



Evidence-Based Series #13-7: Section 1

The Prevention and Management of Acute Skin Reactions Related to Radiation Therapy: A Clinical Practice Guideline

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A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

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Guideline Questions

1. What are the optimal methods to prevent acute skin reactions (occurring within the first six months of irradiation) related to radiation therapy?
2. What are the optimal methods to manage acute skin reactions related to radiation therapy?

Target Population

The recommendations apply to adult patients with cancer of any histology who are undergoing radiation therapy.

Recommendations

Prevention of Acute Skin Reaction

- Skin washing should not be restricted in patients receiving radiation therapy. Recommended washing practices include gentle washing¹ with water alone or gentle washing with mild² soap and water.
- Patients receiving radiation therapy to the head should be advised to follow gentle washing practices with mild shampoo.
- Limiting personal hygiene practices is not recommended as this may lead to psychosocial distress for the patient.
- Limited evidence suggests that calendula ointment may decrease the occurrence of \geq Grade 2 radiation dermatitis in breast cancer patients. Its application in other types of cancer is unknown at this time.

¹ "Gentle washing" involves using lukewarm water and taking care not to scrub the skin. Showers should also be lukewarm and low-pressure.

² "Mild soap" is defined as a pH-balanced, non-scented product that does not contain lanolin. There is no evidence to suggest that one type of mild soap is preferable to another. However, in one study that rated the irritant quality of 18 soaps, "Dove" was the only soap classified as mild and may therefore be considered (1).

- There is insufficient evidence to support or refute other specific topical agents (i.e., corticosteroids, sucralfate cream, Biafine, ascorbic acid, aloe vera, chamomile cream, almond ointment, polymer adhesive skin sealant) for the prevention of acute skin reaction.
- There is insufficient evidence to support or refute specific oral agents (i.e., enzymes, sucralfate) or intravenous agents (i.e., amifostine) for the prevention of acute skin reaction. The side effects of these agents were more oppressive than those reported in the trials assessing topical agents, and therefore the benefits do not outweigh the risks.

Management of Acute Skin Reaction

- There is insufficient evidence to support or refute topical agents such as corticosteroids, sucralfate cream, or specific dressings for the management of acute skin reaction.

Opinions of the Supportive Care Guidelines Group

- In the opinion of the Supportive Care Guidelines Group, clinical experience suggests that initial use of a plain, non-scented, lanolin-free hydrophilic cream is helpful in preventing radiation skin reactions. This type of cream attracts and traps moisture at the skin surface to increase the skin's moisture and maintain skin pliability. The cream should be discontinued when skin breakdown occurs.
- In the opinion of the Supportive Care Guidelines Group, clinical experience suggests that low-dose (i.e., 1%) corticosteroid cream may be beneficial in the reduction of itching and irritation. There does appear to be an inflammatory process associated with radiation-induced erythema (2) that may be alleviated somewhat by corticosteroid creams. More evidence is needed to support firm recommendations.

Qualifying Statements

- Given the evidence for skin washing, it would seem likely that the same recommendations would follow for hair washing with shampoo for patients receiving radiation therapy to the head, but there is limited evidence to support this.
- Only one trial compared calendula ointment to Biafine cream. The promising results of this large trial (n=254) in breast cancer patients suggest that calendula ointment may be beneficial to cancer patients undergoing radiation therapy. However, administration difficulties may lead to treatment discontinuation for some patients. No trial compared calendula to no treatment or placebo. It is currently unclear if calendula is superior to placebo or no treatment or whether these results can be generalized to cancer patients undergoing radiation therapy for other types of malignancies.
- Caution must be used to avoid the overuse of corticosteroid cream (3); however, there is limited evidence to suggest that skin thinning would pose a problem for normal corticosteroid use during an average course of treatment (up to eight weeks). The practitioner must also be aware of potential patient allergies to topical corticosteroids and discontinue use if an allergic reaction occurs.

Key Evidence

Prevention of Acute Skin Reaction

- A total of 23 trials (21 randomized trials and two non-randomized trials) evaluated various topical and oral agents for the *prevention* of acute skin reaction and were considered eligible for this review. The trials evaluated various creams (e.g., steroid, acid, sucralfate, Biafine, aloe vera, chamomile cream, calendula ointment), oral agents (e.g., enzymes, amifostine), washing practices, and dressings (e.g., polymer adhesive skin sealant).
- A significant benefit in terms of a reduction in the severity of skin reaction was detected in two trials that compared washing the skin to not washing in breast cancer patients.

- One randomized trial compared hair-washing practices in patients receiving cranial irradiation. No significant difference in the degree of erythema was detected in the non-washing group compared with the group that followed their normal hair washing routine.
- The largest randomized trial comparing topical skin care agents for the prevention of acute radiation dermatitis detected a significant advantage of calendula ointment compared to Biafine cream both in the reduction of \geq Grade 2 dermatitis and in pain response. However, there was also a significant difference in ease of administration, with calendula patients reporting significantly greater difficulty with application of the ointment.
- A significant reduction in the degree of skin reaction was detected in three randomized trials comparing oral enzymes to no treatment. However, none of the trials were blinded, and the side effects reported were more severe than those reported in the trials on topical agents.
- Sample populations were often small, and substantive heterogeneity in clinical outcomes and methodologies between trials made comparisons difficult. Furthermore, trials were of mixed tumour sites and variable radiation therapy regimens.

Management of Acute Skin Reaction

- A total of four small randomized trials and one non-randomized trial aimed at the *management* of acute skin reaction were included in this review. The number of patients in these trials ranged from twelve to thirty-nine.
- Two of the trials assessed steroid creams, one trial assessed sucralfate cream, and two trials assessed various dressings for the management of acute skin reaction. None of the trials detected a significant advantage for any of the interventions assessed.

Future Research

- Agreement among researchers on outcome assessment tools for degree of skin reaction, pain, itching, and quality of life would enable better synthesis of the evidence. Including quality of life as an outcome in future trials is important.
- Randomized double-blind trials evaluating the benefits of moisturizing cream or lotion in the prevention or management of acute skin reaction are needed.
- More trials aimed at assessing the efficacy of various dressings for the management of moist desquamation are also needed.
- Oral enzymes showed promising results in the prevention of radiation skin reactions. A large double-blind randomized trial is needed to confirm these results.
- More trials are needed on irradiated sites such as the perineum and areas of skin folds, where the risk factors and management may differ.

References

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Evidence-Based Series #13-7: Section 2

The Prevention and Management of Acute Skin Reactions Related to Radiation Therapy: A Systematic Review

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I. QUESTIONS

1. What are the optimal methods to prevent acute skin reactions (occurring within the first six months of irradiation) related to radiation therapy?
2. What are the optimal methods to manage acute skin reactions related to radiation therapy?

II. INTRODUCTION

Of the 135,000 Canadians who develop cancer each year, half will receive radiation therapy as part of their treatment (1). Acute skin reaction is one of the most common side effects of radiation therapy. In the context of skin reaction, acute is defined as occurring within the first six months of irradiation (2). The severity of radiation skin reaction is graded on a continuum ranging from erythema and dry desquamation to the more severe moist desquamation and, eventually, ulceration (Appendix 1). As erythema is not usually experienced until radiation doses of around 2000cGy (3), patients having palliative treatment at low doses will likely not exhibit any skin reaction and may therefore not need any specialized skin care instructions. When dry desquamation occurs, there is no skin breakdown and no potential for infection. Therefore, the primary aims are to alleviate patient discomfort and to reduce itching and skin irritation. Many practitioners will recommend a moisturizing cream or lotion to reduce these symptoms. When moist desquamation occurs, the skin becomes open and susceptible to infection. Many physicians will prescribe an antibacterial or antifungal medication with or without soaks and dressings. However, the routine use of antiseptics, antibiotics, and disinfectants is questionable when no proven infection is present. A questionnaire by Barkham (4) revealed that 52% of radiation therapy centres in the United Kingdom saw dry desquamation as a frequent occurrence, and 85% saw moist desquamation as an occasional event. Skin care for radiation therapy patients is often a controversial subject. Practices differ considerably between institutions and also between individual practitioners. A recent Canadian survey (5) also found considerable differences between institutions in the prevention and management of acute radiation skin reactions.

Many of today's practices have evolved historically and often lack supporting empirical evidence. Inconsistencies between practitioners can lead to patients receiving conflicting, or even erroneous, information. There are differences of opinion on whether to allow the use of washing, soap, creams, or deodorants and in the management of dry and moist desquamation using of steroid creams, saline soaks, gel or occlusive dressings, or topical antibiotics.

Restrictive skin care practices that interfere with normal hygiene can be very distressing to the patient. When asked to suspend normal hygiene practices, the patient may feel socially unacceptable at a time when the maintenance of existing social support is very important (6). Such restrictions may also hinder attempts to establish new supports to help deal with their diagnosis. Social support from family, friends, work colleagues, health care professionals, and the patient's community is vital for healthy and adaptive adjustment to a cancer diagnosis (7).

Traditional reasons for restricting the use of soaps, creams, lotions, and deodorant on the skin are twofold. First, the addition of a layer of product on the skin may lead to a bolus effect (where the presence of significant additional material on the skin increases the surface radiation dose). Second, the presence of metallic elements may produce secondary radiation on the skin surface, which also increases the skin surface dose. A study by Burch (8), however, that tested a variety of commonly used skin care products and deodorants (some containing zinc and aluminium), concluded that skin reactions should not increase if these agents are applied during treatment and that there is no significant bolus effect with normal use of the products.

Due to the inconsistencies in the clinical management and prevention of acute radiation skin reactions, the Supportive Care Guidelines Group (SCGG) found it important to summarize the data from comparative studies.

III. METHODS

This systematic review was developed by Cancer Care Ontario's Program in Evidence-based Care (PEBC) using the methods of the Practice Guidelines Development Cycle (9). Evidence was selected and reviewed by one radiation therapist (AB) of the PEBC SCGG and one methodologist (NL).

This systematic review is a convenient and up-to-date source of the best available evidence on the prevention and management of skin reactions related to radiation therapy. The body of evidence in this review is primarily comprised of mature randomized controlled trial data. That evidence forms the basis of a clinical practice guideline developed by the SCGG published in section 1 of this report (<http://www.cancercare.on.ca/pdf/pebc13-7s.pdf>). The systematic review and companion practice guideline are intended to promote evidence-based practice in Ontario, Canada. The PEBC is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

Literature Search Strategy

A search of PreMEDLINE, MEDLINE, CANCERLIT, and the Cochrane Library (2004, Issue 1) was conducted to identify comparative studies published between 1980 and April 2004. Relevant articles were identified by combining terms and phrases related to skin and specific skin conditions with radiation therapy terms and combining these terms with terms specific to study design. The MeSH terms "dermis", "epidermis", and "skin/re" (radiation effects) and text words and phrases "erythema", "radiation dermatitis", "radiodermatitis", "desquamation" (dry and moist), and "acute skin reaction" were combined with search terms for radiation therapy including "explode radiotherapy", "radiotherapy/ae" (adverse effects) and a text word search for "radiotherapy" or "radiation therapy". These terms were then combined with the search terms for the following publication types: practice guidelines, systematic reviews, meta-analyses, reviews, randomized controlled trials, controlled clinical trials, and comparative studies.

In addition, conference proceedings of the meetings of the American Society of Clinical Oncology (ASCO) were searched for abstract reports published between 1997 and 2003. The Canadian Medical Association Infobase (<http://www.mdm.ca/cpgsnew/cpgs/index.asp>) and the National Guidelines Clearinghouse (<http://www.guideline.gov/>) were also searched for existing evidence-based practice guidelines. Relevant articles and abstracts were selected and reviewed by two reviewers, and the reference lists from these sources were searched for additional trials, as were the reference lists from relevant review articles.

Inclusion Criteria

Articles were selected for inclusion if they met all of the following criteria:

1. They were systematic reviews, meta-analyses, evidence-based practice guidelines, or comparative studies comparing skin care practices administered by any route for the prevention or treatment of acute skin reactions due to radiation therapy.
2. Data were collected prospectively in at least one arm of the trial. Historical controls were permitted.
3. Clinically relevant outcomes to skin reaction were reported. The trial reported degree of skin reaction (using a validated skin reaction score) as an outcome. Other outcomes of interest included pain, itchiness, burning, quality of life, and toxicities.
4. The article was a fully published or abstract report.

Exclusion Criteria

The following articles were excluded from this systematic review of the evidence:

1. Letters, comments, and editorials.
2. Articles published in a language other than English.

Synthesizing the Evidence

The primary outcome of interest for this review was the degree of skin reaction. Secondary outcomes of interest included symptoms such as pain, itchiness, burning, quality of life, and toxicities. Meta-analysis was not performed because the included trials were too clinically heterogeneous, mainly since they evaluated different treatment regimens. For some interventions, only one trial was identified, thereby eliminating the possibility of pooling. In addition, most trials were too heterogeneous in terms of outcome assessment and reporting of results.

IV. RESULTS

Literature Search Results

No systematic reviews, meta-analyses, or evidence-based practice guidelines were identified. Two practice guidelines, one by the British Columbia Cancer Agency (10) and one by the Oncology Nursing Society (11) were identified; however, the recommendations in both guidelines were based on expert opinion and consensus rather than a systematic review of the evidence and, therefore, did not meet the eligibility criteria. Five trials deemed ineligible for this review were excluded for the following reasons: one was a phase II noncomparative study (12), one did not report degree of skin reaction as a primary outcome of interest (13), one was completely retrospective (14), and two trials were excluded because the degree of skin reaction was not assessed using a validated scale (15,16).

Twenty-eight trials meeting the inclusion criteria were identified (17-44) (Table 1). Twenty-three trials were aimed at prevention of skin reaction (17-39) and five trials were concerned with management of existing skin reaction (40-44). Descriptions of the prevention trials and their outcomes are provided in Tables 2 through 4, and Tables 5 through 7 summarize the management trials.

Table 1. Summary of trials included in this practice guideline report.

Intervention	Number of published trials (abstracts)	Reference numbers	Relevant tables
Prevention of acute skin reaction			
Topical steroid cream	3	17-19	2-4
Washing practices	3	20-22	2-4
Sucralfate/sucralfate derivatives	3	23-25	2-4
Biafine cream	3	26-28	2-4
Oral enzymes	3	29-31	2-4
Amifostine	1	32	2-4
Topical acid cream	2	33,34	2-4
Aloe vera	3	35-37	2-4
Chamomile cream vs. almond ointment	1	38	2-4
Dressings	(1)	39	2-4
Management of acute skin reaction			
Topical steroid cream	2	40,41	5-7
Sucralfate/sucralfate derivatives	1	42	5-7
Dressings	2	43,44	5-7

Study Quality

Nineteen of the 28 trials were randomized controlled trials (RCTs) where the patient was the unit of randomization (17,18,20-23,26-31,33,35-37,42-44). Seven of those were double-blind (17,18,23,33,35,37,42), four were single-blind (20,28,31,36), and seven did not incorporate blinding methods (21,22,26,27,30,43,44). In six trials, the unit of randomization was the side to which the experimental agent was applied (19,24,25,34,38,40). Five of those intraindividual comparisons, or left-right studies where the patient served as his or her own control, also used blinding strategies (19,24,25,34,38). Two non-randomized trials met the eligibility criteria (32,41). One of those did not incorporate blinding in the study design (32), and the other was double-blind (41). One open trial evaluated patients in the experimental treatment prospectively but used a historical control group for comparison (39). Blinding methods and how randomization was achieved were not always well described in the primary reports.

Only four trials used a proper intention-to-treat approach to data analysis (24,30,32,42), while 21 trials analyzed evaluable patients only (17-23,25-27,29,31,33-39,43,44). A commonly cited reason for excluding patients from the final analysis was poor compliance to treatment. One small intraindividual comparison simply presented a description of the results without statistical analysis (40). In most trials, a single outcome assessment was made, usually by a radiation therapist, dermatologist, physician, research nurse, radiologist, or the primary investigator (17,19,22,25,29,30,32-36,40,42,43). Some trials, however, did not adequately report on how outcome assessments were conducted (18,23,24,27,31,38,39). Independent outcome assessments were made by two or more assessors in four trials (20,21,26,44). Inter-rater reliability scores and kappa scores were calculated in only one trial (44). One trial compared outcome assessments made by the attending physician or oncology nurse with assessments made by the patients (37).

Table 2. Study descriptions of trials on the prevention of acute radiation skin reactions.

Author, Year (Ref)	Study Design/Unit of Randomization/Blinding	No. of pts ¹	Treatment Arms ²
Topical Steroid Creams			
Bostrom 2001 (17)	RCT/patient/double-blind	25 25	0.1% MMF + emollient emollient
Schmuth 2002 (18)	RCT/patient/double-blind	12 11	0.1% MPA 0.5% dexpanthenol
Løkkevik 1996 (19)	RCT/treatment side/single-blind	86	dexpanthenol (Bepanthen) ³ cream vs. no cream
Washing practices			
Roy 2001 (20)	RCT/patient/single-blind	(49) (50)	no washing washing with soap + water
Campbell 1992 (21)	RCT/patient/open	(14) (14) (16) (14) (21) (16)	bolus ⁴ ; no washing bolus; washing with water bolus; washing with soap + water no bolus; no washing no bolus; washing with soap no bolus; washing with soap + water
Westbury 2000 (22)	RCT/patient/open	54 55	no hair washing (avoid) normal hair washing routine
Sucralfate or sucralfate derivatives			
Lievens 1998 (23)	RCT/patient/double-blind	(38) (45)	oral sucralfate placebo
Evensen 2001 (24)	RCT/treatment side/double-blind	60	NaSOS gel vs. placebo
Maiche 1994 (25)	RCT/treatment side/double-blind	50	sucralfate cream vs. placebo cream
Topical Biafine			
Fenig 2001 (26)	RCT/patient/open	25 24 25	Biafine ointment Lipiderm ointment no treatment
Fisher 2000 (27)	RCT/patient/open	(66) (74)	Biafine ointment best supportive care ⁵
Pommier 2004 (28)	RCT/patient/single-blind	126 128	Calendula ointment Biafine cream
Oral enzymes			
Gujral 2001 (29)	RCT/patient/open	53 47	Wobe-Mugos enzyme no treatment
Dale 2001 (30)	RCT/patient/open	60 60	Wobe-Mugos enzyme no treatment
Kaul 1999 (31)	RCT/patient/single-blind	25 25	Wobe-Mugos enzyme no treatment
Amifostine			
Dunst 2000 (32)	non-randomized controlled trial/patient/open	15 15	Radiochemotherapy ⁶ with IV amifostine Radiochemotherapy without amifostine

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Topical acid cream			
Liguori 1997 (33)	RCT/patient/double-blind	76 76	hyaluronic acid (HA) cream placebo
Halperin 1993 (34)	RCT/treatment side/double-blind	84	ascorbic acid cream vs. placebo
Aloe vera			
Heggie 2002 (35)	RCT/patient/double-blind	(107) (101)	aloe vera cream aqueous cream
Olsen 2001 (36)	RCT/patient/single-blind	33 40	mild soap + aloe vera gel mild soap
Williams 1996 (37)	RCT/patient/double-blind (trial 1)/open (trial 2)	97 97 54 54	aloe vera gel placebo aloe vera gel no treatment
Chamomile cream vs. almond ointment			
Maiche 1991 (38)	RCT/treatment side/single-blind	50	chamomile cream vs. almond ointment
Dressings			
Hazuka 1997 (39) (abstract)	non-randomized controlled trial/patient/open (historical control)	(54) (110)	PASS no treatment

Notes: IV, intravenous; MMF, mometasone furoate cream; MPA, methylprednisolone aceponate; NaSOS, Na-sucrose octasulfate; No., number; PASS, Polymer Adhesive Skin Sealant; pts, patients; RCT, randomized controlled trial; Ref, reference; vs., versus

- 1 – Numbers in parentheses indicate evaluable patients; where a single number is presented under no. of patients, the identical patients were used in each study arm (i.e. intraindividual comparison where the treatment side was the unit of randomization)
- 2 – Treatment arms listed in order of treatment arm versus control arm; complete description of treatment schedule in Appendix 2
- 3 – Concentration of dexpanthenol not reported
- 4 – Patients received 1cm Vaseline bolus applied between 10-15 fractions of the 20-fraction course
- 5 – Institution's product of choice at time of randomization (31% Aquaphor, 34% aloe vera, 19% other, 16% no treatment)
- 6 – Six courses of 5-fluorouracil (5-FU)

Table 3. Tumour type, radiation therapy regimen, adjuvant treatments or co-interventions reported in prevention trials.

Author, Year (Ref)	Tumour Type	Radiation Therapy Regimen ¹	Adjuvant treatments/Co-interventions			
			post-operative (+)	chemotherapy (+/-)		additional skin care agents used
				prior	concomitant	
Topical Steroid Creams						
Bostrom 2001 (17)	Breast	54 Gy in 27#; 5MV	+	NR	-	+ ²
Schmuth 2002 (18)	Breast	56 Gy in 28#; 8MV	+	+	+	-
Løkkevik 1996 (19)	Breast & Larynx	B: 50 Gy in 25#; 5 MV or Cobalt 60; 6-12 MeV; L: 70 Gy in 35#; 5 MV	+ ³	+	+ ³	NR
Washing practices						
Roy 2001 (20)	Breast	45 Gy in 20# of 2.25 Gy or 50 Gy in 25# of 2 Gy; Cobalt 60 or 6MV	NR	NR	NR	-
Campbell 1992 (21)	Breast	45-47 Gy in 20#; 5 MV	+	-	-	+ ⁴
Westbury 2000 (22)	Brain	high dose (>30 Gy) or low dose (≤30 Gy)	NR	NR	NR	-
Sucralfate or sucralfate derivatives						
Lievens 1998 (23)	H & N	55-66 Gy in 25-33#; Cobalt 60 or 6 MV	NR	NR	NR	NR
Evensen 2001 (24)	H & N	50-70 Gy in 25-35#; 4-6 MV	NR	NR	NR	NR
Maiche 1994 (25)	Breast	50 Gy in 25#; 6 MeV	+	NR	NR	NR
Topical Biafine						
Fenig 2001 (26)	Breast	50 Gy in 25#; 6 MV	+	-	-	+ ⁵
Fisher 2000 (27)	Breast	50-64 Gy	NR	NR	-	-
Pommier 2004 (28)	Breast	52 Gy in 10#; 5 MV (lumpectomy pts) 46 Gy; optional 10 Gy boost (mastectomy pts)	+	+	-	- ⁶
Oral enzymes						
Gujral 2001 (29)	H & N	50-70 Gy in 25-35#; Cobalt 60	NR	+	NR	-
Dale 2001 (30)	Uterine Cervix	50-60 Gy in 25#; brachytherapy boost at 20-30 Gy	NR	-	NR	+ ⁷
Kaul 1999 (31)	H & N	50-60 Gy in 25-35#	NR	-	NR	NR
Amifostine						
Dunst 2000 (32)	Stage II/III Rectal	56 Gy in 31#	+	+	+	NR
Topical acid cream						
Liguori 1997 (33)	H & N, Breast, Pelvis	H & N: 66 (1.8-2 Gy/#)-81 (1.15 Gy/#) Gy; <6 MV; <10 MeV; B: 60-66 Gy (30-33#); <10 MV; <15 MeV; P: 60-66 Gy (30-33#); 15 MV	NR	NR	-	-
Halperin 1993 (34)	Brain ⁸	14-70 Gy	NR	NR	NR	NR
Aloe vera						
Heggie 2002 (35)	Breast	50-64 Gy	+	+	+	+ ⁹
Olsen 2001 (36)	NR (gyne & brain excluded)	9-73 Gy	NR	NR	NR	-
Williams 1996 (37)	Breast	45-60 Gy (1.8-2 Gy/#) (22-33#)	+	NR	-	+ ¹⁰
Chamomile cream vs. almond ointment						
Maiche 1991 (38)	Breast	50 Gy 25#; 6 MeV	+	NR	NR	NR
Dressings						
Hazuka 1997 (39) (abstract)	Breast, H & N	50-66 Gy	NR	NR	NR	NR

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Notes: #, fraction(s) ; (+) – yes, (-) – no; B, breast; Gy, gray(s); gyne – gynaecological; H & N, head and neck; L, larynx; MeV, mega-electron volt; MV, megavolt; NR, not reported; P, pelvis; Ref, reference

- 1 – Prescribed dose, fractionation, and beam energy presented unless not reported in trial
- 2 – All patients in both groups also applied non-blinded emollient cream (Diprobase) over radiation area once daily
- 3 – Breast cancer patients only
- 4 – All groups recommended to apply baby powder three times daily to treated skin surface
- 5 – If clinically necessary, patients in control group received topical treatment; maximal level of treatment required based on skin reaction is described in Appendix 2
- 6 – Physicians treated established dermatitis of grade 2 or higher and/or allergy
- 7 – Any use of anti-inflammatories, topical anaesthetics, or mucoprotectants for radiation toxicity and concomitant medication was recorded
- 8 – Primary or metastatic
- 9 – Patients in all groups advised to use only mild baby soap on the skin
- 10 – No other prophylactic topical agents were to be applied during the study period; however, patients with pruritus and/or marked erythema were to use a 1% hydrocortisone cream 2-3 times daily and patients with moist desquamation were to use Domeboro's soak 3-4 times daily; patients in all groups advised not to apply soap directly to the skin

Table 4. Study outcomes of trials on the prevention of acute radiation skin reactions.

Author, Year (Ref)	No. of pts	Treatment Arms	Outcomes Assessed		
			skin reaction	pain	itching
Topical Steroid Creams					
Bostrom 2001 (17)	25 25	0.1% MMF + emollient emollient	max erythema score: p=0.011; total erythema score, p=0.0033 in favour of MMF	p=0.42	p=0.069
Schmuth 2002 (18)	12 11	0.1% MPA 0.5% dexpanthenol	mean severity score: p=0.1	NA	dex arm: 1 pt MPA arm: 2 pts
Løkkevik 1996 (19)	86	dexpanthenol (Bepanthen) cream vs. no cream	erythema grade: p=1.00 desq grade: p=0.027 in favour of dex at 6wk	p=0.56	p=0.43
Washing practices					
Roy 2001 (20)	(49) (50)	no washing washing with soap + water	max erythema score: NS max moist desq score: washing grp 7pts (14%)vs. non-washing grp 16 pts (33%); p=0.03	p>0.05	p>0.05
Campbell 1992 (21)	(14) (14) (16) (14) (21) (16)	bolus; no washing bolus; washing with water bolus; washing with soap + water no bolus; no washing no bolus; washing with soap no bolus; washing with soap + water	mean erythema score: p<0.05 at 6 & 8 wks in bolus and no bolus grps in favour of washing with soap + water	NS	mean itching score: p<0.05 in favour of soap + water
Westbury 2000 (22)	54 55	no hair washing (avoid) normal hair washing routine	degree of erythema/desq: p>0.05	p>0.05	p>0.05
Sucralfate or sucralfate derivatives					
Lievens 1998 (23)	(38) (45)	oral sucralfate placebo	time to mean dermatitis scores: NS (p value NR)	NA	NA
Evensen 2001 (24)	60	NaSOS gel vs. placebo	mean erythema score: p=0.1335 mean desq score : p=0.0172 in favour of placebo	mean score: p=0.2584	mean score: p=0.8546
Maiche 1994 (25)	50	sucralfate cream vs. placebo	G2 rxn: p=0.01 at 4 wks & p<0.05 at 5 wks in favour of sucralfate	NA	no statistical analysis
Biafine cream					
Fenig 2001 (26)	25 24 25	Biafine ointment Lipiderm ointment no treatment	degree of skin rxn: p=0.98 (nurse's grading); p=0.15 (radiotherapist's grading)	NA	NA
Fisher 2000 (27)	(66) (74)	Biafine ointment best supportive care	max skin rxn score: p=0.77; time to G2 toxicity: p=0.44; duration of dermatitis: p=0.11	p=0.48	NA
Pommier 2004 (28)	126 128	Calendula ointment Biafine cream	acute skin toxicity ≥G2: 41% vs. 63% (p<0.001) in favour of calendula	mean max pain: 1.54 vs. 2.10 (p=0.03) in favour of calendula	NA

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Oral enzymes					
Gujral 2001 (29)	53 47	Wobe-Mugos enzyme no treatment	mean max extent of skin rxn: 1.2 enzyme vs. 2.4 control; p<0.001 in favour of enzyme ≥G2 skin rxn: 34% enzyme vs. 76% control; p=0.001 ¹ in favour of enzyme	NS	NS
Dale 2001 (30)	60 60	Wobe-Mugos enzyme no treatment	mean max extent of skin rxn: 0.97 enzyme vs. 1.68 control; p<0.001 in favour of enzyme ≥G2 skin rxn: 22% enzyme vs. 57% control; p=0.0008 ¹ in favour of enzyme	NA	NA
Kaul 1999 (31)	25 25	Wobe-Mugos enzyme no treatment	degree of skin rxn and biopsy scores: p<0.05 in favour of enzyme. >G2 skin rxn at week 6: 28% enzyme vs. 88% control (p<0.01 in favour of enzyme over all grades of skin rxn at weeks 3-11). G4 skin rxn, 4%, 20%, and 40% for control at weeks 6, 7, and 8 vs. 0% for enzyme.	NA	NA
Amifostine					
Dunst 2000 (32)	15 15	Radiochemo with IV amifostine Radiochemo without amifostine	max erythema score: 0.87±0.52 amifostine vs. 1.47±0.64 control; p=0.009 in favour of Amifostine. G2 skin rxn: 7% Amifostine vs 53% control. No G3/4 rxns	NA	NA
Topical acid cream					
Liguori 1997 (33)	70 64	hyaluronic acid cream placebo	skin rxn score: p<0.01 wks 3-7; p<0.05 wks 8 & 10 in favour of HA cream	NA	NA
Halperin 1993 (34)	84	ascorbic acid cream vs. placebo	mean toxicity score: p=0.10	NA	NA
Aloe vera					
Heggie 2002 (35)	(107) (101)	aloe vera cream aqueous cream	erythema: NS; moist desq: NS dry desq: p<0.001 in favour of control (higher cumulative probability in aloe vera arm, 70% vs. 41%)	≥G2 pain higher in aloe vera arm (26% vs. 17%, p=0.03)	p>0.05
Olsen 2001 (36)	33 40	mild soap + aloe vera gel mild soap	time to erythema, p=0.948	NA	time to skin itch, p=0.117
Williams 1996 (37)	97 97 54 54	aloe vera gel placebo aloe vera gel no treatment	max severity of skin rxn: Trial 1: p=0.36; Trial 2: p=0.31	NA	NA
Chamomile cream vs. almond ointment					
Maiche 1991 (38)	50	chamomile cream vs. almond ointment	frequency of G1,G2 or G3 skin rxn: NS (p value NR)	no statistical analysis	no statistical analysis
Dressings					
Hazuka 1997 (39)	(54) (110)	PASS no treatment (historical control)	19/55 treated sites (35%) had ≥G2 desq; treatment interruptions: 1.8% vs. 24% in favour of PASS	NA	NA

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Notes: desq, desquamation; dex, dexpanthenol; G, Grade; grp, group; HA, hyaluronic acid; IV, intravenous; max, maximum; MMF, mometasone furoate cream; MPA, methylprednisolone aceponate; NA, not assessed; NaSOS, Na-sucrose octasulfate; No., number; NR, not reported; NS, not statistically significant; PASS, Polymer Adhesive Skin Sealant; pt(s), patient(s); Radiochemo, radiochemotherapy; Ref, reference; rxn, reaction; vs., versus; wk(s), week(s)

1 – Reviewer's analysis of difference in proportions (http://department.obg.cuhk.edu.hk/researchsupport/Independent_2x2_table.asp)

Table 5. Study descriptions of trials on the management of acute radiation skin reactions.

Author, Year (Ref)	Study Design/Unit of Randomization/Blinding	No. of pts	Treatment Arms
Topical Steroid Creams			
Schreck 2002 (40)	RCT/patient/open	12	cream (Linola® or Bepanthen®) vs. powder
Potera 1982 (41)	non-randomized controlled trial/treatment side/double-blind	21 ¹	0.2% hydrocortisone valerate cream vs. placebo
Sucralfate or sucralfate derivatives			
Delaney 1997 (42)	RCT/patient/quadruple-blind	20 19	10% sucralfate in sorbolene cream sorbolene cream
Dressings			
Shell 1986 (43)	RCT/patient/open	10 11	Moisture Vapor Permeable dressing (Tegaderm®) hydrous lanolin gauze
Mak 2000 (44)	RCT/patient/open	(21) (18)	moist hydrocolloid dressing topical gentian violet

Notes: pts, patients; RCT, randomized controlled trial; Ref, reference; vs., versus

1 - Twenty-four skin areas were evaluated in 19 of the 21 patients who volunteered for the study (two patients not evaluated due to poor compliance)

Table 6. Tumour type, radiation therapy regimen, and adjuvant treatments or co-interventions reported in management trials.

Author, Year (Ref)	Tumour Type	Radiation Therapy Regimen	Adjuvant treatments/Co-interventions			
			postoperative (+)	chemotherapy		additional skin care agents used
				prior	concomitant	
Topical Steroid Creams						
Schreck 2002 (40)	H & N	50-72 Gy; 6 MV, 8 MeV	+	NR	NR	+ ¹
Potera 1982 (41)	H & N, Chest Wall, Abdomen	H & N: 27Gy; B: 63Gy	NR	NR	NR	NR
Sucralfate or sucralfate derivatives						
Delaney 1997 (42)	H & N, Breast, Other	47-53 Gy in 25-28#	NR	+	+	- ²
Dressings						
Shell 1986 (43)	H & N, Chest, Back	30-69 Gy	NR	NR	NR	- ³
Mak 2000 (44)	Neck, chest, axilla, perineum	NR	NR	+ ⁴	+ ⁴	+ ⁵

Notes: #, fraction(s); (+) – yes, (-) – no; B, breast; Gy, gray(s); H & N, head and neck; MeV, mega-electron volt; MV, megavolt; NR, not reported; Ref, reference

1 – Cream group: instructed to clean skin with water and pH-neutral wash syndents daily; powder group: instructed to wash with water twice weekly

2 – Cream washed off prior to radiation treatment

3 – Moderate skin reactions cleansed by gentle washing with normal saline soaked gauze and soap; severe reactions added treatment with ¼ solution hydrogen peroxide and saline (only in hydrous lanolin group), both followed by saline rinse prior to application

4 – Patients were stratified and divided into two subsets: i) those that received chemotherapy and radiation therapy and ii) radiation therapy alone

5 – Cleansed by gentle washing with 0.9% normal saline before application

Table 7. Study outcomes of trials on the management of acute radiation skin reactions.

Author, Year (Ref)	No. of pts	Treatment Arms	Outcomes Assessed		
			skin reaction	pain	itching
Topical Steroid Creams					
Schreck 2002 (40)	12	cream (Linola® or Bepanthen®) vs. powder	no statistical analysis	no statistical analysis	no statistical analysis
Potera 1982 (41)	21	0.2% hydrocortisone valerate cream vs. placebo	erythema, dry/moist desq, ulceration, duration/intensity of symptoms: NS	NA	NA
Sucralfate or sucralfate derivatives					
Delaney 1997 (42)	20 19	10% sucralfate in sorbolene cream sorbolene cream (control)	mean time to healing: p=0.86	mean change in pain grade: p=0.32	NS
Dressings					
Shell 1986 (43)	10 11	Moisture Vapor Permeable dressing (Tegaderm®) hydrous lanolin gauze	mean healing time: 19 (MVP) vs. 24 days; p>0.05	NS	NA
Mak 2000 (44)	(21) (18) ¹	moist hydrocolloid dressing topical gentian violet	mean healing time: 11.42 vs. 11.7 (GV) days; p=0.83	severity & frequency p=0.012, p=0.03 in favour of control	NA

Notes: desq, desquamation; GV, gentian violet; MVP, moisture vapor permeable; NA, not assessed; no., number; NS, not significant; pts, patients; Ref, reference; vs., versus

1 – Analysis was based on 33 versus 32 wounds for moist hydrocolloid and topical gentian violet, respectively.

Trial Characteristics

For those trials categorized under prevention of skin reaction, treatment typically began just prior to or at the start of radiation therapy. However, one trial reportedly aimed at the prevention of radiation dermatitis was categorized under management because application of the study creams did not commence until two weeks after the start of radiation therapy (41). In the trials categorized under management, patients typically had existing radiation skin reactions prior to the start of treatment. In some trials, it was difficult to distinguish whether the aim was prevention or management of skin reaction (18,20,30,31,40). Ultimately, the decision as to how to categorize those studies was based on whether patients had existing skin reactions and whether treatment commenced before or after the start of radiation therapy.

Eleven of the 28 included trials limited the sample population to breast cancer patients (17,18,20,21,25-28,35,37,38). Radiation therapy regimens varied substantively from trial to trial, and even between trials that included the same patient population. The site of the primary tumour and the radiation treatment schedule are outlined in Tables 3 and 6.

The most commonly used scale for assessing the degree of skin reaction was the Radiation Therapy Oncology Group's (RTOG) acute skin reaction scoring system or a modification thereof (Appendix 1). Treatment schedules are fully described in Appendix 2 and complete descriptions of all outcome assessment scales by trial are outlined in Appendix 3.

Outcomes

Acute Skin Reaction, Pain, and Itching

Studies on Prevention of Acute Skin Reaction

Topical Steroid Creams

Three trials evaluated steroid creams for the prevention of acute skin reaction (17-19). None of the trials had the same treatment groups, limiting comparison between trials. Although the trial was relatively small, Bostrom (17) detected a significant benefit in favour of 0.1% mometasone furoate cream in terms of lower maximal erythema scores. Schmuth (18) found no significant difference in the degree of skin reaction between patients randomized to 0.1% methylprednisolone aceponate (MPA) (Advantan®) cream versus 0.5% dexpanthenol cream. The composition of dexpanthenol cream was described by Schreck (40) and can be found in Appendix 2. In an intraindividual comparison (where patients served as their own controls) of dexpanthenol cream versus no treatment, Løkkevik reported no clinically relevant differences between groups (19). In that trial, skin reactions were most severe for all patients at the sixth visit, and this served as the reference time point for evaluation. None of the trials detected a significant difference between groups in patients' experience of pain or itching.

Sixty percent of patients (15/25) in the emollient group in the trial by Bostrom (17) had \geq Grade 4 skin reaction compared with 25% (6/24) in the mometasone furoate (MMF) group. Erythema scores were also reported quantitatively using reflectance spectrophotometer (RFS) readings and a significant difference in favour of MMF ($p=0.0033$) was detected. Although differences between groups in terms of patient-reported itching, burning, or pain were not significant, there was a trend toward patients in the MMF group experiencing less itching and burning compared to patients in the emollient group ($p=0.069$ and $p=0.087$, respectively).

Previously collected data on a group of 15 non-randomized untreated control patients were also used for comparison in the trial by Schmuth (18). Neither cream was successful in preventing radiation dermatitis, as 19 of the 21 patients developed radiation skin reactions. Seventy-six percent (16/21) of patients experienced \geq Grade 2 and 38% (8/21) developed \geq Grade 4 skin reactions. Although a comparison of mean severity scores did not reveal a significant difference between treatment groups, fewer patients in the MPA group had severity scores ≥ 4 compared to the dexpanthenol group ($p<0.05$).

Washing Practices

Three moderately-sized RCTs compared washing the skin or hair to not washing during radiation therapy (20-22). The two trials assessing skin washing both detected less severe skin reactions in the washing groups (20,21). The trial by Westbury (22) however, did not detect a significant difference in skin reaction between hair washing practices in patients receiving cranial irradiation. Patients instructed to *avoid* washing the hair washed at a lower average frequency compared to the control patients. Those patients reported distress but that outcome was not evaluated in patients who followed a normal hair care regimen, thus not allowing for comparison between groups. Pain and itchiness was assessed in all three trials, with no significant differences in pain scores and only one trial reporting lower average scores for itchiness for the washing groups compared to the non-washing group (21).

While no significant difference in maximal erythema score was detected in the trial by Roy (20), there was a significant difference in the incidence of moist desquamation in favour of washing compared with no washing (16/49 (33%) versus 7/50 (14%), $p=0.03$). Fewer patients in the washing group received prior or concomitant chemotherapy than in the non-washing group, but this difference was not significant. There was no significant difference in the mean time to reach maximal toxicity. Lower median scores for pain, itching, and burning were reported for the washing group (pain, 3.1 versus 2.6; itching, 2.7 versus 2.0; burning, 1.7 versus 1.3), but these differences were not significant (20). Patients in the washing group did not all follow the same washing regimen: 18% washed with water alone, 48% with soap and water, and the rest did not follow a consistent washing regimen. A wide variety of soaps were used, and patients included in the statistical analysis comprised both those who complied with the washing policy and those who did not.

Campbell & Illingworth (21) randomized patients to one of three groups (no washing, washing with water, or washing with soap and water). Patients were also categorized into one of two nonrandomized groups, those that applied a 1cm Vaseline bolus to the skin between 10 and 15 fractions of the 20 fraction course ($n=44$), and those that did not apply the Vaseline bolus ($n=51$). There was no significant difference overall between the washing groups (i.e., no difference between soap plus water versus water alone regardless of bolus); the non-washing groups tended to have higher erythema scores, particularly in the Vaseline bolus group (statistically significant at week 6 with bolus and week 8 without bolus). Average desquamation scores followed a similar pattern, with a trend toward higher scores in the non-washing group and some comparisons reaching statistical significance (i.e., lower desquamation scores in both washing groups at eight weeks). Although the data presented in the full report included only the average scores, the authors reported that maximum reactions showed similar results. It is worth noting that the range of washing frequency was seven to 28 times per week, with an average of 11.9 times per week.

Sucralfate/sucralfate derivatives

Three randomized trials compared topical or oral sucralfate against placebo in head and neck (23,24) or breast (25) cancer patients. The two intraindividual trials that assessed topical sucralfate detected conflicting outcomes: Evensen (24) found no significant difference between groups in mean erythema scores but detected a significant difference in mean desquamation scores in favour of the placebo cream, while Maiche (25) detected a significant difference in favour of sucralfate cream. The difference in the patient populations in those two trials might explain the conflicting results, since head and neck patients are more exposed to the elements than breast cancer patients. Lievens (23) reported no significant reduction in dermatitis with the use of oral sucralfate compared with a placebo, but comparison with the trials by Evensen and Maiche (24,25) may not be appropriate since the route of administration was quite different. Furthermore, the composition of sodium sucrose octasulfate (NaSOS) used in the Evensen trial

(24) differs from the cream containing 7% of microionized sucrose sulfate used by Maiche, limiting comparability between the two trials.

Though all three studies were reportedly double-blind, the methods by which blinding was achieved were not described. Only one of the trials provided statistical data on pain and itching and reported no significant differences in mean scores between groups (24). Maiche (25) reported itching as a side effect occurring in nine skin areas treated with sucralfate cream and 12 areas treated with placebo cream (although the total number of treated areas was not provided).

Biafine cream

Two randomized non-blinded trials assessed the effectiveness of topical Biafine cream (26,27) and one randomized single-blind trial compared calendula ointment to Biafine cream (28). Biafine, an oil-in-water emulsion with non-steroidal anti-inflammatory properties, is commonly used for radiation-induced dermatitis. The chemical composition has been well described elsewhere (12). Best supportive care (BSC) in the trial by Fisher (27) was defined as the institution's product of choice, with 31% of patients receiving Aquaphor, 34% aloe vera, 19% other therapy, and 16% receiving no skin care product. There were no significant differences in the degree of skin reaction in the trials by Fisher and Fenig (26,27).

In the largest randomized trial aimed at prevention of acute radiation dermatitis, Pommier (28) compared calendula ointment with Biafine cream in 254 breast cancer patients and found that patients in the calendula group had significantly fewer occurrences of \geq Grade 2 dermatitis than patients receiving Biafine cream (41% versus 63%, $p < 0.001$). Calendula was also significantly superior to Biafine for pain relief ($p = 0.03$). However, patients reported significantly greater difficulty in the administration of calendula versus Biafine (30% versus 5%) with two patients discontinuing treatment because of that difficulty.

Oral enzymes

Three RCTs compared the efficacy of oral hydrolytic enzymes versus no treatment in reducing acute skin reaction in head and neck cancer patients (29,31) or patients with cervical cancer (30). Two trials were open label (29,30) and one blinded the pathologist assessing pre- and post-radiation therapy biopsies but not the person conducting skin assessments (31). All groups were well balanced at baseline, and all three trials detected a significant benefit in favour of enzyme therapy. Gujral (29) and Dale (30) also reported on the frequency distribution of the maximum extent of acute skin reaction by grade; however, those data were not statistically analyzed. The guideline authors performed an analysis of the most clinically significant outcome, namely \geq Grade 2 skin reaction, and found that the proportion of patients with \geq Grade 2 skin reaction was significantly lower in the enzyme group in both trials.

Although the trial by Kaul (31) was reported as a study aimed at *management* of acute radiation reactions, since eligible patients did not have existing skin reactions prior to the start of enzyme therapy and enzyme treatment began at the start of radiation therapy, that trial was categorized as a prevention trial. In that single-blind trial, a significant difference in the degree of skin reaction between the enzyme group and the control group was reported in favour of enzyme therapy. At week six, 88% of control patients had \geq Grade 2 skin reaction compared to 28% of enzyme therapy patients. Grade 4 skin reactions were present in 4%, 20%, and 40% of control patients at weeks six, seven, and eight, respectively, while no patients in the enzyme group experienced skin reactions greater than Grade 3 (31). Significant differences in favour of enzyme therapy were also reported in terms of pre- and post-radiation therapy biopsy scores, although the cut-off scores (reported as + and – ranks) were not clearly reported.

Amifostine

One small non-randomized open trial compared radiochemotherapy with or without intermittent intravenous amifostine, a thiol derivative which protects normal tissues from the cytotoxic effects of radiation therapy and cisplatin chemotherapy (32). A significant difference in maximum erythema grade in favour of amifostine was detected. Erythema sum scores for the six-week trial duration were also significantly lower in the amifostine group (1.40 ± 0.91 versus 3.40 ± 2.10 , $p=0.003$, respectively). The authors also reported the frequency of \geq Grade 2 skin reaction, with fewer patients in the amifostine group compared to the control group having Grade 2 skin reactions (7% versus 53%, respectively). No Grade 3/4 skin reactions were detected in either group. Quality of life, pain, and itching outcomes were not assessed.

Topical acid cream

Two trials compared topical acid cream against placebo (33,34). A significant difference in favour of hyaluronic acid (HA) cream was detected in the double-blind trial by Liguori (33) but no significant differences between treatment groups (ascorbic acid (ASC) versus placebo) were detected in the smaller, intraindividual comparison by Halperin (34). Global judgements of therapeutic efficacy and tolerability were scored (poor to excellent) in the trial by Liguori (33). A significant difference in efficacy was detected by both the physician and patient in favour of HA cream ($p<0.01$ and $p<0.05$, respectively). There was no significant difference between groups in terms of tolerability. In the trial by Halperin (34), data were analyzed on 77% (65/84) of patients. Eighty-five percent of the 65 evaluable patients showed either no preference for either intervention (35/65) or a preference for the placebo (20/65). Only 10 patients (15%) showed a preference for ASC.

Aloe Vera

Three randomized trials assessed the efficacy of aloe vera for the prevention of radiation skin reactions (35-37). Two were large blinded trials, but the radiation treatments varied somewhat between trials (35,37). After the post-hoc observation from the blinded trial wherein patients had less dermatitis than expected, Williams (37) also conducted a non-blinded trial comparing aloe vera gel versus no treatment. None of the trials detected significant differences between groups in cumulative probability, prevalence, or time to or duration of erythema. Williams (37) also assessed maximum severity of dermatitis, time to occurrence of severe (\geq Grade 2) dermatitis, and duration of severe dermatitis but found no significant differences between treatment groups. The only significant benefit of aloe vera was reported by Heggie (35), where the cumulative probability of dry desquamation was significantly lower in the control group (70% versus 41%, $p<0.001$) and patients in the aloe vera group experienced significantly worse dry desquamation than control patients ($p=0.004$). Neither of the two trials that assessed itching detected significant differences between groups (35,36), and pain was assessed in only one trial (35), with a significantly greater cumulative probability of \geq Grade 2 pain reported in the aloe vera group (25% versus 17%, $p=0.03$). There was no significant difference between groups in terms of prevalence or duration of pain.

Chamomile cream versus almond ointment

The extent of acute skin reaction, pain, and itching were reported in the only trial that assessed chamomile cream versus almond ointment (38). No statistically significant difference in the frequency of Grade 1, 2 or 3 skin reaction was detected between treatment groups. Grade 1 skin reactions were observed in 100% of patients assessed. Skin reactions \geq Grade 2 seemed to appear later and less frequently in the chamomile cream-treated areas compared to the almond ointment-treated areas but this difference was not significant (p value not reported). Patients' experience of itching and pain were not quantitatively analysed, but the authors reported no difference between treatment groups.

Dressings

In a comparative study published only in abstract form, the prophylactic use of a polymer adhesive skin sealant (PASS) was compared to a group of no-treatment historical control patients (39). Fifty-four evaluable patients applied the liquid adhesive to the skin in 55 sites. Nineteen out of 55 (35%) treated sites showed \geq Grade 2 desquamation. One patient in the PASS group required treatment interruption compared to 24% (26/110) of the control patients. Statistical analyses were not reported, and it should be noted that detailed information on the control group (i.e., radiation therapy regimen, disease site) was not provided.

Studies on Management of Acute Skin ReactionTopical Steroid Creams

Two small trials used patients as their own controls to assess topical steroid creams for the management of radiation skin reactions (40,41). Neither trial detected a significant difference in the degree of skin reaction. Potera (41) also compared the duration and intensity of skin reactions and found no significant differences between groups. Due to the small numbers of patients, Schreck (40) simply described the study results but did not perform statistical analyses. No relevant differences in patients' scores of local warmth, tension, itch, pain, or general discomfort were reported (40). The Potera (41) trial was categorized under management because the study aim was to determine whether hydrocortisone cream was effective in *reducing* acute radiation dermatitis and the application of the creams did not commence until two weeks after the start of radiation therapy (in the prevention studies, cream application typically began prior to or at the initiation of radiation therapy).

Sucralfate/sucralfate derivatives

One small randomized trial assessed sucralfate cream for the management of moist desquamation (42). Patients were eligible if they had developed a measurable area of moist desquamation (\geq Grade 3 by RTOG criteria). There was no significant difference in the mean time to healing (sucralfate 14.8 days versus control 14.2 days) or in the rate of pain improvement. Significant heterogeneity between treatment arms was detected at baseline: sucralfate patients were prescribed a higher total skin dose (53.4Gy versus 47.2 Gy), and more fractions (28.5 versus 25.2), had more prescribed days of radiation remaining after randomization (11.3 days versus 6.2 days), and had larger areas of moist desquamation than control patients. Several patients receiving sucralfate, but no control patients, reported itching at the treatment site.

Dressings

Neither of the two small trials (43,44) that compared dressings for the management of acute skin reaction detected a significant difference in the time to healing. This was true even after adjustment for the use of concomitant chemotherapy ($p=0.62$) (44). Pain scores were not significantly different in the trial by Shell (43); however, Mak (44) reported a significant reduction in pain severity and frequency in the gentian violet group. Shell (43) reported a trend toward faster healing time in the MVP group, but this difference was not statistically significant. Furthermore, there were only 21 patients included in the trial.

Patients in the Mak (44) trial were first stratified according to whether or not they had received chemotherapy in addition to radiation therapy, and then randomized. The unit of analysis was the number of wounds, which corresponded to 33 evaluable wounds (21 patients) in the treatment group and 32 evaluable wounds (18 patients) in the control group. More patients in the hydrocolloid group received chemotherapy compared to patients in the gentian violet group, but this difference was not significant (61.1% versus 38.9%, $p=0.41$). Bi-weekly outcome assessments were performed by three study nurses who were not blinded to treatment

allocation. Mean wound sizes were significantly smaller in the gentian violet group. Patients receiving the hydrocolloid dressing had significantly higher ratings of dressing comfort ($p=0.002$) and aesthetic acceptance ($p=0.007$) compared to control patients.

Burning and Quality of Life

Only three trials (17,18,20) assessed patients' experience of burning of the skin. No significant differences between treatment groups were detected.

Two trials (18,27) reported on quality of life (QOL) using validated assessment tools. One of those trials was double-blind (18) while the other did not incorporate blinding techniques (27). In a comparison of Biafine cream versus BSC, patients with Grade 2 toxicity had significantly worse QOL ($p=0.048$), but there was no significant difference in QOL between treatment groups, since both groups were balanced in terms of the overall rate of \geq Grade 2 toxicity (27). In the comparison of MPA versus dexpanthenol cream (18), general QOL (as measured by the 36-item short form health survey (SF-36)) improved in both groups after the termination of radiation therapy, but no significant differences between groups were detected. The more specific Skindex scale detected significant or near significant differences between treatment groups on three of the seven dimensions ($p<0.05$) (18) in favour of the corticosteroid (MPA) group compared with the dexpanthenol group.

Adverse Events

Most trials did not distinguish adverse effects related to treatment from adverse effects related to radiation therapy. This situation presented a challenge for interpreting data from the many trials that reported pain, itching, and other side effects that may have been due to radiation or the treatment agent or both.

Adverse events were generally mild to moderate for those trials that assessed topical agents (17-22,24-28,33-44). The most common treatment-related toxicities were allergic reaction to the topical agent, itching, burning, and moist desquamation. Overall, there were no significant differences in adverse events between treatment groups for those trials evaluating topical agents, aside from one trial (35) that reported significantly less pain in the aqueous cream group compared to patients in the aloe vera cream group. Allergic reaction was the most commonly reported adverse reaction in the aloe vera trials.

Toxicities were more severe where oral or intravenous agents were used (23,29-32). Gastrointestinal upset was the most common adverse effect and led 19 patients to withdraw from the trial by Lievens (12 in sucralfate group, seven in placebo group) (23). One of the shortcomings of the three trials assessing oral enzymes (29-31) is that they did not distinguish between radiation therapy-induced and enzyme therapy-induced side effects, when some of the common side effects of oral enzyme therapy (i.e., gastrointestinal) are also typical side effects of radiation therapy. No significant differences in toxic events between treatment groups were reported (29-31). Toxicities reported by Gujral (29) included pain/body ache, fever, weakness, vomiting, itching, hemoptysis, and swelling, which were generally mild and of short duration. The most common treatment-related toxicity in the amifostine trial (32) was grade I nausea, which occurred in seven out of 15 (47%) patients (32). Two patients (13%) in the treatment group experienced grade II nausea. Maximum nausea scores and maximum hypotension scores were significantly higher in the amifostine group compared to the control group ($p=0.002$ and $p=0.008$, respectively). Despite the significant reduction in the degree of skin reaction detected in the group receiving intravenous amifostine, the increase in adverse effects experienced by those patients should not be overlooked.

One of the management trials (43) reported that five patients (24%) were eliminated from the original study population due to development of significant wound complications (two patients in the MVP group and one in the lanolin group developed Staphylococcus infections; one patient in the lanolin group developed folliculitis; and one patient in the lanolin group

developed a sensitization reaction) (43). There were no treatment-related toxicities reported in the remaining management trials (40-42,44).

DISCUSSION

Quality of the Evidence

Twenty-three trials evaluated various agents for the prevention of acute radiation skin reaction. There were only four small randomized trials and one small non-randomized trial aimed at the management of these reactions. The variety of interventions assessed made it difficult to thoroughly evaluate individual interventions. The available evidence varied greatly in methodology, clinical outcomes measured, tumour sites evaluated, radiation therapy regimens, and the sample populations were often small.

In terms of methodology, an advantage to using intraindividual (left-right) comparisons is that each patient serves as their own control thereby reducing heterogeneity. This is especially advantageous in trials that are double-blind. However, the disadvantage in the many trials that used this design was that patients were often excluded due to non-compliance. In fact, the most commonly cited reason for not including patients in the final analysis was poor compliance to treatment. In this respect, the trials where patients (rather than the *side* of treatment) were the “unit” of randomization could be considered of superior quality. Another important consideration in the overall assessment of study quality is that many trials did not employ blinding techniques. Although double-blinding was not possible in the trials assessing washing practices, the trials assessing the other various interventions could have incorporated appropriate blinding techniques to minimize bias.

In terms of adverse effects, it was often difficult to differentiate whether authors reported toxicities such as pain, burning, and itching, as effects of the treatment agent or effects of radiation therapy, which made comparisons between trials problematic. Furthermore, not all the trials reported whether other skin care practices, such as washing or the application of other topical agents were restricted, which could have an impact on effect size.

Interpretation of the Evidence

Prevention of Acute Skin Reaction

The main recommendation arising from this review of the evidence is that gentle skin and hair washing should be unrestricted in patients receiving radiation therapy. Although only two of the three trials examining washing practices detected a benefit in the washing group (20,21), the evidence was felt to be sufficient to support recommendations. In the Westbury trial (22), patients randomized to not washing were instructed to *avoid* (rather than restrict) washing, which could explain why a positive effect was not detected in that trial.

There would seem to be no barrier to using a mild soap and gentle washing during radiation therapy, and indeed being permitted to wash during radiation therapy was felt by 78% of patients in the trial by Campbell (21) to be very important. In that trial, patients randomized to washing were instructed that they could wet the treated skin surface in a warm shower or by immersion in a warm bath and were told not to soak in the bath nor to rub the treated skin and to either drip dry or pat dry with a towel. Patients who washed with soap and water were given similar instructions and instructed to use baby soap or mild soap (but no bubble bath, shower gel, or body lotion) (21). Patients in the other positive trial by Roy (20) were instructed to gently wash with warm water and mild soap (i.e., Dove®, Ivory®), but not to use the shower or bath, very cold or very hot water, and to use soft patting to dry the skin. There was, however, no definition of “mild” soap elucidated in any of the washing trials.

The largest randomized trial included in this review of the evidence compared calendula versus Biafine and a significant reduction in \geq Grade 2 dermatitis and in pain response was detected in the calendula group. Nonetheless, the shortcomings of the trial should be considered in a treatment recommendation, namely that the trial was only single-blind

(physician-blinded) and that 30% of patients found calendula difficult to apply compared to only 5% of patients reporting difficulty in the Biafine group.

As mentioned, the quality and quantity of studies evaluating the use of topical and oral agents did not allow for specific recommendations in those areas. There is some evidence to suggest that the use of certain topical steroid creams (17,19) and topical acid creams (29) has a radioprotective effect, but more studies are needed to support recommendations. There is limited evidence to support the use of sucralfate, Biafine cream, aloe vera, chamomile cream, or dressings for the prevention of acute radiation skin reactions.

One non-randomized open trial evaluated amifostine in a total of 30 patients receiving radiochemotherapy and detected significantly lower maximal erythema scores in the amifostine group. However, randomized trials are needed to confirm whether intravenous amifostine administration is beneficial in preventing acute skin reactions. A disadvantage to the use of this agent is the requirement of a permanent venous access for daily injections. The three trials that evaluated oral enzymes detected a significant benefit in favour of enzyme therapy. The side effects reported in those trials, however, were more oppressive than those reported in trials evaluating topical agents and should be considered. Moreover, that enzyme is not currently available in Canada and no further trials are currently underway. Overall, the benefits do not outweigh the risks in the trials evaluating the efficacy of oral and intravenous agents.

Management of Acute Skin Reaction

The agents examined in this area were steroid creams, sucralfate cream, and various dressings. No two trials evaluated the same treatment regimen, limiting comparisons between studies. There is a lack of strong evidence on the management of radiation therapy-related wounds such as moist desquamation. There is a need to match the care of moist desquamation with the best available wound care, such as wound dressings that promote a moist wound environment. Since none of the trials demonstrated a positive effect on skin reaction, recommendations on the best management of radiation skin reactions cannot be made.

ONGOING TRIALS

The National Cancer Institute (NCI) clinical trials database on the Internet (http://www.cancer.gov/search/clinical_trials/) was searched for reports of ongoing trials. No ongoing trials addressing the prevention or management of acute radiation skin reactions were identified by the authors of this practice guideline report.

CONFLICT OF INTEREST

Members of the SCGG disclosed potential conflict of interest information and no conflicts were declared.

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Appendix 1. Radiation Therapy Oncology Group (RTOG) acute radiation morbidity criteria.

0	1	2	3	4
no change over baseline	follicular, faint or dull erythema, epilation, dry desquamation and/or decreased sweating	tender/bright erythema, patchy moist desquamation and/or moderate edema	confluent, moist desquamation, other than skin folds, pitting edema	ulceration, hemorrhage, necrosis

Appendix 2. Description of treatment schedules.

Study	Treatment schedule
Bostrom 2001	pts applied cream on irradiated area twice weekly up to 24Gy then once daily until 3w after completion of RT
Campbell 1992	pts randomized to no-washing grp instructed not to wash or wet the treated skin surface at all; pts randomized to washing with water instructed that they could wet the treated skin surface in a warm (not hot) shower or by immersion in a warm bath, told not to soak in the bath and not to use soap, told not to rub the treated skin and to either drip dry or pat dry with a towel; pts randomized to washing with soap and water given same instructions as the former grp but were instructed to use baby soap or simple soap (but no bubble bath, shower gel, or body lotion)
Dale 2001	Wobe-Mugos: 3 tablets q.i.d. 7d prior to start of RT for 9w
Delaney 1997	liberal amount of cream applied to tx area t.i.d.; salt water bath preceding each application
Dunst 2000	CT: six courses of 5-FU (1w 5-FU, 3w breaks); two courses of 5-FU given simultaneously with RT, 1-2 prior to RT, remaining 2-3 after RT; 120h continuous infusion on d1-5 and 29-33 (1000 mg/m ² /24h); RT: postoperative RT began 4-10w after surgery; 50.4 Gy to posterior pelvis followed by 5.4 Gy boost to presacral space 5x 1.8 Gy/w pelvis + boost; Amifostine: (500 mg infusion over 5-10 min daily on CT days; immediately prior to daily RT on first and fifth radiation w)
Evensen 2001	NaSOS started on d1 of RT course; applied b.i.d. during RT and 2w thereafter
Fenig 2001	Biafine/lipiderm cream applied twice daily 10d prior to RT and continuing 10d post-RT; topical treatment started in control grp (if necessary); maximal level of tx required based on skin rxn graded on scale of 1-5: 1=no treatment (control grp only); 2=Biafine or lipiderm; 3=steroid ointment; 4=antibiotic (±steroid component) preparation; 5=pause in RT
Fisher 2000	tx applied t.i.d. (not within 4h of RT) from d1 of RT and 2w thereafter
Gujral 2001	Wobe-Mugos tablets delivered orally t.i.d. starting 3d prior to RT, continuing up to 5d after completion
Halperin 1993	topical solution applied twice daily, prior to and throughout RT, to left & right sides of head; one side receiving ascorbic acid solution, the other placebo
Hazuka 1997	PASS applied prophylactically to skin on d1 and every other day during RT up to 4w post-RT
Heggie 2002	experimental arm received topical 98% aloe vera gel; control received topical aqueous cream; applied to irradiated breast t.i.d. (including immediately after RT) during and for 2w after RT
Kaul 1999	Wobe-Mugos tablets given; 3 tablets, t.i.d. beginning 3d prior to RT until 1w after RT
Lievens 1998	oral intake of sucralfate starting at beginning and continuing throughout RT (1g 6 times daily)
Liguori 1997	HA 0.2% cream or placebo (0.4 mg/cm ²) applied twice daily, morning (i.e., 1-2h post-RT) and night, for 10w (6w during RT, 4w post-RT)
Løkkevik 1996	Laryngeal pts: treated one side with dexpanthenol cream, opposite side with no cream; Breast pts: treated half of targeted area with dexpanthenol cream and not the other half; cream started the from d1 of RT, twice daily
Maiche 1991	drugs applied gently to skin twice daily (30 min before RT and before bed)
Maiche 1994	sucralfate cream (7% micronized sucrose sulfate) or base cream (PEG 400, PEG 400MS, arachis oil, isopropyl, myristat, glycerine, lanoline, and ion exchanged sterile water) applied by pt twice daily during 5w RT and 2w thereafter
Mak 2000	dressing changed by nurse every 2d in hydrocolloid arm; pts applied gentian violet to wound b.i.d. in gentian violet arm
Olsen 2001	skin care began on first day of RT; pts gently cleansed irradiated area with mild, unscented soap; in aloe vera arm, gel applied liberally to affected area following RT each day and subsequently 6-8 times/d

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Pommier 2004	pts began topical application of the ointment at onset of RT, twice daily or more, depending on dermatitis and pain, until completion of RT
Potera 1982	pts applied hydrocortisone valerate to one-half of the irradiated area and placebo to other half beginning 2w after start of RT and continuing 3w post-RT; creams applied twice daily; pts used cream from 5 to 9w
Roy 2001	washing arm instructed to gently wash with warm water and mild soap (i.e. Dove®, Ivory®), but no shower or bath, very cold or very hot water, soft patting to dry skin; pts in no-washing grp instructed not to wash the skin within the treatment field during RT; pts in both grps recommended not to apply deodorant, lotion, cream, make up, perfume, or any other product on irradiated areas and to avoid sun exposure
Schmuth 2002	assigned cream applied twice daily; tx initiated at start of RT and continuing 2w after completion of RT; pts instructed not to apply any other topical medications, emollients, or powders during the study period
Schreck 2002	skin care with cream: cleaning with water and pH-neutral syndets daily (at onset of RT), Linola cream twice daily (during discomfort/erythema), Bepanthen cream twice daily (during dry desq), Opsite dressing (when moist desq <4 cm), Opsite or Comfeel dressing (when moist desq >4 cm); skin care with powder: Azulon powder twice daily, wash with water 2/w (at onset of RT), Azulon powder 4-5/d (during discomfort/erythema + dry desq), physiologic saline soln and methylviolet soln twice daily (when moist desq <4 cm), physiologic saline soln and Bepanthen cream (when moist desq >4 cm); Linola cream=linolic acid 0.13 g; Bepanthen cream=dexpanthenol 1 g/20 g and paraffin, vaseline, almond oil, bleached wax, non-ionogenic emulgators, wool wax, cetylstearyle alcohol, water, cetyl alcohol; Azulon powder=dry extraction of chamomile flowers 10 mg/g and wool wax, magnesium carbonate high dispers silicium dioxide, zinc oxide, talcum
Shell 1986	moderate skin rxns: cleansed by gentle washing (normal saline and soap followed by saline rinse), skin patted dry prior to applying assigned dressing; severe skin rxns: same cleansing technique and skin additionally washed with a ¼ soln of hydrogen peroxide followed by saline rinse. MVP grp did not receive peroxide wash. Hydrous lanolin spread on a sterile gauze was applied to the radiation site and secured with roller gauze and tape (on the gauze). Sterile MVP dressings were applied to the radiation site without tension covering a margin of normal skin at the periphery. Dressings were changed daily in the lanolin grp and every 3-4d in the MVP grp
Westbury 2000	pts in the no-washing grp were advised not to wash hair during RT and for 10d after RT. They were also advised not to apply any creams or lotions on the scalp but were allowed to cover the head with a scarf or hat. Pts in the washing grp were advised to continue normal scalp care
Williams 1996	aloe vera versus placebo: pts applied study medication lightly to the treatment field twice daily within 3d of start of RT. Pts followed 'usual' skin care precautions (i.e., not applying soap directly to the skin; no other prophylactic creams applied)

NOTE: 5-FU, 5 Fluorouracil; b.i.d., twice daily; CT, chemotherapy; d, day(s); desq, desquamation; grp, group(s); Gy, gray(s); HA, hyaluronic acid; h, hour(s); i.e., example; i.v., intravenously; min, minute(s); MVP, Moisture Variable Permeable dressings; NaSOS, Na-sucrose octasulfate; PASS, polymer adhesive skin sealant; pt(s), patient(s); q.i.d., four times daily; RT, radiation therapy; rxn, reaction; soln, solution; t.i.d., three times daily; tx, treatment; w, week(s)

Appendix 3. Description of clinical and patient-reported skin outcome scales.

Study	Description of Skin Assessment Scales	
	Clinical Assessment Scales	Patient Reported Outcome Scales
Bostrom 2001	Adverse skin rxn (7 point scale): 0=no rxn, 1=just perceptible erythema, 2=mild erythema, 3=moderate erythema, 4=severe erythema, 5=severe erythema and edema, 6=moist desq or ulceration/bullae	Itching, burning and pain classified by patient using VAS 0= no symptom, 10= worst
Campbell 1992	modified EORTC/RTOG acute skin rxn scoring system Erythema (4 point scale): 0=none, 1=follicular/faint, 2=dull, 3=tender or bright; Desq (5 point scale): 0=none, 1=dryness of the skin, 2=moderate flaking, 3=severe flaking, 4=patchy moist desq	itching and pain (4 point scale): 0=none, 1=mild, 2=moderate, 3=severe
Dale 2001	max extent of observed side effects graded according to EORTC/RTOG criteria by single observer	NR
Delaney 1997	area of moist desquamation measured and photographed	assessment form completed daily indicating level and change in discomfort, and degree of pain when applying cream (linear analogue scale); adverse effects & time to pain improvement also noted
Dunst 2000	NR	NR
Evensen 2001	modified EORTC/RTOG acute skin rxn scoring system Erythema (4 point scale): 0=none, 1=mild, 2= moderate, 3=severe Desq (5 point scale): 0=none, 1=dryness of skin, 2=moderate flaking, 3=severe flaking, 4=patchy or moist desq	Itching/pain (4 point scale): 0=none, 1=mild, 2= moderate, 3=severe
Fenig 2001	RTOG cutaneous toxicity scale (5 point scale) Maximal treatment level (5 point scale): i=no treatment (control grp only), ii= Biafine or Lipiderm, iii=steroid ointment, iv=antibiotic (±steroid), v=pause in RT	NR
Fisher 2000	NR	NR
Gujral 2001	skin rxn graded by RTOG/EORTC criteria (5 point scale):	NR
Halperin 1993	criteria of RT committee of CNS consortium (5 point scale): Skin: G0=no change, G1=hyperpigmentation, G2=dry skin desq, G3=moist skin desq, G4=moist skin desq with focal ulceration	NR
Hazuka 1997	NR	NR
Heggie 2002	morbidity rating scale (4 point scale) erythema: none, mild, moderate, or severe; area of dry desq: 0-100%; moist desq (0-100% and site)	morbidity rating (4 point scale) itching/pain: none, mild, moderate, or severe
Kaul 1999	pre & post-RT biopsy eval for ulceration, inflammation, dysplasia, spongiosis, and atrophy; also assessed skin changes, according to EORTC	NR
Lievens 1998	dermatitis (7 point scale): 0=none, 1=slight erythema, 2=deep erythema, 3=dry desq, 4=spotted epidermolysis, 5=confluent epidermolysis, 6=necrosis	subjective tolerance (5 point scale): 0=no side effects, 1=few side effects, 2=moderate side effects, 3=many side effects, 4=very important side effects
Liguori 1997	skin surface (6 point scale): 0=normal skin, 1=light epidermal irritation, 2=erythema with dry desq, 3=exudate<50%, 4=exudate>50%, 5=ulcer	therapeutic efficacy and tolerability (4 point scale): 0=poor, 1=fair, 2=good, 3=excellent
Løkkevik 1996	Erythema (4 point scale): G0=none, G1=mild, G2=moderate, G3=severe Desq (5 point scale): G0= none, G1=dryness, G2=moderate flaking, G3=severe flaking, G4=patchy	Itching/pain (4 point scale): G0=none, G1=mild, G2=moderate, G3=severe

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	moist desq	
Maiche 1994	skin rxn (5 point scale): 0=no rxn, 1=light erythema, 2=dark erythema, area painful, 3=wet desq, 4=necrosis of the skin	NR
Maiche 1991	acute skin rxn (4 point scale): 0=no change, 1=light erythema, 2=dark erythema, 3=moist desq	NR
Mak 2000	wound size & pain: frequency: 1=at dressing changes, 2=intermittently, 3=continuously severity (Wong/Baker Faces Rating Scale - 6 point scale): 0=no pain to 5=very painful incidence of infection (erythema and/or edema of surrounding normal tissue, increased drainage or change from serous to purulent, increased tenderness in and around rxn site, fever and leukocytosis), time required for healing	pt satisfaction (dressing comfort & aesthetic acceptance - 5 point scale): 1=poor to 5=excellent
Olsen 2001	RTOG acute radiation morbidity criteria (5 point scale)	NR
Pommier 2004	RTOG acute radiation morbidity criteria (5 point scale)	pain: 10cm VAS
Potera 1982	Erythema (4 point scale): 0=clear, 1=minimal, 2=mild, 3=moderate, 4=severe dry desq (3 point scale): 1=dry skin, 2-peeling, 3=cracking moist desq (including vesiculation, ulceration (necrosis)), duration and intensity of symptoms ¹	NR
Roy 2001	RTOG acute skin toxicity scale (5 point scale)	pain, itching, & burning: VAS
Schmuth 2002	erythema, desq, erosion, induration, and hyperpigmentation (4 point scale): 0=none, 1=mild, 2=moderate, 3=severe	NR
Schreck 2002	modified RTOG skin toxicity scales: erythema (grade I,II), dry desq (<4 cm, >4 cm), moist desq (<4 cm, >4 cm), pigmentation (grade I,II)	local warmth, tension, itch, pain, general discomfort using categorical 4 point scale: "not at all", "rather", "quite", or "very"
Shell 1986	radiation skin rxn grading: moderately severe=dry scaling desq and brisk erythema severe=vesicle formation and moist desq with areas of partial and full thickness skin loss and pronounced erythema	Level of pain/discomfort: A=none, B=small amount, C=moderate, D=severe, E=excruciating
Westbury 2000	modified RTOG/EORTC acute skin rxn scoring system: Erythema: 0-3=none, faint/follicular, dull, tender/bright Desq: 0-4=none, dryness, moderate flaking, severe flaking, patchy moist Pain & Itching: 0-3=none, mild, moderate, severe	frequency of hair washing: 0=not at all, 1=once or twice a week, 2= frequently (3-6X a week), 3=daily, DK=washed but can't remember how often distress: 1=not at all upsetting, 2=slightly upsetting, 3=quite upsetting, 4=very upsetting
Williams 1996	skin rxn score: 0=normal, 1=mild erythema, 2=marked erythema with or without dry desq, 3=moist desq and/or ulceration	skin rxn score: 0=normal, 1=mild erythema, 2=marked erythema with or without dry desq, 3=moist desq and/or ulceration

Notes: CNS, central nervous system; desq, desquamation; EORTC, European Organisation for Research and Treatment of Cancer; eval, evaluation; G, Grade; grp, group; max, maximum; NR, not reported; pt(s), patient(s); RT, radiation therapy; RTOG, Radiation Therapy Oncology Group; rxn, reaction; VAS, visual analogue scale
1 – based on Wilcoxon signed rank test



Evidence-Based Series #13-7: Section 3

The Prevention and Management of Acute Skin Reactions Related to Radiation Therapy: Guideline Development and External Review—Methods and Results

A. Bolderston, N.S. Lloyd, R.K.S. Wong, L. Holden, L. Robb-Blenderman, and members of the Supportive Care Guidelines Group

A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

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THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) (1). The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, called Disease Site Groups (DSGs) and Guideline Development Groups (GDGs), mandated to develop the PEBC products. These panels are comprised of clinicians, other health care providers, methodologists, and community representatives from across the province.

The PEBC is well known for producing evidence-based practice guideline reports, using the methods of the Practice Guidelines Development Cycle (1,2). The PEBC reports consist of a comprehensive systematic review of the clinical evidence on a specific cancer care topic, an interpretation of and consensus agreement on that evidence by our DSGs and GDGs, the resulting clinical recommendations, and an external review by Ontario clinicians in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each clinical practice guideline report, through the periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original clinical practice guideline information.

The Evidence-Based Series: A New Look to the PEBC Practice Guidelines

Each Evidence-Based Series is comprised of three sections.

- *Section 1: Clinical Practice Guideline.* This section contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the DSG or GDG involved and a formalized external review by Ontario practitioners.

- *Section 2: Systematic Review.* This section presents the comprehensive systematic review of the clinical and scientific research on the topic and the conclusions reached by the DSG or GDG.
- *Section 3: Guideline Development and External Review - Methods and Results.* This section summarizes the guideline development process and the results of the formal external review by Ontario practitioners of the draft version of the clinical practice guideline and systematic review.

DEVELOPMENT OF THIS EVIDENCE-BASED SERIES

Development and Internal Review

This evidence-based series was developed by the Supportive Care Guidelines Group (SCGG) of CCO's PEBC, which is comprised of palliative care physicians, nurses, radiation therapists, medical, radiation and surgical oncologists, psychologists, psychiatrists, an anaesthetist, and methodologists. A list of the current SCGG members is available at http://www.cancercare.on.ca/index_supportiveCaregg.htm. The series is a convenient and up-to-date source of the best available evidence on the prevention and management of skin reactions related to radiation therapy, developed through systematic review, evidence synthesis, and input from practitioners in Ontario.

Supportive Care Guideline Group Consensus

During the initial discussion of this guideline topic, the SCGG agreed that the evidence should be separated into trials aimed at the prevention of acute radiation skin reactions and those aimed at the management of acute radiation skin reactions. The first draft of the practice guideline report was circulated to the SCGG in March 2004. Overall, the SCGG approved the draft guideline with some suggestions for clarification that were subsequently incorporated in the draft sent out for external review. A suggestion was made that more information on specific dressings for wound management be provided in the Interpretive Summary section; however, the authors felt this to be beyond the scope of this guideline report. A companion document on wound management will be considered as a future topic.

Feedback from the non-physician health care professional members of the SCGG suggested that a statement on the definition of “evidence-based” might provide some clarity. A nursing representative of the group commented that since the evidence does not lend itself to definitive recommendations for the majority of the interventions assessed, it might be worthwhile producing a document on “best practice”. The authors considered this comment in the context of two types of documents produced by the Program in Evidence-based Care (PEBC) at that time, clinical practice guidelines and evidence summaries, and felt it was important to delineate the two and explain how these differ from the Registered Nurses Association of Ontario's (RNAO) “Best Practice Guidelines”.

The PEBC's evidence-based reports are based on a systematic review of the best available research evidence. The newer three-part Evidence-Based Series reports replace Practice Guideline reports and Evidence Summary reports. The former consisted primarily of mature randomized trials that contributed to the development of recommendations. When insufficient evidence precluded the development of definitive recommendations an Evidence Summary Report was produced, offering opinions of the SCGG until more mature research evidence on which to base recommendations became available. Of importance is the fact that the PEBC approach places great emphasis on the evidence base, and the SCGG, a multidisciplinary guideline panel, interprets this evidence to provide recommendations. The evidence source for our documents differs from that of the RNAO, which, in addition to using research evidence, also considers evidence from expert committee reports, expert opinions, clinical experience, or expert authorities.

External Review by Ontario Clinicians

Following the review and discussion of Sections 1 and 2 of this evidence-based series, the SCGG circulated the clinical practice guideline and systematic review to clinicians in Ontario for review and feedback. Box 1 summarizes the draft clinical recommendations and supporting evidence developed by the panel.

<p>BOX 1: DRAFT RECOMMENDATIONS (approved for external review, April 2004)</p>
<p><i>Target Population</i></p> <p>The recommendations apply to adult patients with cancer of any histology who are undergoing radiation therapy.</p>
<p><i>Recommendations</i></p> <p><i>Prevention of Acute Skin Reaction</i></p> <ul style="list-style-type: none"> • Skin washing should not be restricted in patients receiving radiotherapy. Recommended washing practices include gentle washing with water alone or gentle washing with mild soap and water. • Patients receiving radiotherapy to the head should be advised to follow gentle washing practices with shampoo. • Limiting personal hygiene practices is not recommended as this may lead to psychosocial distress for the patient. • There is insufficient evidence to recommend specific topical agents (i.e., corticosteroids, sucralfate cream, Biafine, ascorbic acid, aloe vera, chamomile cream, almond ointment, polymer adhesive skin sealant) for the prevention of acute skin reaction. • There is insufficient evidence to recommend specific oral agents (i.e., enzymes, sucralfate) or intravenous agents (i.e., amifostine) for the prevention of acute skin reaction. The side effects of these agents were more oppressive than those reported in the trials assessing topical agents, and therefore the benefits do not outweigh the risks. <p><i>Management of Acute Skin Reaction</i></p> <ul style="list-style-type: none"> • There is insufficient evidence to recommend topical agents such as corticosteroids or sucralfate cream or specific dressings for the management of acute skin reaction.
<p><i>Qualifying Statements</i></p> <ul style="list-style-type: none"> • Given the evidence for skin washing, it would seem likely that the same recommendations would follow for hair washing with shampoo for patients receiving radiotherapy to the head, but there is limited evidence to support this.
<p><i>Future Research</i></p> <ul style="list-style-type: none"> • Agreement among researchers on outcome assessment tools for degree of skin reaction, pain, itching, and quality of life would enable better synthesis of the evidence. Including quality of life as an outcome in future trials is important. • Randomized double-blind trials evaluating the benefits of moisturizing cream or lotion in the prevention or management of acute skin reaction are needed. • More trials aimed at assessing the efficacy of various dressings for the management of moist desquamation are also needed. • Oral enzymes showed promising results in the prevention of radiation skin

reactions. A large double-blind randomized trial would be necessary to confirm these results.

- On irradiated sites such as the perineum and areas of skin folds, where the risk factors and management may differ, more trials are needed.

Methods

Feedback was obtained through a mailed survey of 264 practitioners and health care professionals in Ontario (86 radiation oncologists, 146 oncology nurses, and 32 radiation therapists). The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations above should be approved as a practice guideline. Written comments were invited. The practitioner feedback survey was mailed out on April 15, 2004. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The SCGG reviewed the results of the survey.

Results

One hundred thirty responses were received out of the 264 surveys sent (49% response rate). The response rate by discipline was 44% (38/86) for the radiation oncologists, 44% (64/146) for the nurses, and 88% (28/32) for the radiation therapists. Of the 130 returns, 123 (95%) were valid questionnaires and seven (5%) were invalid (i.e., retired, on sabbatical, not applicable). Responses include returned completed surveys as well as phone, fax, and email responses. One hundred eleven of the 123 respondents (90% of returns) indicated that the report was relevant to their clinical practice, and they completed the survey. Key results of the practitioner feedback survey are summarized in Table 1.

Table 1. Practitioner responses to eight items on the practitioner feedback survey.

Item	Number (%)		
	Strongly agree or agree	Neither agree nor disagree	Strongly disagree or disagree
The rationale for developing a clinical practice guideline, as stated in the "Choice of Topic" section of the report, is clear.	105 (96%)	2 (2%)	2 (2%)
There is a need for a clinical practice guideline on this topic.	96 (86%)	11 (10%)	4 (4%)
The literature search is relevant and complete.	73 (68%)	23 (21%)	12 (11%)
The results of the trials described in the report are interpreted according to my understanding of the data.	94 (89%)	10 (9%)	2 (2%)
The draft recommendations in this report are clear.	97 (87%)	7 (6%)	7 (6%)
I agree with the draft recommendations as stated.	91 (82%)	11 (10%)	9 (8%)
This report should be approved as a practice guideline.	72 (69%)	23 (22%)	10 (10%)
If this report were to become a practice guideline, how likely would you be to make use of it in your own practice?	Very likely or likely	Unsure	Not at all likely or unlikely
	76 (70%)	11 (10%)	22 (20%)

Summary of Written Comments

Fifty-seven respondents (51%) provided written comments. The main points contained in the written comments were:

General comments

1. Twenty-two respondents commended the SCGG on their effort and agreed with the draft guideline report. A few respondents mentioned that they hope this will promote change from

current practice in their centre(s), since some centres are still encouraging the use of cornstarch. Three respondents commented that the conclusions of the draft guideline mirror those reached by the Skin Care Guideline Working Group at their institution.

Comments concerning recommendations

2. With regard to the first recommendation on gentle washing with water alone or with mild soap and water, a suggestion was made to limit this to one option (i.e., gentle washing with mild soap and water) to promote consistency within practice centres and not to confuse patients.
3. Several respondents commented that lack of evidence does not serve as a treatment guideline and questioned the value of a document that does not make “useable” recommendations. Many stated that the lack of evidence to recommend specific topical agents will still leave confusion and inconsistencies in practice. Several respondents suggested including opinions of the SCGG or guidance on “best practice” until more evidence from trials is available. Many felt that more value should be placed on expert opinion, and a suggestion was made that the guidelines from the British Columbia Cancer Agency (BCCA) and Oncology Nursing Society (ONS) should be considered. A few respondents were concerned that the current guideline may negatively affect patient care in instances where products are being used based on expert opinion and experience. Moreover, several respondents noted that patients want treatment and that providing no direction or telling them that “nothing makes any difference to healing” is not likely to be acceptable to patients, nurses, or physicians. Several respondents noted that they had observed improvement with some interventions and that although the trials have not confirmed statistically significant benefits of some agents, clinically significant effects have been observed and hence, a section with opinions of the SCGG would be useful.
4. One respondent suggested not using the word “prevention” rather, “the recommendations reflect the best opportunity to *reduce the impact* of radiation to the skin”. This respondent also suggested qualifying the statement that there is insufficient evidence to *support* the use of topical agents and to include the areas of study that have shown *no harm* during radiation therapy (e.g., aloe vera). He/she agreed that research is necessary to guide practice but noted that patients need symptom management and comfort measures of products that do not harm them until research proves a particular product to be most beneficial. He/she also commented that the guideline makes no mention of normal saline compresses, which he/she stated have been proven to be effective in reducing the inflammatory reaction.
5. One respondent commented that there is no evidence for preventive use of topical agents. He/she noted that the histology and clinical course of radiation dermatitis is similar to other conditions for which there is ample evidence for the use and/or avoidance of topical agents directed at symptom relief. He/she expressed concern that people reading this guideline will interpret it as though all topical agents are forbidden.
6. One respondent disagreed with the guideline recommendations concerning topical steroid creams stating that the conclusions reached were based on a small number of very small trials that were inadequately powered to detect a benefit. Furthermore, the respondent stated that changing standard practice and decreasing recommended options to a patient population already seeking and using topical agents outside of those recommended by the oncology team will have little benefit for the patient population or health care costs while decreasing patient confidence in the oncology team.
7. Nine respondents agreed with the recommendations on prevention but disagreed with the management recommendations. Two respondents questioned why ulcer and burn literature were not considered and noted that the focus on radiation therapy was too narrow. Two respondents suggested providing recommendations from the principles of wound management and recommended a comfort approach to open, draining, painful malignant

wounds. One respondent commented that he/she has found low dose topical steroids, flomazine, and gentian violet effective in easing discomfort of radiation skin reactions. Two respondents mentioned that clinical experience has demonstrated that 1% hydrocortisone is an effective, non-toxic palliative treatment for dry erythema and dry desquamation. One of these respondents noted that he/she felt there is insufficient evidence to classify the document as a practice guideline. One respondent noted that topical steroids are used successfully to treat itchy skin, rashes, and other dermatological conditions that may not directly result from radiation therapy. The respondent felt that the current guideline was too specific and questioned whether the focus should have been on radiation therapy as another “skin irritant” to investigate the benefits or harms of steroidal creams. One respondent commented that he/she believes moisturizing creams to be beneficial despite the lack of evidence from trials and noted that a trial on “Proshield” is currently being developed at his/her center. One respondent commented that he/she specifically recommends unscented Lubriderm to breast cancer patients undergoing radiation treatment. Another respondent questioned whether the guideline should include the names of specific proprietary products (i.e., Dove or Ivory soap) since many others are available.

Rationale and scope of evidence summary

8. One respondent questioned whether unpublished studies were included. Three respondents provided citations of trials that had been excluded from the draft guideline report.
9. One respondent suggested adding the recently published phase III trial on calendula cream.
10. One respondent commented that it would be beneficial to have a guideline for each disease site undergoing a course of radiation therapy since practitioners have different schools of thought on the use of creams, topicals, antifungals, washing, etc.
11. One respondent commented that the guideline does not provide skin care recommendations after radiation treatment and asked whether moisturizers can or should be used. He/she also questioned when the patient can be advised to return to normal skin washing.
12. One respondent commented that revising all patient literature would be very costly. All patient education sheets would need to be updated. He/she asked whether CCO would consider drafting a skin care policy sheet so as to promote consistent practice among centers.
13. One respondent asked whether there was evidence that some agents are detrimental (i.e., gentian violet). He/she also questioned whether the Burch study (8) was methodologically sound enough to make recommendations about the safety of deodorants. He/she also asked whether there was any evidence to suggest that certain patient education approaches were more effective at reducing the severity of skin reactions than others and noted that this information would help program administrators with planning.
14. One respondent commented that quality of life is the targeted outcome in prevention and management of acute radiation skin reactions. In terms of prevention, the focus should be on overall wound management; dry desquamation should be managed through hydration of the skin, moist desquamation should involve pain management, promotion of moist wound healing, and long term prevention measures should involve maintenance of skin hydration and protection from trauma.

Editorial comments

15. One respondent commented that the term “radiotherapy” is rarely used and suggested replacing this with “radiation therapy”. Two respondents requested clearer definitions for the following terms: “gentle” washing and “mild” soap. One of these respondents suggested defining “mild” soap as a product that maintains the acid mantle of the skin. Furthermore, the product should not contain lanolin (a known sensitizer), should be pH balanced, and

preferably be non-scented. “Gentle washing” should be clarified as the pouring of fluid onto the affected area. Shower heads vary in the amount of pressure produced per square inch and caution should be taken so as not to induce symptoms of pain, bleeding, etc. One respondent also asked what type of shampoo should be recommended.

16. One respondent suggested clarification of “personal hygiene practices” and suggested that the report should state that washing and deodorant use should be encouraged.

Future Trials

17. Several respondents noted that they agree with the suggestions for future research presented in the guideline report. One respondent provided the following additional recommendations for future trials: use of pure vitamin E oil as preventative or treatment of erythema, itching, dry desquamation; silver leaf dressing for acute reaction/moist desquamation. Four respondents expressed great interest in the outcome of future well-designed trials, with a few also willing to be involved in future trials. One respondent suggested that CCO become involved in developing the recommended trials.
18. One respondent mentioned that hydrocortisone was previously evaluated at their center as prevention to acute radiation skin reaction and he/she offered to share the results of the study. He/she also mentioned that another study is currently underway involving head and neck patients. Another respondent commented that they hope the guideline will lead to further trials on the management of dry and moist desquamation and he/she asked whether the use of hydrocortisone and its potential skin-thinning effects would be investigated.

Modifications/Actions

1. No modifications required.
2. There is no evidence on whether or not soap causes additional problems. In the opinion of the SCGG, the decision whether or not to recommend soap should be made by assessment of the patient’s dermatological history, in particular allergies and skin sensitivity.
3. The guideline report was modified as per the respondents’ suggestions by adding opinions of the SCGG and by modifying the recommendations.
4. To clarify the distinction between *prevention* versus *management* trials, the former included trials aimed at attempting to delay the onset of symptoms, while the latter included trials whose aim was the management of existing side effects. The SCGG revised the recommendations regarding insufficient evidence to state that “there is insufficient evidence to *support or refute*”, rather than “*recommend*”, specific topical agents. Opinions from the SCGG were also provided. The SCGG hopes that these modifications will promote change (as needed) and consistency in clinical practice. There is no evidence to support or refute the use of normal saline compresses.
5. It is clearly stated that only evidence from *radiation-induced* skin reactions was considered. It is beyond the scope of the guideline to look at evidence outside of radiation skin reactions.
6. The guideline report was modified as per the respondent’s suggestions by adding *Opinions of the SCGG* and by modifying the recommendations to include hydrophilic moisturizing cream and low dose corticosteroids.
7. Once again, only evidence from radiation-induced wounds was considered. The guideline authors identified the need to clarify the term “malignant wound” as there was some confusion in the literature and in practitioner perceptions between the extreme end of the radiation therapy skin reactions scale (i.e., severe moist desquamation or radiation-induced necrosis) and the management of advanced malignant wounds. Consequently, members of the SCGG proposed a future investigation into the optimal management of malignant wounds in the form of a practice guideline or evidence summary.

Topical antibiotics (i.e., Flamazine (silver sulphadiazine)) should only be used in the presence of known infection. Gentian violet has been used traditionally for its antifungal and

antiseptic properties but it is messy, dries the dermis, and is reportedly carcinogenic and thus its use has widely been discontinued and is not recommended (6).

Given the lack of empirical evidence on which to base recommendations, the choice of cream should be hydrophilic, lanolin-free, and relatively neutral but primarily related to patient comfort and preference. There is no evidence to suggest that one type of mild soap is preferable or should be recommended over another. However, in one paper by Frosch (45), in which the irritant qualities of 18 soaps was rated, “Dove” was the only soap classified as mild and may therefore be considered.

8. The inclusion criteria state that only fully published trials and abstracts were considered. Unpublished data were not included. One of the suggested papers was a review paper and therefore not considered.
9. The trial by Pommier et al. was published after the practitioner feedback questionnaires were printed and mailed. It was added to the final guideline report.
10. Due to lack of disease site-based evidence, it is impossible to make such recommendations.
11. Again, the lack of trials on post-radiation therapy skin care precludes recommendations. Usual clinical practice is to advise the patient to slowly resume normal skin care practices when the skin has healed but to permanently limit sun exposure.
12. The guideline authors agreed with this suggestion; whether it is feasible for CCO to provide patient education literature is to be determined.
13. The guideline was reworded to emphasize that “there is insufficient evidence to *support or refute*”, rather than “*recommend*”, specific topical agents. The SCGG has made it apparent where there is evidence that an agent has a detrimental effect. The SCGG makes no specific recommendations regarding deodorant use, as there is insufficient evidence to comment. The Burch study was included for information only. Studies that investigate the effect of differing educational approaches on the severity of skin reaction are beyond the scope of this guideline (however, there is a large body of literature dealing with the effectiveness of cancer patient educational approaches).
14. The SCGG considered this comment but made no modifications to the guideline report.
15. The terminology was modified and where possible, clarification of terms was provided.
16. Personal hygiene practices described in the report are defined in the Recommendations and Opinions of the SCGG sections. The SCGG made no specific recommendations regarding deodorant use, as there is insufficient evidence to comment. Likewise, there is insufficient evidence to recommend a specific mild shampoo.
17. The SCGG agreed that further studies are needed in areas where a promising intervention is being used. These studies should be of high quality in order to influence practice.
18. The SCGG agrees that further studies are needed in both areas. Any conducted studies should be of a high quality in order to influence practice. Opinions of the SCGG were added in response to the query about corticosteroid use.

Practice Guidelines Coordinating Committee (PGCC) Approval Process

The practice guideline report was circulated to 15 members of the PGCC for review and approval. Ten of fifteen members of the PGCC returned ballots. Six PGCC members approved the practice guideline report as written, one member approved the guideline and provided suggestions for consideration by the SCGG, and three members of the PGCC were also members of the SCGG and were therefore not eligible to review the report. The main comment for consideration was to include a list of suggested products that fall under the label “mild” shampoo, so that these can be recommended to patients. Likewise, it was suggested that product names be included in reference to the plain non-scented, lanolin-free hydrophilic cream suggested in the *Opinions* section of the document.

Modifications/Actions

The SCGG considered the above comment but decided not to suggest specific products because of a lack of supporting evidence. Further, there may be products on the market that could be considered “mild” that the group members are not aware of, in which case endorsing one product over another would introduce bias. Dove® soap was mentioned because one study (45) demonstrated that this is a “mild” soap; the authors are not aware of any other such studies. No changes were made in response to feedback from the PGCC.

Peer Review Feedback

The systematic review and practice guideline sections of this report were submitted for publication to the journal *Supportive Care in Cancer* in November 2005. Feedback from the reviewers was positive, although they suggested reporting data only from 'positive trials'. The SCGG indicated that inclusion of all relevant data meeting predefined selection criteria is an integral part of a systematic review and exclusion of negative data would present a biased picture of the performance of the treatment being examined. Therefore, both positive and negative trials were retained in the published review (3).

ONGOING DEVELOPMENT AND MAINTENANCE

This report reflects the integration of the draft recommendations with feedback obtained from the internal and external review processes and has been approved by the SCGG. PEBC reports are reviewed within five years of completion and updated reports will be posted on the CCO web site at: www.cancercare.on.ca.

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