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Therapeutic management of anal eczema: an evidence-based review

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SUMMARY

Aim: To conduct a systematic review of treatments for anal eczema (AE). **Methods:** We conducted a Medline search for clinical trial data for the treatment of perianal diseases including AE, including papers not published in the English language. We assessed the study reports using the system recommended by the Oxford Centre for Evidence-based Medicine. No meta-analysis was attempted. **Results:** The evidence base for topical treatments used to treat AE is very poor: there are very few studies and many of those that exist are of poor quality. The best evidence was found for medications that are yet to be licensed for AE. Among products with existing licences for the treatment of eczema, our assessment found some evidence to support the continued use of mild-to-moderate corticosteroids first line in most patients. **Discussion:** Features of the perianal region, and the fact that it is almost always occluded, mean that not all medications recommended in the general treatment guidelines for eczema are appropriate for AE. However, there are no specific treatment guidelines for these patients. This may in part be because of the lack of high-quality evidence-based medicine in this therapy area. Many frequently prescribed medications were developed and licensed many years ago, in an era when clinical trial design was not expected to be as rigorous as it is today. **Conclusion:** This review highlights the need to conduct more high-quality clinical trials in patients with AE in order that specific guidelines for the management of this difficult proctological condition can be prepared.

Review criteria
This review was based on a Medline search for clinical studies of treatments for anal eczema (AE), either alone or comorbid with other perianal diseases. Once identified, the clinical evidence was assessed using the scheme recommended by the Oxford Centre for Evidence-based Medicine.

Message for the clinic
Very few clinical studies have focussed specifically on treatments for AE, even though the anatomy and function of the perianal region mean that the treatment of eczema here can be more challenging than in other areas. More clinical studies of higher quality than those identified here would enable specific guidelines for the treatment of AE to be prepared.

Background and rationale

Anal eczema (AE) is an inflammatory disease that can have a significant effect on patients' quality of life. It is characterised by severe pruritus, pain, erythema and oedema (1). GPs, gastroenterologists, proctologists, gerontologists, surgeons and paediatricians – as well as dermatologists – are frequently confronted with patients with AE and the need for efficient and safe therapies is high.

The challenges of treating AE

The management of eczema in the perianal region is a particular challenge for physicians. It is hidden on a part of the body often associated with embarrassment, and therefore patients may have advanced disease before they present to a doctor for help (1). Moreover, the unique anatomy and environment of the perianal region means that AE is more likely than eczema in other areas of the body to present with underlying or secondary disease. Even without an underlying cause, however, regular defaecation and cleaning habits can cause permanent skin irritation in the anal area or delay the healing of existing AE. The perianal skin is very sensitive; therefore severe itch and especially pain are more frequent features of AE than of eczema generally.

General guidelines for the treatment of eczema

For eczema generally, there is a large body of evidence to support the choice of therapy. This was recently the subject of an extensive systematic review and meta-analysis conducted jointly by the European Dermatology Forum, the European Academy of Dermatology and Venereology, the European Task Force on Atopic Dermatitis, the European Federation of Allergy, the European Society of Paediatric Dermatology and the Global Allergy and Asthma European Network, which resulted in the publication of guidelines for the treatment of atopic eczema (2,3). The American Academy of Allergy, Asthma and Immunology (the AAAAI) also

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produces practice guidelines for atopic eczema, which are updated annually (4).

Both the European guidelines and the AAAAI practice guideline recommend starting treatment with basic skin care – gentle but thorough cleansing using emollient oils and soap substitutes, followed by liberal application of emollient creams and ointments, and avoidance of allergens and irritants (including foodstuffs) (2,4). Where non-medical methods fail to control atopic eczema, the guidelines recommend topical mild-to-moderately potent corticosteroids for short periods to reduce inflammation and itch. Topical calcineurin inhibitors (TCIs) are also effective for reducing inflammation and itch and are particularly useful in areas such as the groin and anogenital area, where use of more potent corticosteroids is not recommended because of their greater absorption. Systemic gamma interferon and narrow-band UVB therapy are recommended for symptomatic treatment of severe pruritus. There is some evidence that other medications – including local anaesthetics, capsaicin, doxepin and naltrexone – alleviate symptoms of pruritus, but not enough on which to base a recommendation. Bacterial and fungal suprainfections should be treated with antibiotic or antimycotics (2,4).

Aims of treatment for AE

The aims of treatment for any form of AE are rapid relief of symptoms, healing of eczema and prevention of recurrence by avoiding contact with allergens and irritants and/or long-term cure of underlying disease. The choice of treatment must take into account the different types of the disease, i.e. atopic dermatitis, irritant contact dermatitis (ICD) and allergic contact dermatitis (ACD) within the perianal region (5).

Therapeutic management

Therapeutic management of AE begins with the classification of AE (ACD, ICD or atopic dermatitis) and commencement of treatment for any underlying or secondary disease (haemorrhoids, fistulae, incontinence, etc.) (1,5).

Treatment for anal irritation, such as experienced in AE, begins with non-medical management (changes in washing and toileting habits and isolation of irritants and/or allergens where appropriate) (6–8). Where these measures prove insufficient, topical treatments should be added to reduce inflammation and itch (1). Systemic therapy may be required in the case of severe and/or persistent symptoms (9,10). Table 1 lists the most frequently prescribed drugs for AE – it is noticeable that most of these are fixed combination products containing drugs with different modes of action (11).

A few products have been licensed with specific indications for proctological diseases; however, some of these were developed around 50 years ago, and were not subjected to rigorous testing in well-designed randomised controlled trials (RCTs). Neither have many of the studies that were conducted been published in peer-review publications. Physicians, then, have to rely on empirical evidence for these products (which have been used for many years, after all) and for products licensed more generally for atopic and contact dermatitis.

Aim

To conduct an evidence-based review of therapeutic management for AE as a foundation to preparing guidelines for the treatment of this difficult proctological condition.

Methods

Study design and systematic search

We initially conducted a Medline search for reports of clinical trials involving patients specifically with AE. Our general search terms were 'anal eczema', 'anal atopic dermatitis', 'anal contact dermatitis', 'perianal eczema', 'perianal atopic dermatitis' and 'perianal contact dermatitis'. We also searched by chemical class and individual names of medications recommended for the treatment of eczema (2) and chemical class and individual names of any other medications used in commonly prescribed medications for AE (see Table 1). Because of the age of some of the products, we did not time limit our search.

We found very few published RCTs investigating efficacy and safety of treatments specifically for AE. To broaden the scope, we extended the search to studies for which the main focus was not AE (but in which AE was a comorbidity – e.g. haemorrhoids). In addition to revisiting the existing search results, we performed another Medline search using the terms 'anus', perianal and 'pruritus ani'. We also included papers that were not published in the English language. Scrutiny of the references cited in these papers alerted us to the existence of other useful references.

In total, we identified 197 papers. Of these, 85 were eliminated because we were not able to get translations of the paper (e.g. for Japanese and Chinese papers), we were not able to get hold of the actual paper (e.g. because the journal had gone out of print) or because, on closer inspection, the study did not separate the discussion of treatment for AE from other perianal diseases. Of the remaining 112 references, only 16 were reports of clinical studies.

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Table 1 Marketed topical products most commonly prescribed* for the treatment of dermatitis in the anal area (11)

Active ingredients	Brand name(s)
Single active agents	
Hydrocortisone	Procto-Kit, DermoPosterisan
Tribenoside	Borraza G
Cinchocaine	Dolaposterne
Glyceryl trinitrate	Rectogesic
Combination products containing corticosteroids + local anaesthetics	
Hydrocortisone + pramocaine or cinchocaine or lidocaine or benzocaine + amylocaine + aesculin	Pramosone, Proctofoam, Proctocreme HC, Porctosedyl, Xyloproct
Prednisolone + cinchocaine or + desonide + lidocaine + heparin + vitamins A and E	Scheriproct, Cirkan
Diflucortolone + lidocaine	Neriproct
Fluocinonide + lidocaine	Jelliproct
Fluocortolone + lidocaine or cinchocaine	Doloproct, Ultraproct
Fluocinolone + lidocaine (+ menthol + bismuth)	Synalar Rectal
Combination products containing corticosteroids + antimicrobials/antiseptics	
Hydrocortisone + benzyl benzoate + Peru balsam + bismuth + zinc with or without resorcinol	Anusol HC
Combination products containing corticosteroids + local anaesthetics + antimicrobials/antiseptics	
Hydrocortisone + cinchocaine with neomycin + aesculin or framycetin	Proctosedyl
Combination products containing local anaesthetics + antimicrobials/antiseptics	
Cinchocaine + polycresulin	Faktu
Other combination products	
Trimebutine + ruscogenin	Proctolog
Peru balsam + bismuth + zinc	Anusol
Hydrocortisone + *Escherichia coli* suspension	Posterisan
Hydrocortisone + phenylephrine + paraffin oil + fish oil	Preparation H
Lidocaine (+ carraginates + zinc)	Titanoreine

*Products with > 10,000 prescriptions in 2011 according to IMS data for Brazil, France, Germany, Japan, UK and USA.

Data synthesis

The system used in the assessment was based on that recommended by the Oxford Centre for Evidence-based Medicine (Table 2) (12).

Table 2 Grades of clinical evidence

Grade	Qualifying level of evidence
1a	Meta-analysis of RCTs
1b	Single RCT
2a	Systematic review of cohort studies
2b	Single cohort study Single RCT of limited value
3a	Systematic review of case studies
3b	Single case–control study
4	Case series Case cohort studies Single cohort study of limited value
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or first principles

RCT, randomised controlled trial.

Non-medical management of AE

- Perianal hygiene
- Withdrawal of irritant or allergen
- Avoiding dampness and scratching

The most important form of non-medical management is to improve hygiene to ensure that the perianal area is cleansed of faecal deposits or urine, that irritate the skin, in a way that does not further irritate the skin (e.g. by excessive rubbing or exposure to harsh soaps and detergents or allergens) (6–8). Instead, bidets (or baths), soft wet washcloths (or cotton balls) or unscented baby wipes are recommended (6,7,13–16) followed by gentle dabbing to dry the area using cotton balls, unbleached, unscented tissue or a soft cloth (6–8,13,15). Cleansing is an appropriate therapy for all forms of AE.

Identification and avoidance of irritants – for example, foodstuffs that cause loose stools and/or greater stooling frequency and/or mechanical trauma because of use of rough toilet paper – are important early steps in the treatment of confirmed ICD (5,16,17). In cases of ACD, where the cause is

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discovered to be, for example, a preservative found in food or cosmetics (e.g. sodium metabisulphite, isothiazolinones, or iodopropynyl butylcarbamate), or a medicament used to treat AE, other proctological condition or an unrelated condition (18,19), early management strategies involve withdrawing the allergen.

Miscellaneous non-medical approaches include wearing cotton underwear to keep the area dry and avoiding pantyhose, which can trap moisture (6–8), relief of scratching by applying a cold compress or taking a lukewarm bath (6). Patients should also be advised to adjust their diet to ensure that they have regular bowel movements (6,8).

Non-medical approaches may still need to be accompanied by a short course of topical treatment to halt the itch–scratch cycle (18).

Evidence: *Medline search using general search terms*.

Water-based wipes vs. cloth and water

Visscher et al. conducted a part-blinded, three-arm, randomised, control trial in 130 premature babies in a neonatal intensive care unit (14). It assessed the effects of routine cleansing on the condition of the skin in the diaper area in babies with mild or moderate diaper dermatitis. The study compared a non-woven water-based wipe containing benzyl alcohol preservative (wipe A – pH 5.2; $n = 45$), a non-woven water-based cloth with an acid-based preservative (wipe B – pH 4; $n = 45$) and a soft non-woven wash cloth with sterile water (control – pH 5.2; $n = 40$). The mean duration of the study was 10.4 days; cleansing was performed up to eight times a day (14).

Both wipes A and B were associated with improved integrity of the stratum corneum and reduced transepidermal water loss compared with the wash cloth plus sterile water, but wipe B may facilitate barrier repair and acid mantle development and lower instances of skin colonisation with Gram-negative bacteria (Level 2B).

Water vs. dry toilet paper vs. wipes containing Euxyl K 400 and polyethylene glycol as preservatives

This non-randomised study recruited 221 ambulatory adults with anal diseases including eczema (13). Prior to the study, 55% of these patients ($n = 120$) used dry toilet paper to clean themselves after defaecation. Of these patients, 60% who changed from dry toilet paper to water (bidet) after defaecation had improved itching and burning symptoms; this was compared with 32% who changed from wipes to water, 30% who changed from dry toilet paper to wipes and 9% who changed from water to wipes (13). The authors concluded that cleaning with water was most effective. Patients who changed from wipes to water had a statistically significantly greater improvement in symptoms than patients who changed from water to wipes ($p = 0.01$). There was no statistically significant difference between patients who changed from wipes to water and from dry toilet paper to wipes (Level 2B).

Topical treatments

The following substances are used for treatment of AE:

- Corticosteroids
- Calcineurin inhibitors
- Local anaesthetics
- Antifungals, antibiotics, antiseptics
- Combination therapies
- Natural remedies
- Others

As is recommended for atopic eczema generally (2), topical treatments – mild-to-moderate corticosteroids, TCIs and lidocaine, either alone or in combination – are the main pillars of treatment for AE (Table 3). The World Health Organization recommends corticosteroids over TCIs because of their improved cost–benefit ratio (20).

The type of formulation chosen depends on the chronicity of the eczema and its location, since marked differences have been noted in the permeability, proclivity to irritation, microbial ecology and blood flow in the anogenital region compared with skin in other parts of the body (21). Creams and lotions are useful when the skin is highly inflamed or weeping in the acute phase of AE. Lotions may be easier to apply where the skin is very hairy. Ointments should be avoided in acute AE but may provide needed moisturisation of dry chronic eczematous skin because of their occlusive effect (22).

A small study has reported high rates of acute contact dermatitis with corticosteroids, neomycin, bacitracin, dibucaine and benzocaine used in preparations for application to the vagina and haemorrhoids (19). In the case of corticosteroids, the authors postulated that this might be explained by enhanced penetration in the anogenital area. Hyperallergenic products may exacerbate the patient's condition, leading to acute allergic reaction and may help to mask the underlying condition.

Corticosteroids

These are typically used first line in moderate and severe eczema. The anatomy of the perianal region and skin mucosa requires that treatment duration with topical corticosteroids should be rather

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Table 3 Published evidence of topical treatment options for anal eczema

Type	Use notes	Side effects/contraindications	Highest level of evidence
Corticosteroids (1)	Treat the underlying causes of eczema Typically used short-term as first line treatment for moderate and severe eczema	Long-term use, especially or more potent types, can result in skin atrophy and tachyphylaxis Rebound phenomenon can accompany short-term use Should not be used in patients with bacterial and fungal infections unless the infection is also being treated	2B
Calcineurin inhibitors (1)	Macrolide immunomodulators that address the underlying causes of eczema May be useful in steroid-sparing treatment strategies Suitable for use on the face, eyelids and skin folds	Pruritus, burning and irritation may occur at first Not indicated for treatment of viral infections (e.g. eczema herpeticatum)	4
Local anaesthetics (31–34)	Useful for rapid symptomatic relief of itch and pain Can be combined with other classes of drugs for a broader spectrum of symptom relief and disease control	Not all local anaesthetics are suitable as they can act as contact allergens	N/A
Antifungals (37)	Essential for treating fungal infections associated with AE, including candidiasis Can be given systemically for severe skin involvement and immuno-compromised patients	Topical antifungals may cause irritation, burning, pruritus and oedema	2B
Antiseptics and antimicrobials	Important treating superficial bacterial infections secondary to AE	Burning, stinging, pruritus and erythema in irritant and allergic contact dermatitis	N/A
Combination therapies (corticosteroids, local anaesthetics, antimicrobials/ antifungals/antiseptics) (22,38)	Use to achieve rapid symptom relief with disease control or reduction in symptoms of AE along with control of primary or secondary infections Short-term use only	See entries for individual components	2B
Natural remedies (18,26,42,43)	Some plant extracts, bacterial extracts and traditional Chinese medicines have been reported to be efficacious and well tolerated in ICD and pruritus ani	Capsaicin is associated with burning sensations that persist on prolonged treatment	2B
Others (cooling lotions with menthol, camphor and/or phenol; zinc oxide; doxepin hydrochloride 5% cream; topical salicylic acid 5–40%) (1)	Provide symptomatic relief without addressing underlying causes of eczema Very little clinical trial data exist for these products and they are not licensed in AE	May be associated with burning sensation when applied to broken skin, *zinc oxide is not formulated with lanolin and may be particularly useful in patients with allergies*, doxepin may act as a skin sensitiser, topical salicylic acid may cause systemic symptoms if used extensively	4

short term (1). Mild- to moderately potent topical corticosteroids (e.g. hydrocortisone and betamethasone) are recommended for once- or twice-daily application. Physicians should start with low-potency corticosteroids for ICD and ACD, although atopic dermatitis may require more potent products (8,16). Mid- to high-potency topical corticosteroids should never be used in occlusion (16). Many of these products are also indicated in the treatment of haemorrhoidal diseases, which are a frequent cause of irritative AE.

Corticosteroids regulate proinflammatory cytokines and cells, inhibit cellular proliferation, dermal oedema and capillary dilation, and reduce vascular permeability (23). Use should be carefully monitored as extended duration of therapy (longer than a few weeks, or even shorter with more potent products and/or when diapers occlude the skin), can result in side effects, such as skin atrophy, telangiectasia and tachyphylaxis, or (rarely, after extended therapy with very potent corticosteroids on larger body areas) more serious, systemic, side effects such as Cushing's syndrome or hypothalamic–pituitary–adrenal axis suppression. Some patients experience a rebound of symptoms when treatment is discontinued (24,25). Short (temporary) courses of topical corticosteroids are suitable for use in all forms of AE.

Evidence: Medline searches for general search times plus 'corticosteroid', 'hydrocortisone' 'fluocortolone', 'betamethasone', 'prednisolone' and 'triamcinolone'.

No references were obtained for methylprednisolone aceponate, difluocortolone, desoximetasone, betamethasone valerate and prednisolone hexanoate in monotherapy, but difluocortolone has been studied

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in combination products and is discussed in a later section.

Hydrocortisone (26,27)

A six-arm, multicentre, randomised, double-blind, parallel-group study compared the safety and efficacy of ointments containing either a bacterial culture suspension of *Escherichia coli* (BCS) or BCS combined with hydrocortisone in patients with anal disease including AE and haemorrhoids: BCS vs. vehicle (Groups 1–3); BCS + hydrocortisone vs. vehicle vs. phenol (Group 4); BCS + hydrocortisone (0.25%) vs. hydrocortisone (0.25%) (Groups 5 and 6) (26). The BCS consists of the corpuscular components and metabolic products of 330 million apathogenic *E. coli* bacteria per 1 g of ointment. The mechanism of action of BCS is not fully understood, but is thought to involve non-specific stimulation of the immune system. Assessment of overall efficacy was based on the physician's assessment of changes using a scale from 1 (very good) to 4 (poor) and on individual symptom scores [from 0 (absent) to 3 (severe)] for burning, redness, itching and soiling.

Group 5 ($n = 172$) included patients with acute AE only. Group 6 ($n = 174$) included patients with acute anal disease including AE. The combination product gave significantly greater reductions in summed symptom scores compared with hydrocortisone alone (80 vs. 75%; $p = 0.036$ for Group 5, and 72 vs. 57%; $p = 0.019$ for Group 6). Physician overall assessment, found the combination to be significantly better in Group 6 ($p = 0.021$) but not in Group 5 ($p = 0.156$) (26). Overall in groups 4–6, the combination treatment was more effective at reducing signs and symptoms of haemorrhoids than of AE. All treatments were well tolerated, and results with BCS with or without hydrocortisone were rated as good or very good by > 70% of patients (Level 2B) (26).

In Groups 1 and 2, a total of 207 patients with acute or chronic AE and haemorrhoids received BCS and 210 received vehicle. Despite the design being the same, there was no significant difference in the relative reductions in summed symptom scores with BCS ($n = 99$) and vehicle ($n = 102$) in Group 1 (76 vs. 66%; $p = 0.095$), while in Group 2 ($n = 108$ in each arm) the difference was significant (75 vs. 62%; $p = 0.006$) (26). Physician assessment of overall efficacy was significantly greater for BCS in both groups (1.97 vs. 2.27; $p = 0.028$ and 2.23 vs. 2.56; $p = 0.016$, respectively) (Level 2b) (26).

Group 3 contained patients with haemorrhoids only, and the authors do not specify that Group 4 contained patients with AE, therefore these are not be discussed further here.

Al-Ghnaniem et al. conducted a pilot, randomised, double-blind, placebo-controlled, crossover trial of hydrocortisone (HC) ointment (1%) in 10 patients with pruritus ani with minimal clinical findings of eczema (27). Patients were randomised to HC or vehicle for 2 weeks, then underwent a 2-week washout period and then switched to the other treatment for 2 weeks. Hydrocortisone treatment was associated with significantly greater reduction in itch compared with vehicle measured qualitatively via a visual analogue score and Eczema Area and Severity Index score. Most patients also reported increased quality of life scores as measured by the Dermatology Life Quality Index (Level 2b).

Calcineurin inhibitors

These are macrolide immunomodulators which block the action of T-lymphocytes in the immune system, reducing inflammation and pruritus. They can be used as an alternative to corticosteroids in atopic AE, but are used off-label in other forms of eczema. They are contraindicated where viral infection is present. Initial treatment may be associated with pruritus, burning and irritation, but generally they are less likely to exhibit adverse local effects (including tachyphylaxis) and less rebound – especially in longer term use – than topical corticosteroids (28,29).

Evidence: Medline searches for general search terms plus 'calcineurin inhibitor', 'tacrolimus' and 'pimecrolimus'.

Pimecrolimus (28)

In a small, single arm, open-label study with pimecrolimus (1%) cream in 10 patients with moderate perianal eczema, patients applied the cream once daily for 2 weeks, and then once weekly for 6 weeks (28). Effectiveness was assessed using a semi-quantitative clinical score before and after therapy. Pruritus resolved within 1 week of treatment. After 2 weeks of treatment, the symptoms of AE had cleared and there was a significant reduction in clinical score (from 5 ± 1.5 at baseline to 2 ± 0.9 at 2 weeks; $p < 0.05$). No symptoms were apparent at 4 weeks. Treatment was well tolerated (Level 4).

Tacrolimus (29)

In a single arm, open-label study, 24 patients with perianal eczema applied ointment containing tacrolimus 0.1% to the affected area twice daily for 2 weeks (29). At the end of the study, the skin was visibly better and the patients' SCORAD ratings had improved (Level 4).

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Local anaesthetics

Topical local anaesthetics can be useful to provide a cooling sensation and to reduce pain and pruritus. In the anal area particularly, their value lies in the rapid relief of painful symptoms. A degree of caution is required though because some of these can cause contact allergy after repeated use, in particular cinchocaine (also known as dibucaine), bufexamac and benzocaine, which have been associated with sensitisation in 6.6%, 3.5% and 2.4% of users, respectively (30). Allergy to one local anaesthetic does not confer allergy to all, however – patch testing needs to include more than one example (31–33). Repeated applications of topical lidocaine (5%) in the perianal area were not associated with adverse events and did not result in systemic effects (34).

Local anaesthetics are frequently used in combination with topical corticosteroids for the treatment of AE.

Evidence: Medline searches for general search terms plus 'lidocaine' and 'cinchocaine'.

No reports of clinical studies with local anaesthetics as monotherapy in the treatment of AE were found; however, local anaesthetics are frequently used in combination products and evidence for these is reported in the combination therapy section.

Antifungals, antibiotics and antiseptics

Anal eczema can be colonised, but is also associated with fungal and bacterial superinfections and then it is important that these are also treated (35). Treating the infection may eradicate the AE (16). It is noteworthy that topical antibiotics are increasingly rarely prescribed for AE because of the risk of allergic hypersensitivity and bacterial resistance. Their place is being taken by antiseptics, which have the added advantage of working against bacterial and fungal infections.

Local bacterial skin infections are addressed with topical bacteriostatic and bactericidal drugs (e.g. neomycin, mupirocin, bacitracin, erythromycin, clindamycin, fucidic acid), sometimes treatment with systemic antibiotic may be needed (2). Topical antiinfectives may be associated with burning, stinging, pruritus and erythema in irritant and ACD (36). Mupirocin is an antibiotic which appears to have additional activity against *Candida* – which is frequently associated with secondary bacterial infection in the perianal region in any case. Research indicates that mupirocin is actively transported into the yeast cells by a high-affinity amino acid transport system, accounting for its antifungal activity (37).

The most common fungal infection associated with AE is perianal candidiasis (37).

Some combination treatments for AE (see next section) also contain an antibiotic or an antifungal.

Evidence – Antibiotics: Medline searches for general search terms plus 'antibiotic', 'bacitracin', 'neomycin', 'clindamycin', 'erythromycin', 'fucidic acid', 'metronidazole' and 'mupirocin'.

In addition to the studies reported below, there was one small study involving bacitracin in combination with oral antibiotics, which is discussed later.

Mupirocin and nystatin (37)

de Wet et al. conducted a prospective, randomised comparative study in 20 infants with irritant dermatitis and secondary *Candida* skin infections. The children were randomised to mupirocin ointment (2%; $n = 10$) or nystatin cream (100,000 U/g; $n = 10$) applied at every diaper change (at least three times per day). Daily examination and microscopy of patients who received mupirocin indicated eradication of all *Candida* strains within a mean 2.6 days, healing of exudative, excoriated wounds within a mean 4.7 days; eradication of attendant Gram-positive organisms within 2 days; and reduction of Gram-negative species during the course of the study (37). Daily examination and microscopy of the 10 infants randomised to nystatin (100,000 U/g; $n = 10$) found eradication of *Candida* infection in a mean 2.8 days; however, there was no healing of exudative, excoriated wounds or eradication of bacterial infections (Level 2b).

No reports of clinical studies with bacitracin, neomycin, clindamycin, erythromycin, fucidic acid or metronidazole in the treatment of AE were found.

Evidence – Antifungals: Medline searches for general search terms plus 'antifungal', 'nystatin' and 'ketoconazole'.

Apart from the de Wet et al. study (see above), no reports of clinical studies with antifungals in the treatment of AE were found.

Evidence – Antiseptics: Medline searches for general search terms plus 'antiseptic', 'triclosan' and 'bismuth'.

No reports of clinical studies with antiseptics in the treatment of AE were found.

Combination therapies

Topical combination therapies for AE include mixtures of corticosteroids and/or local anaesthetics and/or antimicrobials and/or other substances (e.g. natural remedies).

Fixed corticosteroid plus local anaesthetic combinations have greater efficacy than either product used separately when severe pain and itch is a key symptom of AE (22). They provide rapid reduction in pain and local inflammation, and also reduce pruritus. Corticosteroid-containing combination products

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should not be used in patients with concomitant bacterial or fungal infections unless the infection is also being treated, neither are they recommended for more than 2 weeks of treatment. Fixed combination products mainly contain low or medium potent corticosteroids (e.g. hydrocortisone, prednisolone, fluocinolone) to avoid local damage and systemic toxicity. The addition of an antimicrobial drug to the combination product is useful in cases where patients have underlying or secondary infections (38). The risk of sensitisation and contact allergy, however, may be increased by the use of combination products.

Evidence: As noted above, Medline searches conducted for local corticosteroids, anaesthetics, antimicrobials, antifungals and antiseptics found studies with combinations of products from more than one of these groups. These studies are reported here. In addition, we report some unpublished trials that have previously been summarised in Reference 22.

Policresulen + cinchocaine (38)

Espinosa reviewed a series of case reports from seven medical centres investigating the safety and efficacy of combination of policresulen (an antiseptic) and cinchocaine (given as ointments or suppositories) in patients with haemorrhoidal symptoms including AE (38). Physicians reported 'highly satisfactory' results in 1909 patients (83%). A total of 1881 patients (82%) rated the treatment as 'most satisfactory'. No patient reported a serious adverse event, but transient, mild adverse events (local discomfort, pruritus, burning, irritation) were seen in ~10% of the population. Espinosa attributes the success of the product to the highly acidic nature of policresulen, which rapidly and selectively causes coagulation in and desquamation of necrotic tissues thus promoting wound healing and re-epithelialisation (38). The acid environment also arrests infection by common pathogens and *Candida albicans* (Level 4).

Fluocortolone pivalate + lidocaine hydrochloride (39,40)

The safety and efficacy of suppositories containing fluocortolone pivalate (0.01%) plus lidocaine hydrochloride (0.2%) and a cream containing fluocortolone plus lidocaine plus chlorquinaldol were evaluated in 92 patients with haemorrhoids and concomitant conditions, including AE (in 10% of patients) (39). Patients were treated for between 4 and 30 days depending on the disease duration with once, twice or three-times daily doses of cream only, suppositories only or cream plus suppositories. Patients reported > 90% reduction in pain and itching. Of patients, 92% rated the treatment as 'good' or 'very good'. Both treatments were generally well tolerated (Level 4).

Herms conducted a single arm, open-label, multicentre study involved 209 adult patients with inflammatory anal and perianal disease (mostly AE) (40). In most cases, fluocortolone pivalate plus lidocaine hydrochloride plus chlorquinaldol in an oil and water emulsion base was applied twice daily for a mean 16 days; some patients required three times daily applications for up to 2 months. Evaluation was made by physicians' assessment of symptom reductions, and physician and patient assessment of treatment effects, but there was no statistical analysis of the results. The incidence and severity of unexpected side effects were also recorded.

At baseline, the most common symptoms were redness (98%), itching (86%) and burning sensation (71%). The proportions of affected patients were notably reduced at the end of treatment (to 38%, 30% and 13%, respectively). Pain was present in 32% of patients at baseline and 3% at end of treatment. Of physicians, 87% classified the treatment effect with the combination therapy as 'good' or 'very good'. The cream was well tolerated (Level 4).

Prednisolone hexanoate + cinchocaine (22,41)

Chlebarov conducted a 2-week, comparative, parallel-group, double-blind study to compare prednisolone hexanoate plus cinchocaine hydrochloride ($n = 49$) with bufexamac plus lidocaine ($n = 51$) in patients with haemorrhoidal symptoms including AE (41). Patients received suppositories (prednisolone 1.3 mg plus cinchocaine 1 mg) in Week 1 and ointment (prednisolone plus cinchocaine) in Week 2. Both formulations gave statistically significant reductions in burning ($p \leq 0.01$) and other symptoms ($p \leq 0.001$) compared with baseline and both were very well tolerated, more patients rated prednisolone plus cinchocaine as 'good' or 'good' (85.7% vs. 72.6% for bufexamac plus lidocaine) (Level 2b).

Non-peer-reviewed studies

During the 1980s, a number of trials were conducted with fixed corticosteroid plus local anaesthetic combination products. These studies were not conducted to the rigorous standards expected of today's clinical trials (22).

In one study, patients with AE secondary to haemorrhoids were randomised to fluocortolone pivalate (0.01%) plus lidocaine hydrochloride (0.2%) ($n = 117$) or a reference standard [betamethasone valerate plus lidocaine hydrochloride plus phenylephrine hydrochloride ($n = 115$) or triamcinolone acetonide plus lidocaine hydrochloride plus nystatin ($n = 117$)]. Treatment with ointment was applied twice daily for up to 20 days (22). Patients rated their symptoms as 'severe', 'slight' or 'absent' at

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baseline, on treatment and at the end of the study. Patients and physicians also rated the therapeutic effect of therapy as 'good', 'moderate' or 'poor'.

At the end of the study, 72–85% of physicians and patients in all three arms rated treatment as 'good' and great improvements in symptoms were seen with all three treatments. Results for fluocortolone plus lidocaine were similar or superior to standard treatments, but the differences were not statistically significant (Ungraded).

A series of single arm, open-label studies assessed the efficacy and tolerability of fluocortone plus lidocaine and prednisolone plus cinchocaine (ointments and suppositories) in > 1500 patients with haemorrhoidal symptoms (including AE) (22). Most patients achieved substantial improvement or complete relief of symptoms within 21 days. Treatments were generally well tolerated (Ungraded).

Natural remedies

A number of natural remedies – including plant extracts and traditional Chinese medicine – have been reported to be efficacious and well tolerated in ICD and pruritus ani (18,42–44).

Evidence: Medline search using general search terms.

Chinese medicine (43)

Zhi-Chao et al. (43) conducted a randomised, open-label, four-arm study in patients with persistent AE associated with haemorrhoids and anal fistulae. One hundred and sixty patients were randomised to A: traditional Chinese medicine (consisting of a solution containing extracts of *Natrii suifas exsiccatub*, *Pericarpium zanthoryli*, *Herba schizonepetae*, *Fructus cnidii*, *Flos lonicerae*, *Radix sophorae flavescentis*, *Rhizoma atractylodis* and *Radix glycyrrhizae*) plus zinc oxide cream; B: surgery; C: Chinese medicine plus zinc oxide cream followed by surgery; or D: surgery followed by Chinese medicine plus zinc oxide cream. After 4 weeks, 22.5%, 32.5%, 57.5% and 45.0% of patients in groups A, B, C and D, respectively had no signs or symptoms of disease, and at least 60% of lesions were absent in 40.0%, 52.5%, 85.0% and 75.0% of patients, respectively. Chinese medicine followed by surgery was statistically significantly more effective than each of the other groups ($p = 0.0001$). Intergroup comparisons found significant differences in efficacy between groups C and A, groups C and B, and groups D and A (all $p < 0.05$), but not between groups A and B, groups B and C, and groups C and D (43) (Level 2b).

Aloe vera and Calendula officinalis *(44)*

Panahi et al. compared ointments containing extracts of *Aloe vera* and *C. officinalis* in a randomised, double-blind comparative trial in infants with diaper dermatitis (44). The children were randomised to receive *Calendula* cream ($n = 34$) or Aloe vera ointment ($n = 32$) three times daily until symptoms had resolved, or for a maximum of 10 days (patients with concomitant infections or who were receiving corticosteroids were excluded). At the end of the study, symptoms in both groups were significantly reduced compared with baseline ($p < 0.001$). In the aloe vera group, the proportion of patients with no or mild symptoms of dermatitis increased from 3.1% at baseline to 56.2% at end of the study. In the *Calendula* group, the proportion of patients with no or mild symptoms increased from 0% to 70.6%. The reduction in symptoms of dermatitis was statistically significantly greater in the *Calendula* group ($p = 0.001$ vs. treatment with aloe vera) (44). Both treatments were well tolerated (Level 2b).

Other agents used to alleviate symptoms of AE

Some ingredients in topical preparations do not treat AE, but can temporarily reduce symptoms. For example, menthol, camphor and/or phenol are cooling substances that provide temporary relief from pruritus ani, but do not address the underlying cause of eczema. They may be associated with a burning sensation when applied to eroded skin and may cause drying of the skin over time.

Zinc oxide-based lotions and creams act as skin protectant, which can help to dry eczematous skin with exudation, prevent irritation of the perianal area by forming a physical barrier on the skin avoiding contact of the skin with irritants. This barrier reduces irritation, giving the skin the opportunity to heal, reducing itching, pain and burning (22). Unlike some soothing creams and lotions, these products do not tend to contain lanolin, which is a known allergen (1). Zinc oxide paste is a very effective skin barrier; however, it may be very difficult to wash away, which can be a disadvantage when the delicate skin in the anal area is inflamed. It is important to note that it is not necessary to remove the zinc oxide paste prior to re-application, thus avoiding any mechanical trauma through washing (44).

Topical salicylic acid (5–40%) is used mainly in keratotic forms of eczema. Extensive application to eroded skin and in infants is not recommended as the increased absorption of salicylates from eroded skin may lead to neurologic and gastrointestinal intoxication (45,46).

Doxepin hydrochloride cream (5%) has antihistamine, antimuscarinic and antiserotoninergic activity, which may be used in eczematous dermatitis, e.g. AD and contact dermatitis and for symptomatic

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treatment of pruritus. It can cause contact allergy when applied for longer than 8 days (2,47).

Evidence: Medline search using general search terms plus 'menthol', 'camphor', 'phenol', 'zinc oxide' 'salicylic acid' and 'doxepin'.

Zinc oxide

Patrizi et al. enrolled 25 children aged between 1 month and 4 years who presented with napkin dermatitis. Among this group, 20 patients were diagnosed with irritant contact diaper dermatitis, three had atopic dermatitis, one had perianal streptococcal dermatitis and one was affected by psoriasis (48).

A barrier cream containing zinc oxide, vitamin E and panthenol was applied at each diaper change for 4 weeks. Children with evidence of *Candida* infection also received antifungal cream twice daily. The children were assessed for symptoms of burning and itching as well as erythema, oedema, exudation/vesiculation at baseline and at the end of the study.

After 4 weeks, 13 patients were clinically healed and nine had marked improvements in their symptoms. Two had no improvement in symptoms, and one was withdrawn from the study. Tolerability was good or excellent in 22 of 25 patients (48) (Level 4).

Although Medline searches did not reveal any studies on zinc oxide in AE, studies have investigated its use a skin protectant in peri-wound areas showing that zinc paste is an effective barrier (49). A recent literature review on the use of topical zinc in the treatment of chronic venous leg ulcers also highlighted the limitations of existing studies with zinc (in the form of topical creams and pastes) as small scale, outdated and methodologically inconsistent, emphasising the need for new rigorous studies in this area (50).

The Medline search identified no clinical trial evidence to support the use of menthol, camphor, phenol, salicylic acid or doxepinin in the treatment of AE.

Discussion

The location, function and anatomy of the anus all conspire to make AE more difficult to treat than eczema patches on other parts of the body. AE is more likely to be associated with secondary conditions, or to be itself secondary to another condition (especially haemorrhoids), than eczema in other locations. Patients tend also to experience more pain and intense itching because of the highly sensitive nature of the perianal skin, which develops eczema more rapidly because it is permanently occluded. These factors must influence the choice of management strategy for patients with AE.

The evidence base for medications used specifically in the treatment of AE and other proctological conditions is scant and generally of low quality, including those therapies that are long established (such as zinc oxide-based pastes and creams). Trials frequently lacked a robust comparator product, were open-label, did not include follow-up periods and relied on qualitative measurements, making comparisons between studies difficult. Based on this assessment, the best evidence (at level 2B) exists for hydrocortisone, mupirocin, nystatin and natural product-based medicines such as *E. coli*-based bacterial culture solution, Chinese medicine and *Calendula* extract. Most of the evidence for established corticosteroids, calcineurin inhibitors and fixed combination products containing corticosteroids, however, is at level 4 – despite the fact that, according to sales data (11), the latter are the most widely used products for AE and other perianal diseases. Nevertheless, nothing indicates that general guidance for the treatment of eczema should be different in AE. For now, physicians must continue to rely on their clinical experience in other forms of eczema and/or other proctological conditions to select a therapy for a patient with AE.

Limitations

This cannot be considered a rigorous systematic review. We restricted our search to papers available on Medline and did not specifically seek out studies that did not support the use of recommended therapies for eczema generally or in AE specifically – although in some instances, this information has come out of our research. To begin with, studies that did not have treatment of AE as their main focus were excluded, but we had to widen our inclusion criteria to encompass many of these studies in order to be able to discuss many of the products that can be prescribed for AE. We were unable to include all of the studies that might have provided data for some of the older products because those publications were not available to read. The older studies that we were able to find often were not conducted to rigorous standards.

Conclusion

More high-quality RCTs with new and existing products are required in order to establish a gold standard therapy for AE against which new products can be judged, to establish how products that provide symptom relief can best be used alongside those that address the underlying causes of AE, and whether natural product-based medications have a place in the treatment of AE and/or whether they offer a

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starting point in the development of new synthetic medications. With more reliable data in place, ultimately it should be possible to establish international guidelines for the treatment of the challenging proctological condition.

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Author contributions

Dr Havlickova was responsible for the concept of the review. Both authors critically reviewed the results of the literature survey and the assessment of the clinical study reports. Both authors critically reviewed and amended the first and subsequent drafts of the manuscript.

References

1 Schauber J. Topical therapy of perianal eczema. *Hautarzt* 2010; **61**: 33–8 [In German].
2 Ring J, Alomar A, Bieber T et al.; for the European Dermatology Forum, and the European Academy of Dermatology and Venereology, the European Task Force on Atopic Dermatitis, European Federation of Allergy, the European Society of Pediatric Dermatology, and the Global Allergy and Asthma European Network (GA2LEN). Guidelines for treatment of atopic eczema (atopic dermatitis) Part I. *J Euro Acad Dermatol Venereol* 2012; **26**: 1045–60.
3 Ring J, Alomar A, Bieber T et al.; for the European Dermatology Forum, and the European Academy of Dermatology and Venereology, the European Task Force on Atopic Dermatitis, European Federation of Allergy, the European Society of Pediatric Dermatology, and the Global Allergy and Asthma European Network (GA2LEN). Guidelines for treatment of atopic eczema (atopic dermatitis) Part II. *J Euro Acad Dermatol Venereol* 2012; **26**: 1176–93.
4 Schneider L, Tilles S, Lio P et al. Atopic dermatitis: a practice parameter update 2012. *J Allergy Clin Immunol* 2013; **131**: 295–9.
5 Wienert V. Anal eczema – an interdisciplinary diagnostic challenge [in German] *Wien Klin Wochenschr* 2006; **118**(3–4): 69–71.
6 Alexander-Williams J. Causes and management of anal irritation. *Br Med J (Clin Res Ed)* 1983; **287** (6404): 1528.
7 Alexander-Williams J. Pruritus ani. *Br Med J* 1983; **16**(287): 159–60.
8 Markell KW, Billingham RP. Pruritus ani: etiology and management. *Surg Clin North Am* 2010; **90**(1): 125–35.
9 McGirt LY, Martins CR. Dermatologic diagnoses in the perianal area. *Clin Colon Rectal Surg* 2004; **17**: 241–5.
10 Werfel T, Claes C, Kulp W, Greiner W, von der Schulenburg JM. Therapy of atopic eczema. *GMS Health Technol Assess* 2006; **2**: Doc 19.
11 IMS Health Inc. *Prescribing Insights*. Danbury, CT: IMS, 2011.
12 Oxford Centre for Evidence-based Medicine. Levels of evidence March (2009). http://www.cebm.net/index.aspx?o=1025 (accessed 27 November 2013).
13 Brühl W, Schmauz R. Anal hygiene in perianal skin diseases – compatibility of water moist and dry toilet paper. *Zentralbl Hyg Umweltmed* 1998; **200**: 562–70 [In German].
14 Visscher M, Odio M, Taylor T et al. Skin care in the NICU patient: effects of wipes versus cloth and water on stratum corneum integrity. *Neonatology* 2009; **96**: 226–34.
15 Zoli V, Tosti A, Silvani S, Vincenzi C. Moist toilet papers as possible sensitizers: review of the literature and evaluation of commercial products in Italy. *Contact Dermatitis* 2006; **55**: 252–4.
16 Humphrey S, Bergman N. Practical management strategies for diaper dermatitis. *Skin Therapy Lett* 2006; **11**(7): 1–6.
17 Siddiqi S, Vijay V, Ward M, Mahendran R, Warren S. Pruritus ani. *Ann R Coll Surg Engl* 2008; **90**: 457–63.
18 MacLean J, Russell D. Pruritus ani. *Aust Fam Physician* 2010; **39**: 366–70.
19 Warshaw EM, Furda LM, Maibach HI et al. Anogenital dermatitis in patients referred for patch testing: retrospective analysis of cross-sectional data from the North American Contact Dermatitis Group, 1994–2004. *Arch Dermatol* 2008; **144**: 749–55.
20 International League of Dermatological Societies, World Health Organization. *Proposals for the Revision of the WHO Essential Drugs List Concerning Drugs that are Used to Treat Skin Diseases*. Geneva, Switzerland: WHO, 2008. www.who.int/selection_medicines/committees/subcommittee/2/ILDS.pdf (accessed 27 November 2013).
21 Elsner P. Anatomical and physiological basis of topical therapy of the mucosa. In: Surber C, Elsner P, Farage MA, eds. *Topical Applications and the Mucosa*. *Curr Probl Dermatol* 2011; **40**:1–8.
22 Havlickova B. Topical corticosteroid therapy in proctology indications. In: Abramowitz L, ed. *The Diagnosis and Management of Haemorrhoidal Disease from a Global Perspective*. *Aliment Pharmacol Ther* 2010; **31**(Suppl. 1): 19–32.
23 Spergel JM. Immunology and treatment of atopic dermatitis. *Am J Clin Dermatol* 2008; **9**: 233–44.
24 Adams BB, Sheth PB. Perianal ulcerations from topical steroid use. *Cutis* 2002; **69**: 67–8.
25 Buchman AL. Side effects of corticosteroid therapy. *J Clin Gastroenterol* 2001; **33**: 289–94.
26 Wienert V, Heusinger JH. Local treatment of hemorrhoidal disease and perianal eczema. Meta-analysis of the efficacy and safety of an *Escherichia coli* culture suspension alone or in combination with hydrocortisone. *Arzneimittelforschung* 2002; **52**: 515–23.
27 Al-Ghnaniem R, Short K, Pullen A, Fuller LC, Rennie JA, Leather AJ. 1% hydrocortisone ointment is an effective treatment of pruritus ani: a pilot randomized controlled crossover trial. *Int J Colorectal Dis* 2007; **22**: 1463–7.
28 Kreuter A, Hochdorfer B, Altmeyer P, Gambichler T. Pimecrolimus 1% cream for perianal atopic dermatitis. *Br J Dermatol* 2005; **152**: 186–7.
29 Schauber J, Weisenseel P, Ruzicka T. Topical treatment of perianal eczema with tacrolimus 0.1%. *Br J Dermatol* 2009; **161**: 1384–6.
30 Kügler K, Brinkmeier T, Frosch PJ, Uter W. Anogenital dermatoses – allergic and irritative causative factors. Analysis of IVDK data and review of the literature. *J Dtsch Dermatol Ges* 2005; **3**: 979–86 [In German].
31 Bauer A, Geier J, Elsner P. Allergic contact dermatitis in patients with anogenital complaints. *J Reprod Med* 2000; **45**: 649–54.
32 Kearney CR, Fewings J. Allergic contact dermatitis to cinchocaine. *Australas J Dermatol* 2001; **42**: 118–9.
33 Jussi L, Lammintausta K. Sources of sensitization, cross-reactions, and occupational sensitization to topical anaesthetics among general dermatology patients. *Contact Dermatitis* 2009; **60**: 150–4.
34 Zimmermann J, Schlegelmilch R, Mazur D, Seiler D, Vens-Cappell B. Proof of systemic safety of a lidocaine ointment in the treatment of patients with anorectal pain. *Arzneimittelforschung* 2007; **57**: 12–9.
35 Winkler R. Viral-induced tumours and pre-malignant cutaneous diseases of the perianal region. *Zentralbl Chir* 2005; **130**: 60–4 [In German].
36 Spring S, Pratt M, Chaplin A. Contact dermatitis to topical medicaments: a retrospective chart review from the Ottawa Hospital Patch Test Clinic. *Dermatitis* 2012; **23**: 210–3.
37 de Wet PM, Rode H, van Dyk A, Millar AJ. Perianal candidosis – a comparative study with mupirocin and nystatin. *Int J Dermatol* 1999; **38**: 618–22.
38 Espinosa DJ. Analytical review of multicenter studies with polycresulene for hemorrhoidal pathologies. *Acta Gastroenterol Latinoam* 2000; **30**: 177–86 [In Spanish].
39 Neiger A, Herms E. The symptomatic therapy of hemorrhoids and anal eczema – a report of experiences from proctology practice. *Schweiz Rundsch Med Prax* 1990; **79**: 918–20 [In German].
40 Herms E. Studies on the local tolerance and clinical efficacy of Doloproct Creme in the perianal area. *Akt Dermatol* 1988; **14**: 385–8 [In German].
41 Chlebarov C. The treatment of haemorrhoidal symptom complexes. *Therapiewoche* 1985; **35**: 27 [In German].

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42 Vlachojannis JE, Cameron M, Chrubasik S. Medicinal use of potato-derived products: a systematic review. *Phytother Res* 2010; **24**: 159–62.
43 Zhi-Chao L, Jian-Gang L, Zhe L, Qing S. Clinical efficacy of combined therapy for perianal eczema caused by anal diseases in 160 cases. *Indian J Dermatol* 2007; **52**: 27–9.
44 Panahi Y, Sharif MR, Sharif A et al. A randomized comparative trial on the therapeutic efficacy of topical aloe vera and *Calendula officinalis* on diaper dermatitis in children. *Sci World J* 2012; **2012**: 810234.
45 Gloor M, Beier B. Keratoplastic effect of salicyclic acid, sulfur and a tensio-active mixture. *Z Hautkr* 1984; **59**: 1657–60 [In German].
46 Lukacs I. Frequent dermatologic diseases in the newborn and children. *Minerva Med* 1975; **66**: 1341–51 [In Italian].
47 Drake LA, Fallon JD, Sober A. Relief of pruritus in patients with atopic dermatitis after treatment with topical doxepin cream. The Doxepin Study Group. *J Amer Acad Dermatol* 1994; **31**: 613–6.
48 Patrizi A, Neri I, Varotti E, Raone B. Clinical evaluation of the efficacy and tolerability of the 'NoAll Bimbi Pasta Trattante' barrier cream in napkin dermatitis. *Minerva Pediatr* 2007; **59**: 23–8 [In Italian].
49 Cameron J, Hoffman D, Wilson J, Cherry G. Comparison of two peri-wound skin protectants in venous leg ulcers: a randomised controlled trial. *J Wound Care* 2005; **14**(5): 233–6.
50 O'Connor S, Murphy S. Chronic leg ulcers: is topical zinc the answer? A review of the literature. *Adv Skin Wound Care* 2014; **27**(1): 35–44.

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