Review

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Skin Microbiome and Radiation-Induced Skin Injury: Unraveling the Relationship, Mechanisms, and Therapeutic Implications

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Abstract: Radiotherapy (RT) is a commonly used treatment method in oncology. A vast majority of patients undergoing RT suffer from radiation-induced skin injury (RISI), which results from complex biochemical reactions in the irradiated skin. Current strategies for preventing and managing RISI are insufficient for achieving full skin regeneration. Multiple studies have shown that alterations in the skin microbiome correlate with the development and severity of RISI. These studies suggest that dysbiosis is a crucial factor in promoting radiation-associated dermatitis. Targeting the skin microbiota presents a potential therapeutic approach that could significantly improve the quality of life for patients undergoing RT. This review aims to present current findings on the interplay between the skin microbiome and radiation-induced skin damage, as well as to discuss potential therapeutic strategies for preventing and mitigating this condition.

Keywords: skin; cancer; microbiome; radiation; injury

1. Introduction

Radiotherapy (RT) is a valuable treatment in cancer management, leveraging ionizing radiation to selectively target and destroy malignant cells. More than half of all cancer patients receive RT as a part of their treatment regimen [1]. The therapeutic efficacy of RT contributes to approximately 40% of tumor control in multimodal treatment approaches. The specific frequency, duration, and combination with other treatments depend on multiple factors, including the type and stage of the cancer, the patient's overall health, and the treatment goals as well as radiation dosages and duration. However, the primary problem is the damage it causes to the surrounding normal tissues of the malignant tumor [2]. Observed side effects of RT include chromosomal aberrations, secondary cancers, infertility, internal organs, and skin damage [3–5].

One of the prevalent adverse effects of RT is radiation-induced skin injury (RISI), also described as radiodermatitis or radiation dermatitis, which at some levels affects up to 95% of patients undergoing RT. Acute RISI (aRISI) manifests within the first 90 days of radiation treatment and presents as erythema, pigmentation changes, edema, and dry or moist desquamation. Noteworthy,

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in severe cases, aRISI may necessitate temporary or permanent cessation of RT, jeopardizing the success of the treatment. Chronic RISI, on the other hand, can appear months to years post treatment and includes symptoms such as skin hypersensitivity, dyspigmentation, xerosis, telangiectasia, alopecia, fibrosis, ulcers, and radiation-induced morphea (RIM)[6,7]. Although chronic RISI does not interfere directly with the effectiveness of RT, it significantly impacts the patient's quality of life.

The risk and severity of RISI are influenced by several factors, including higher radiation doses per fraction, greater cumulative doses, concurrent chemotherapy or immunotherapy, and treatment in anatomically sensitive regions in areas with thin skin or skin folds, such as head, neck, breast, and axilla [8,9]. The RT induced damage occurs at the molecular level, leading to extensive DNA damage and generation of reactive oxygen species (ROS), which disrupt critical cellular metabolic processes and induce a complex cascade of signaling pathways [10]. Within the skin, these effects initiate a cascade of inflammatory responses, including the activation of nuclear factor kappa B (NF-κB) and the release of chemokines, adhesion molecules, and pro-inflammatory cytokines, including eotaxin, intercellular adhesion molecule 1 (ICAM-1), interleukin (IL)-1, IL-3, IL-5, IL-6, IL-8, and tumor necrosis factor-alpha (TNF-α). Together, they contribute to endothelial cell damage, increased vascular permeability, and immune cell recruitment, ultimately leading to local inflammation and skin breakdown [11]. Monocyte migration to the irradiated skin sites results in their differentiation into macrophages, which secrete platelet-derived growth factor (PDGF) and transforming growth factor-beta (TGF-β). These factors, in turn, promote migration of fibroblasts and activation of pro-fibrotic pathways [12].

Skin damage induced by RT includes direct destruction of the skin layers.
A prospective study conducted by Pazdrowski et al. revealed statistically significant differences in transepidermal water loss (TEWL), an indicator of the compromised epidermal barrier, in irradiated skin across various time points [13]. Furthermore, in patients who had previously undergone RT for head and neck cancer, TEWL was significantly elevated in irradiated regions compared to non-irradiated areas. Notably, the median time since RT was 6 years, and increased TEWL was observed irrespective of the presence of clinical manifestation of cRISI [14].

The intact epidermal lipid barrier plays a crucial role in inhibiting the overgrowth of pathological microbiota due to the antibacterial properties of skin fatty acids [15]. Additionally, for many skin commensals, skin lipids serve as an essential nutrient source [16]. Therefore, damage to the skin barrier induced by RT is a plausible factor contributing to alterations in the skin microbiome in cancer patients. Figure 1 illustrates changes in skin cells and cell signaling following RT.

The skin microbiome, a vast and diverse community, has been suggested to play a key role in the development and progression of RISI [17]. The aim of this review is to present current findings on the interaction between skin microbiome and radiation-induced skin damage, and to discuss potential therapeutic strategies for its prevention and management.

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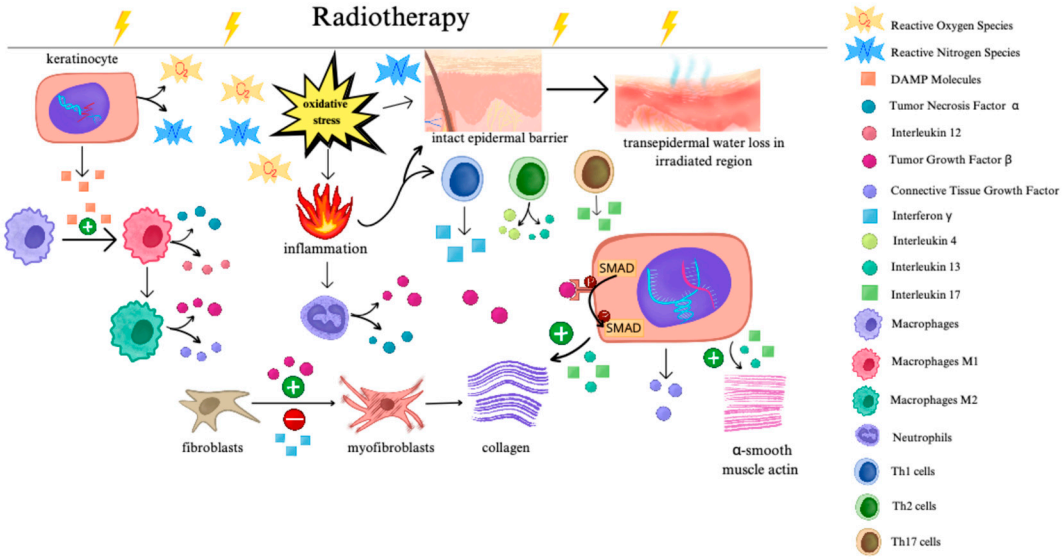

Figure 1. A schematic representation of the subsequent changes in immune cells, skin cells, and skin barrier following radiotherapy.

2. Skin Microbiome

Skin, the largest organ of the human body, serves as a protective barrier against environmental factors. It is estimated to harbor thousands to millions of microbial cells per square centimeter, depending on the specific region. This diverse microbial population includes bacteria, viruses, fungi, and micro-eukaryotes (e.g. mites), which co-exist in symbiotic relationship with the host. Numerous internal and external factors, influence the distribution and abundance of these microbial communities including age, sex, hormone levels, stress, climate, exposure to ultraviolet (UV) radiation, pollution, or chemicals, as well as hygienic and cosmetic practices [18–20]. Additionally, the local composition of glands and hair follicles affects bacterial colonization in different body regions. Sebaceous areas such as face and back are enriched with lipophilic *Cutibacterium* species. Moist areas, including the axillary vault, interdigital spaces, and inguinal crease, favor the growth of *Corynebacterium* and *Staphylococci species*. In contrast dry areas like the inner forearms, are more commonly colonized by *Proteobacteria* and *Flavobacteriales* [21]. Among fungi, *Malassezia* is the most prevalent genus, accounting for 80% of the skin fungal flora [22] and is particularly dominant in sebum-rich areas such as face, trunk, and scalp [23]. *Demodex* mites, a type of microeukaryote inhabit pilosebaceous follicles, predominantly on the face [24]. Viruses remain the least studied component of the skin microbiome, with the majority being bacteriophages belonging to families such as *Caudovirales*, *Siphoviridae*, and *Myoviridae* [25].

The presence of commensal microbiota contributes to upregulation of genes associated with immune and inflammatory response, as well as keratinocyte differentiation. Skin colonization by microorganisms stimulates the production of proinflammatory cytokines such as IL-1α and IL-1β by immune cells. Furthermore, the commensal microbiota modulates epidermal proliferation and differentiation by influencing the gene expression of structural proteins, such as filaggrin, repetin, and psoriasin [26].

Importantly, the skin microbiota plays an essential role in maintaining the skin's barrier function. For example, *Staphylococcus epidermidis* produces sphingomyelinase, an enzyme that facilitates host ceramide synthesis- waxy lipid molecules that prevent dehydration [27]. In addition, microbes are also responsible for secreting agents that activate aryl hydrocarbon receptor (AHR) in keratinocytes, supporting epidermal differentiation and skin integrity [28]. Skin also maintains microbial balance through antimicrobial peptides (AMPs) and enzymes that regulate the skin's pH and moisture levels. Defensins, including human neutrophil peptides (HNPs), are a class of AMPs-

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secreted by both keratinocytes and immune cells during inflammation. These peptides exhibit broad-spectrum antimicrobial activity, directly targeting pathogens and preventing their colonization [29].

Furthermore, human skin is an active immune organ populated by various immune cells, including Langerhans cells, dermal dendritic cells, macrophages, mast cells, and different subtypes of T cells and B lymphocytes [30]. Immune cells within the skin interact dynamically with the skin microbiota, and this mutual relationship is crucial for maintaining skin homeostasis. *Staphylococcus epidermidis* has been shown to activate gamma delta (GD) T cells and induce the expression of antimicrobial perforin-2 (P-2) [31]. In murine models, early life colonization of skin with *Staphylococcus epidermidis* promotes activation of regulatory T (Treg) cells in the neonatal skin, thereby establishing immune tolerance to commensal microbes [32]. Interestingly, neonatal colonization with *Staphylococcus aureus* but not with *Staphylococcus epidermidis* upregulates IL-1β expression and increases the ratio of helper T helper 17 (Th17) cells to Tregs, suggesting a more inflammatory immune response [33]. Furthermore, commensal colonization with *Staphylococcus epidermidis*, *Staphylococcus xylosus*, *Staphylococcus aureus*, *Corynebacterium pseudodiphtheriticum*, and *Cutibacterium acnes* leads to an accumulation of IL-17A- and IFN-γ-expressing T cells in the skin, which in turn upregulates the expression of antimicrobial alarmins S100A8 and S100A6 [34]. Therefore, colonization with commensal species is a crucial element of effective protection against invasive microbes. Keratinocyte expression of major histocompatibility complex class II (MHCII) is another factor contributing to homeostatic immunity to commensal colonization, primarily through the accumulation of Th1 cells in the skin [35]. Importantly, T cells induced by *Staphylococcus epidermidis* have been demonstrated to accelerate wound healing in mice [36]. Interestingly, *Cutibacterium acnes* regulates immune tolerance through the production of short-chain free fatty acids (SCFAs), which inhibit the activity of histone deacetylase (HDAC) 8 and 9, and therefore downregulate the expression of pro-inflammatory IL-6 and IL-8 [37]. These evidence altogether indicate that alterations in the skin microbiome, accompanied by disrupted skin barrier, increase the susceptibility to multiple skin diseases. On the other hand, the presence of inflammation in different skin disorders significantly contributes to dysbiosis [38].

3. Skin Microbiota in RISI

Studies have shown that RT alters the skin microbial barrier by significantly reducing its abundance and diversity. Noteworthy, the composition of the skin microbiome before the beginning of RT significantly impacts the occurrence and severity of RISI, providing a possible prediction for the disease outcome. However, the results of studies conducted so far are inconclusive. Research by Huang et al. on aRISI rat models revealed a significant predominance of Firmicutes, especially *Streptococcus, Staphylococcus, Acetivibrio ethanolgignens, Peptostreptococcus,* and *Anaerofilum* in rats that developed aRISI after RT, compared to the control group with no previous contact with RT. Researchers additionally analyzed patient data from BioProject 665,254 and observed an overall significant reduction in bacterial diversity following RT, as well as a greater abundance of *Klebsiella, Pseudomonas,* and *Staphylococcus* in patients with RISI compared to healthy subjects. Interestingly, the analysis revealed a significant predominance of Proteobacteria and a low abundance of Firmicutes after RT in the group of patients who developed chronic ulcers [39].

Another study explored the cutaneous microbiota of 78 patients with RISI, both acute and chronic. Compared to the control group with no RT history, RISI patients exhibited a predominance of Firmicutes and Proteobacteria. RISI was associated with a predominance of *Klebsiella, Staphylococcus, or Pseudomonas,* while the skin of healthy subjects was mainly inhabited by *Klebsiella*, *Cutibacterium*, *Corynebacterium*, *Bacillus,* and *Paracoccus.* In addition, a longer duration of RISI was negatively correlated with the diversity of cutaneous bacteria. A slower healing of RISI was associated with greater amounts of *Pseudomonas, Staphylococcus*, and *Stenotrophomonas*. Consistent with the previous study, chronic ulcers were linked to the predominance of Proteobacteria and a low abundance of Firmicutes. The skin microbiota of these patients consisted mainly of *Klebsiella* or

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Pseudomonas, *Cutibacterium,* and *Stenotrophomonas*. The coexistence of *Pseudomonas*, *Staphylococcus*, and *Stenotrophomonas* was strongly correlated with the development of chronic ulcers [17].

Another study exploring skin microbiota in RISI detected a significantly higher abundance of *Ralstonia*, *Truepera,* and *Methyloversatilis* genera and a lower abundance of *Staphylococcus* and *Corynebacterium* genera in patients with no/mild aRISI (RTOG 0/1) compared to patients with severe aRISI (RTOG 2 or higher), both before and after RT [40]. On the other hand, research by Hülpüsch et al. revealed the association between a low number of commensal skin bacteria, i.e. *Staphylococcus epidermidis, Staphylococcus hominis,* and *Cutibacterium acnes* at the beginning of the treatment and the development of severe aRISI. Additionally, a non-species-specific overgrowth of skin bacteria has been proven to occur right before the onset of RISI symptoms [41]. Similarly, another study assessed the composition of cutaneous *Staphylococcus* species before RT and linked the low abundance of *Staphylococcus hominis* and *Staphylococcus aureus* to the development of severe aRISI [42]. In addition, research by Kost et al. explored the impact of nasal colonization with *Staphylococcus aureus* before RT on the development of aRISI in patients with breast and head and neck cancer. The baseline colonization with *Staphylococcus aureus* in nares was higher in patients who developed grade 2 or higher aRISI compared to those with grade 1. Interestingly, after RT, the *Staphylococcus aureus* colonization was higher in nares, irradiated skin region, and contralateral skin in patients with grade 2 compared to patients with grade 1 aRISI [43].

Ulceration is one of the most severe clinical manifestations of RISI. Acute ulcers are less frequent and develop on the base of wet desquamation. Conversely, chronic ulcers typically occur in the later stages of the disease [44]. Patient-related risk factors for ulcer development include concomitant diseases, and a particular composition of the skin microbiota, which, as mentioned above, exhibits several differences when compared to RISI patients without chronic ulcers [17,39]. Although the ulceration is a clinical manifestation of RISI, assumptions about its microbiome should not be extrapolated solely from data regarding typical bacteria in RISI. Table 1 summarizes studies on microbiota in RISI.

It is essential to highlight the bidirectional influence of RISI and skin microbiome. On one hand, RT induces a cascade of events that cause alterations in immune cells and damage to the skin barrier, subsequently leading to dysbiosis. On the other hand, changes in the proportion of different microorganism species residing on the skin have been linked to the development of various types of dermatosis, such as atopic dermatitis (AD), seborrheic dermatitis (SD), among others, and therefore could potentially aggravate RISI. Apart from significantly reducing the diversity of skin microorganisms, the cause-and-effect sequence between RT and skin microbiome needs further investigation.

Overall, the findings suggest a significant impact of RT on creating a potentially favorable environment for the excessive proliferation of pathogens, and as a result, for an exacerbation of inflammatory process and severe skin injuries. First of all, a few studies showed that the predominance of bacterial species from the Firmicutes and/or Proteobacteria phylum was associated with prolonged healing of aRISI. The most frequently detected genera of cutaneous microbiota in patients with aRISI were *Staphylococcus, Klebsiella, and Pseudomonas.* On the other hand, research linked the low abundance of *Staphylococcus* species, specifically *Staphylococcus epidermidis, Staphylococcus hominis,* as well as *Staphylococcus aureus* before RT to either the development of aRISI or severe course of aRISI, suggesting that the cutaneous microbiota composition before RT might be one of the predictors of the RISI course. The major limitation of certain studies is the absence of specification of exact Staphylococcus species that are overgrowth in RISI patients. This information could provide a better understanding of the microbiota characteristics both before and after radiotherapy, as well as its influence on the clinical outcomes. Further research focusing on skin microbiota is needed to help identify these associations. Noteworthy, results were unequivocal regarding the predominance of Proteobacteria and low abundance of Firmicutes in patients who developed chronic ulcers.

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Table 1. A summary of the findings regarding microbiota in radiation-induced skin injury (RISI).

authors and year of publication	research group	time of sample collection	results	reference
Ramadan et al. 2021	78 cancer patients and 20 control subjects with no RT history	RISI recovery after 2, 3, 4, 5, 6, or 7 weeks, or chronic ulcers	• RISI group – predominance of Firmicutes and Proteobacteria, predominance of *Klebsiella, Staphylococcus or Pseudomonas* • Group with a longer healing of RISI – predominance of *Pseudomonas, Staphylococcus*, and *Stenotrophomonas*. • Chronic ulcers - predominance of Proteobacteria, low abundance of Firmicutes, predominance of *Klebsiella* or *Pseudomonas*, *Cutibacterium* and *Stenotrophomonas*, coexistence of *Pseudomonas*, *Staphylococcus*, and *Stenotrophomonas*	[17]
Huang et al. 2022	29 male rats	• healthy subjects (control group) - skin samples taken before RT • aRISI model - 2 weeks after RT	predominance of Firmicutes in aRISI (*Streptococcus, Staphylococcus, Acetivibrio ethanolgignens, Peptostreptococcus,* and *Anaerofilum*)	[39]
	patient data from BioProject 665254	• Study group - after RT • Control group of healthy subjects with no RT history	• greater abundance of *Klebsiella, Pseudomonas, and Staphylococcus* after RT compared to control group • chronic ulcers were associated with predominance of Proteobacteria and a low abundance of Firmicutes after RT	
Kost et al. 2023	76 patients with head and neck or breast cancer	before and after RT	• among 16 patients with positive nasal *Staphylococcus aureus* colonization prior to RT, 10 of them developed grade 2 or higher aRISI (34,5% of all patients with grade 2 or higher, and 62,5% of patients with positive colonization) and 6 of them developed grade 1 (12,8% of all patients with grade 1, and 37,5% of all patients with positive colonization) • among 60 patients with negative nasal *Staphylococcus aureus* colonization prior to RT, 19 of them developed grade 2 or higher aRISI (65,5% of all patients with grade 2 or higher, but 31,6% of patients with negative colonization), 41 of them developed grade 1 (87,2% of all patients with grade 1, 68,3% of all patients with negative colonization).	[43]
Shi et al. 2023	100 patients with breast cancer	before and after RT	significantly higher abundance of *Ralstonia, Truepera,* and *Methyloversatilis* genera and lower abundance of *Staphylococcus* and *Corynebacterium* genera in patients with no/mild aRISI (RTOG 0/1) compared to patients with severe aRISI (RTOG 2 or higher) both before and after RT	[40]
Hülpüsch et al. 2024	20 patients with breast cancer	before and after RT	• low (<5%) abundance of commensal bacteria *Staphylococcus epidermidis, Staphylococcus hominis, Cutibacterium acnes* before RT was associated with the development of severe aRISI with an accuracy of 100%	[41]

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			• overgrowth of skin bacteria before the onset of severe aRISI during or after RT	
Miyamae et al. 2025	9 head and neck cancer patients who received chemoradiotherapy	before RT	lower abundance of *Staphylococcus hominis* and *Staphylococcus aureus* before RT in severe aRISI compared to the non-severe group	[42]

RISI – radiation-induced skin injury, aRISI – acute radiation-induced skin injury, RT – radiotherapy, RTOG – Radiation Therapy Oncology Group.

4. Management of RISI by Supporting the Skin Microbiome

4.1. Skin Care Products

Implementing preventative actions might alleviate severe cases of aRISI and improve patients' condition. Proper skin care is well-established and regarded as essential in the prevention and treatment of RISI. The skin should be washed with gentle cleansing products that do not disrupt the hydrolipid barrier, such as synthetic detergents (syndets), while concurrently using emollients to maintain skin moisture and UV protection. Noteworthy, washing irradiated skin solely with water during RT is associated with increased severity of RISI, as well as a higher frequency of moist desquamation and itching compared to washing with water and mild soap [45].

Emollients are fundamental in the treatment of AD, which, as mentioned before, shares several pathophysiological similarities with RISI [46,47]. Emollients are composed of a mixture of lipids, typically in a 3:1:1:1 ratio of cholesterol, ceramides, essential free fatty acids, and non-essential free fatty acids. Additionally, they may contain other lipids, such as mevalonic acid, which has been demonstrated to accelerate the restoration of the hydrolipid barrier. Emollients in AD have been shown to reduce TEWL and restore the hydrolipid barrier, likely by decreasing involucrin, claudin-1, and caspase-14 expression [48,49]. Additionally, they reduce the *Staphylococcus aureus* population and restore the balance between *Staphylococcus aureus* and *Staphylococcus epidermidis*, as involucrin is crucial for *Staphylococcus aureus* adhesion to skin cells via the staphylococcal adhesion receptor [50]. "Emollient plus" refers to emollients that contain additional active agents designed to enhance their therapeutic efficacy. Bioactive compounds such as flavonoids, riboflavins, quinones, tannins, catechins, and phenols, commonly derived from botanical extracts such as *Aloe vera*, *Curcuma longa*, *Calendula officinalis*, *Matricaria chamomilla*, among others, are incorporated for their bacteriostatic and antioxidant properties [51,52]. These compounds act through mechanisms such as inactivating microbial adhesins and cell envelope transport proteins by binding to nucleophilic amino acids in these proteins, as demonstrated *in vitro* and in animal models [52–54]. However, efficacy data from only a limited number of randomized controlled trials are available for these formulations in the context of RISI, therefore they are not currently recommended in clinical practice [55]. It is important to highlight that while plant-derived compounds are generally safe, there is a growing number of cosmetics and topical products containing whole-natural botanical extracts. In susceptible individuals, these extracts might cause allergic contact dermatitis [56].

Moreover, topical probiotics, such as *Vitreoscilla filiformis* biomass (VFB) or *Bifidobacterium longum*, have been studied [57,58]. VFB is widely used in emollient products and has been proven to stimulate the production of antimicrobial peptides through toll-like receptor 2 (TLR2)/protein kinase C, zeta pathway (PKCζ), thus modulating the activity of free-radical scavenger mitochondrial superoxide dismutase (SOD) [59,60]. Prebiotics, such as fructooligosaccharides (FOS), galactooligosaccharides (GOS), lactosucrose, glucomannan, lactulose, isomalto-oligosaccharides, sorbitol, xylitooligosaccharides, and xylitol, are frequently incorporated into emollient formulations [57]. Limited knowledge exists regarding the efficacy of topically applied prebiotics, as they are always studied in products with complex formulations. However, they are believed to stimulate the activity of beneficial skin microbiota, thereby suppressing the expansion of pathogenic skin flora, such as *Staphylococcus aureus*, among others.

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The skin affected by RISI is highly susceptible to UV radiation due to disruptions in the hydrolipid barrier and alterations in the natural skin microbiota [61]. *Staphylococcus epidermidis*, for instance, produces 6-N hydroxyaminopurine (6-HAP), which inhibits UV-induced cell proliferation. *Cyanobacteria* produce mycosporine-like amino acids (MAAs) that absorb UV radiation, while *Micrococcus luteus* synthesizes an endonuclease that enhances the efficacy of DNA repair enzymes, thereby bolstering the skin's defense against UV-induced damage. *In vitro* studies have shown that *Lactobacillus* species prevent the development of skin cancers due to the activity of cell wall-embedded lipoteichoic acid (LTA). Moreover, post-RT patients exhibit an elevated risk of developing both melanoma and non-melanoma skin cancers (NMSCs). Daily application of sun protection factor (SPF)-containing products is essential for all individuals; however, it is particularly significant for patients receiving RT, as the disrupted hydrolipid barrier and cutaneous microbiota increase sensitivity to UV radiation, necessitating rigorous photoprotection to mitigate potential skin damage [62,63].

4.2. Treatment Options and the Skin Microbiome

The management of RISI remains without universally accepted treatment protocols. Despite extensive literature describing treatment modalities, significant disparities exist in clinical practice. The data available for acute RISI (aRISI) is considerably more substantial than that for cRISI, with minimal evidence addressing the appropriate management of cRISI [55,64].

Topical glucocorticoids (GCSs) remain the mainstay in the treatment of RISI. They have anti-inflammatory, antiproliferative, and immunosuppressive effects [65]. They suppress multiple immune cells, including neutrophils, monocytes, lymphocytes, and skin-resident Langerhans cells, through the inhibition of various pro-inflammatory cytokines such as IL-1α, IL-1β, IL-2, TNF-α, and granulocyte-macrophage colony-stimulating factor (GM-CSF) [65]. On the other hand, topical GCSs disrupt the synthesis of cholesterol, ceramides, and free fatty acids, leading to the impairment of the hydrolipid barrier [66]. This results in increased TEWL and compromises the antimicrobial function of the skin barrier. While topical GCS therapy decreases inflammation and the clinical signs of RISI, it can further impair the already damaged skin barrier due to RT. As previously noted, the microbiome in RISI is significantly less diverse, with a predominance of certain opportunistic pathogens. However, even in the absence of clinical signs of skin infection, topical GCSs reduce inflammation and promote healing [67]. Another study indicates that topical GCSs alone and the addition of topical mupirocin to topical GCSs can reduce *Staphylococcus aureus* colonization, resulting in a significant clinical improvement in patients with AD [68].

The alternative to topical GCSs could be topical calcineurin inhibitors (CI), although it is important to note that these have not yet been extensively studied in RISI and are not included in current consensus statements and recommendations. They appear to be safe in the RT setting and, together with topical GCSs, form a cornerstone of AD treatment [69–73]. Experimental studies using rat models of radiotherapy-induced cystitis demonstrated that intravesical administration of tacrolimus exhibited protective effects against this condition [72]. Furthermore, patients receiving systemic administration of calcineurin inhibitors, such as those undergoing organ transplantation, did not appear to exhibit increased levels of radiotherapy-related toxicities [73]. Topical CI inhibit the activation of T cells, thereby suppressing the production of IL-2, IL-4, IL-10, interferon (IFN)-γ, and TNF-α, with no effect on Th cells and Langerhans cells [74,75]. Furthermore, topical pimecrolimus has been observed to reduce involucrin levels, thereby restoring the hydrolipid barrier and reducing the adhesion of *Staphylococcus aureus* [50].

Silver sulfadiazine and silver-containing dressings are frequently utilized in patients with aRISI and clinical signs of infection [76,77]. Noteworthy, silver sulfadiazine should not be used for longer than 14 days, as it may slow down re-epithelization [78]. Silver exerts its antimicrobial activity by binding to bacterial DNA, thereby inhibiting the replication process [79]. Additionally, silver inhibits the microbial electron transport system and respiration. It has demonstrated efficacy against pathogenic species of bacteria commonly implicated in skin infections, such as *Staphylococcus aureus*

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and *Pseudomonas aeruginosa*, which are also prevalent among RISI patients [80]. As anticipated, this may also result in bacteriostatic effects on positive, commensal bacteria on the skin. While comprehensive studies on antimicrobial silver-containing agents are lacking, research has explored the impact of silver-thread-enriched clothing on human skin [81]. Findings indicate that individuals wearing silver-containing clothing exhibit increased bacterial biomass, contradicting expectations given silver's antimicrobial properties. Predominant species identified include *Staphylococcus*, *Corynebacterium*, and *Cutibacterium*, associated with heightened production of monounsaturated fatty acids (MUFAs) such as myristoleic acid, contributing to elevated sebum production and skin inflammation [82]. This investigation suggests that the application of silver-containing agents in RT patients could perturb the natural microbiota of the skin, thereby compromising the integrity of the skin barrier and promoting the proliferation of pathogenic species, leading to RISI exacerbation. Table 2 summarizes the main treatment options in RISI, as well as their effect on the skin microbiome.

Current recommendations suggest that there is no need to use topical or systemic antibiotics in the absence of clinical signs of infection. However, a recent study by Kost et al. indicated a significant reduction in the risk of RISI following bacterial decolonization of the nose and skin [83]. The researchers used chlorhexidine, which is known to be allergenic and to damage the skin barrier. Therefore, we propose using sodium hypochlorite baths, which are successfully used in patients with atopic dermatitis and recurrent bacterial skin infections and are currently considered the least aggressive antiseptic [46,84,85]. Hypochlorous acid non-selectively eradicates *Staphylococcus aureus*, along with other bacteria, such as *Staphylococcus pyogenes, Pseudomonas aeruginosa, Propionibacterium acnes*, fungi, such as *Candida* species, and viruses [85–87]. Additionally, it exhibits anti-inflammatory properties by reducing the levels of IL-1, IL-4, IL-6, IL-12, and IL-13, as well as TNF-α. Importantly, it does not significantly affect the TEWL parameter but improves the stratum corneum integrity, thus reinforcing the skin barrier [85,88]. Furthermore, it alleviates itching by decreasing the levels of pruritogenic cytokines and inhibiting mast cell degranulation [89,90].

Table 2. Summary of the main radiation-induced skin injury (RISI) treatment approaches and their effect on the skin microbiome.

Treatment option	Effect on the skins' microbiome	Reference
Emollients	Reduction of the pathogenic *Staphylococcus aureus* colonization with simultaneous increase in commensal (*Staphylococcus epidermidis*) skin microbiota	[48,49]
Topical GCSs	Reduction of the pathogenic *Staphylococcus aureus* colonization	[65,68]
Topical CI	Reduction of the pathogenic *Staphylococcus aureus* colonization	[50,74]
Silver-containing agents	Reduction of both pathogenic (*Staphylococcus aureus*, *Pseudomonas aeruginosa*) and commensal skin microbiota	[80,81]

GCSs – glucocorticoids, CI – calcineurin inhibitors.

5. Conclusions and Future Perspectives

Human skin is home to a vast number of different species of bacteria, viruses, and fungi. Its complex microbiome is crucial for proper barrier function, and dysbiosis has been associated with the pathogenesis of numerous skin disorders and diseases. RISI has recently emerged as being characterized by significant alterations in the abundance of certain bacterial species. Given the complex symbiotic and pathomechanistic relationships of the development of RISI, which includes a cascade of immunological processes and damage to the epidermal barrier, it is crucial to further explore the mutual relationship between skin microorganisms before, during, and after RT to provide valuable insights into the dynamics of microbial communities in response to radiation exposure. Importantly, it remains unknown whether microbial cells or their metabolites impact skin cells and surrounding cells like immune, neuronal and other sensory, sweat and other activities. Further research should also explore the long-term effects of irradiation on the destabilization of skin

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microbiota. In addition, the development of microbiome-based interventions with either probiotics or bacterial metabolites should be a future therapeutic target to prevent and manage RISI.

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