated for ARD prevention and management. A total of 235 original studies were included in this review, including 149 randomized controlled trials (RCTs). Most interventions could not be recommended due to a low quality of evidence, lack of supporting evidence, or conflicting findings across multiple trials. Overall, photobiomodulation therapy, Mepitel® film, mometasone furoate, betamethasone, olive oil, and oral enzyme mixtures showed promising results across multiple RCTs mainly as ARD prevention methods.

Several reviews have been conducted to summarize the current evidence on ARD prevention and management methods. A review by Chan et al. (2014) identified 47 RCTs on interventions for ARD care and recognized six intervention types: oral systemic medications, skin care practices, steroidal topical therapies, non-steroidal topical therapies, dressings, and other.[247] An oral enzyme mixture was found to be effective in preventing ARD and minimizing ARD severity, which was similarly found in our review through studies by Dale et al. (2001) and Gujral et al. (2001).[161,162] Additionally, similar to our findings, the use of deodorant did not contribute to increased ARD severity among breast cancer patients. Other reviews have also been conducted on this area and produced similar results, but were limited due to their lack of a systematic approach,[248,249] restricted inclusion criteria,[250,251] or sole focus on one type of intervention.[252–254] Among most reviews, hygienic skin

care practices, such as washing with water and/or soap and the use of antiperspirant or deodorant, were consistently found to have minimal impact on ARD severity.

Like other authors who have reviewed ARD care regimens in the past, several key limitations were identified which make it challenging to develop clinical practice recommendations using the current evidence base alone. First, there are limited publications discussing the management of ARD in low-limited income environments. In less developed areas of the world, patients may struggle with poor sanitation and nutrition, as well as access to recommended effective modalities, which all impact skin healing. ARD management may be limited to washing with mild soap and topical steroids, resulting in discontinuation of RT in cases with moist desquamation. It is important for the field of ARD to overcome the barriers in low-resource countries for adequate management of ARD. Another recurring challenge in the field of ARD research has been the high heterogeneity in study design, symptom assessment methods, outcomes reported, and representation of all skin types. Discrepancies in assessment timing thus made comparisons between studies less reliable. Diverse patient demographics and treatment characteristics further added to this challenge, such as dose fractionation (e.g., hypofractionation vs conventional fractionation), use of a boost and/or bolus, use of concurrent systemic agents, RT modality received, use of concurrent chemotherapy, and anatomical location treated. RT-specific demographic information for included studies has been summarized in Appendix D; future research should be undertaken to determine the impact of treatment-specific factors on the efficacy of each intervention. Furthermore, the majority of studies included breast cancer and head and neck cancer patients as these cancer sites are most at-risk of developing ARD given the dose and RT techniques used, the nature of skin folds in these regions; as such, other cancer sites, such as anorectal, skin, or bone cancers, were not adequately reflected in this review due to the limited literature available.

In addition, there was considerable variability of outcome measures within intra- and inter-agent studies. While many studies used validated scoring scales to measure ARD, many other studies used internally-developed scoring systems, which in turn minimized comparability between studies. With over 50 available assessment methods for ARD severity and associated symptoms, including clinician-reported outcome (CRO) measures, patient-reported outcome measures, and biophysical parameters, it has become difficult to discern the true benefit of interventions in minimizing ARD severity. The high variability in ARD assessment reveals a need for the establishment of an international consensus on a "gold standard" method for ARD measurement. Furthermore, while the most commonly reported outcomes across the majority of studies included moist desquamation incidence, overall ARD grade (based on standardized CRO scales), and subjective measures, such as pain and pruritus, this review revealed other clinically important outcomes that were less often reported and therefore could not be compared. Such outcomes included treatment delays, patient satisfaction with intervention, treatment costs, skin hydration levels, time to ARD resolution, and tolerability of intervention. Despite the vast amount of evidence conducted on ARD, minimal conclusions can be drawn from the evidence alone on the clinical feasibility of each intervention due to the lack of comparability among trials.

Other general trends were found with the proposed agents. The majority of studies had methodological challenges (such as a small sample size and/or lack of blinding), resulting in a low QoE. A limited ability to blind is an inherent flaw in many dermatological trials that is understandably difficult to control; nevertheless, it presents a challenge in the objective assessment of interventions that are visible to observers, such as barrier films and dressings or certain procedural interventions (e.g., acupuncture, massage therapy, laughter therapy). Additionally, the majority of interventions also had few studies evaluating their efficacy. Recommendation of an intervention is only typically justified upon clear demonstration of efficacy across several high-quality randomized trials, yet only few interventions on ARD have been investigated across multiple RCTs. Combined, these challenges made it difficult to assess many of the proposed therapeutic agents.

In addition to common challenges across the field of ARD research, several other limitations were found in our methodology. First, while the 1996 Hadorn criteria for evaluating the quality of research studies has been beneficial in other settings, such as the development of the MASCC Mucositis Clinical Practice Guidelines,[255] it may have not have been suitable for the purpose of this review due to the overly generalized assessment criteria. For example, a study was automatically deemed to be of "poor" QoE for using an open-label approach, despite restrictions against blinding with certain interventions. As such, some studies may have been designated a "doubtful" QoE for the sole reason that the intervention could not be blinded. The use of the Hadorn criteria likely overemphasized certain flaws because it was not designed to assess QoE in dermatological trials, thus highlighting the need for a QoE assessment tool tailored specifically to dermatology trials.

Next, since the initial literature search was conducted in September 2020, several RCTs have since been published supporting interventions for the prevention and management of ARD, such as *Calendula officinalis*,[256] photobiomodulation therapy,[257] and topical

steroid.[212] In light of this limitation, an updated search has been conducted from September 22nd, 2020 to January 21st, 2023 and revealed 65 new studies, of which 38 are RCTs; a list of the latest RCTs has been provided in Appendix E, along with a summary of RCT characteristics. RCTs were recently published on interventions already identified through the present review, such as Mepitel film,[258] topical corticosteroids,[259,260] heparinoid,[261] photobiomodulation,[257,262,263] aloe vera gel,[264] calendula,[256] and others. Additional RCTs were identified on new interventions not previously explored before September 2020, such as the use of compound Kushen injection,[265] epigallocatechin-3-gallate,[201,266] bacterial decolonization,[267] and others. For example, in a population of 81 breast cancer patients, Siddiquee et al. (2020)[256] reported no difference in grade 2+ ARD severity between patients receiving Calendula and standard of care ($p = 0.92$); this finding supported previous findings by Sharp et al. (2013)[116] and helps to confirm the potential inefficacy of Calendula in preventing ARD. Robijns et al. (2021) added to the existing evidence base on photobiomodulation therapy research in head and neck cancer patients ($n = 46$), whereby patients who received photobiomodulation therapy were found to have a lower percentage of grade 2–3 ARD when compared to the control group (77.8% control group vs. 28.6% photobiom8odulation group, $p = 0.002$).[257] A 2022 trial on Mepitel film similarly demonstrated benefits of Mepitel film in preventing ARD in a population of 376 patients (15.5% vs. 45.6% $p < 0.0001$).[258] The findings of these recent trials demonstrate a positive trend in the evidence supporting photobiomodulation therapy, topical steroids, and Mepitel film for the prevention of ARD. Overall, among the RCTs identified, 27 demonstrated some significant improvement in RD severity; these latest findings may influence the recommendations made in future guidelines, thus further highlighting a need for regular updates of the literature to reflect ongoing changes in the evidence base.

With regards to the inclusion of studies, we only included studies published in the English language and did not use a translation tool for non-English studies to avoid any risk of mistranslation; this may have resulted in the exclusion of relevant studies. Additionally, there may be non-reporting bias, due to the exclusion of studies that (1) were conducted but never published, and (2) studies that calculated a measure of interest but did not mention this in their report(s), for various reasons. To minimize the risk of non-reporting bias, the databases were searched comprehensively according to the Cochrane Handbook for Systematic Reviews of Interventions[268] and under the supervision of a medical librarian, though some bias may still be present.

Lastly, in the past decade, advanced RT modalities have shown promising results in minimizing ARD severity. Our review was limited in that we only included agents directly administered with the intent of reducing skin toxicities and therefore excluded advanced RT techniques. IMRT,[269] helical tomotherapy,[270] prone positioning (in breast patients),[271] proton RT,[272] and extreme hypofractionation[273] have demonstrated efficacy in reducing ARD severity to some extent in past trials. Additionally, there were limitations in the diversity of populations in many of the clinicals trials reviewed, including underrepresentation of skin of color and English-only speaking populations. Further research should broaden inclusion across languages and skin types to encourage development of evidence-based recommendations on appropriate RT modalities to reduce the burden of ARD in all patients.

Conclusions

In spite of the significant amount of available literature, the evidence supporting interventions for ARD prevention and management is highly variable, most likely due to the differences in study design, outcomes assessed, intervention type, and patient population between studies. Further trials should be conducted on interventions that have shown promising results thus far, such as photobiomodulation therapy, Mepitel film, Hydrofilm, olive oil, oral enzyme mixtures, mometasone furoate, and betamethasone, to confirm efficacy in larger, diverse cohorts of patients. Additional work should also be undertaken to investigate the use of advanced RT modalities in minimizing severe skin toxicity. It is essential that clinical practice guidelines on ARD care not only reflect the current evidence, but the clinical, real-world experience of healthcare providers as well. Expansion of research to include real-world evidence will assist in overcoming the current issues in ARD management with resource-limited environments unable to use any of the potential interventions discussed. As such, to inform evidence-based skin care recommendations on behalf of MASCC, a Delphi consensus process will be reported in a separate publication to reflect the opinions of a panel of experts in treating ARD.

Contributors

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by T.B., D.G., S.F., P.P., L.K., S.F.L., A.W.C., H.C.Y.W., S.M., and S.K., H.L., S.F.L., A.W.C., and H.C.Y.W. performed the literature search. S.C. advised on the analysis methodology. The first draft of the manuscript was written by T.B. and D.G., and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data sharing statement

Not applicable.

Declaration of interests

Julie Ryan Wolf declares BARDA funding for clinical trial for safety of Silverlon dressing for radiation dermatitis and UpToDate coauthor royalties. Tara Behroozian received a travel grant from the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Group (Fall 2022). Edward Chow conducted a clinical trial and

received materials free of cost from Mölnlycke Health Care. All other authors declare that they have no conflict of interest.

Acknowledgements

T.B. and D.G. contributed equally to this work. P.B. and E.C. are joint senior authors. J.R.W. and C.v.d.H. are chair and vice chair of the MASCC Oncodermatology Study Group, respectively. All authors are members of the MASCC Oncodermatology Study Group. Thenugaa Rajeswaran BSc (Candidate) and Milena Gojsevic BSc (Candidate) assisted in the data verification. No funding was received.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.eclinm.2023.101886.

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