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GUIDELINES

Guidelines for the management of lichen sclerosus

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Summary These guidelines for the management of lichen sclerosus have been prepared for dermatologists on behalf of the British Association of Dermatologists. They present evidence-based guidance for treatment, with identification of the strength of evidence available at the time of preparation of the guidelines, and a brief overview of epidemiological aspects, diagnosis and investigation.

Key words: guidelines, lichen sclerosus

Disclaimer

These guidelines have been prepared for dermatologists on behalf of the British Association of Dermatologists and reflect the best data available at the time the report was prepared. Caution should be exercised in interpreting the data; the results of future studies may require alteration of the conclusions or recommendations in this report. It may be necessary or even desirable to depart from the guidelines in the interests of specific patients and special circumstances. Just as adherence to the guidelines may not constitute defence against a claim of negligence, so deviation from them should not necessarily be deemed negligent.

Introduction

The aim of the British Association of Dermatologists is to provide guidelines for the management of skin diseases using as much evidence-based data as possible. There are few published randomized controlled trials to support the following guidelines for the management of lichen sclerosus (LS); the recommendations made are those that are currently considered best practice but will be modified at intervals in the light of new evidence. Levels of evidence to support the guidelines are quoted according to the criteria stated in Appendix 1. Appraising and grading the evidence for the treatment of LS is not easy, particularly as it is a disorder in which many treatments have a large placebo effect; additionally, disease definition has been unreliable or unclear in some of the reports so it is possible that 'therapy-resistant cases' may have had some atypical features.

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Definition

LS is a lymphocyte-mediated dermatosis that has a predilection for the genital skin in both sexes and was first formally described at the end of the nineteenth century by Hallopeau and Darier as a variant of lichen planus (LP).[1–3] Use of the terms leucoplakia and kraurosis vulvae[4] in older literature is a source of confusion. Balanitis xerotica obliterans, a term used for LS of the penis, was only recently coded as part of LS in literature search tools such as Medline. Not all LS is histologically atrophic, and the term 'lichen sclerosus et atrophicus' has now been replaced with LS alone.

Currently, LS is considered as a separate entity from LP on the basis of its specific distinguishing clinical and histological features. However, it is recognized that

some cases of LS may represent an overlap syndrome, sharing features of both LS and LP, and perhaps the two conditions represent different parts of a spectrum of the same process. Such overlap cases are often associated histologically with squamous cell hyperplasia, and are best categorized as 'complicated' LS, as response to a topical ultrapotent corticosteroid is often poorer.[5]

These guidelines are in the main for uncomplicated LS with the classical histological features of the disorder.

Pathogenesis

The aetiology of LS is uncertain but there is mounting evidence to suggest that autoimmune mechanisms are involved in its pathogenesis;[6–8] there is an increased incidence of tissue-specific antibodies[9] and associations with other autoimmune diseases in patients with LS,[10,11] as well as positive associations with HLA class II antigens.[12–14] There is still controversy regarding the implication of *Borrelia* infection as an aetiological agent; although several studies have shown that this association does not occur in the U.S.A., some doubt still remains in Europe.[15,16]

Incidence

It is clear from the number of patients attending a vulval clinic that LS is a common disease. LS in females has two peak ages of presentation. The first of these occurs in prepubertal girls[17] and may resolve or continue beyond the menarche.[18] The other peak of incidence is in postmenopausal women;[17] although this suggests a hormonal influence, hormone replacement therapy neither improves existing disease nor provides any protection against its development. Interestingly, pregnancy seems to improve the symptoms and signs, and a normal vaginal delivery is usually possible.

The incidence of LS in males is lower than in females but there is also a bimodal onset, with peaks of disease presentation occurring in young boys and then again in adults.[19]

Clinical features

Female anogenital: adult

The typical lesions are porcelain-white papules and plaques, often with areas of ecchymosis. Follicular delling may be prominent. The lesions occur in the interlabial sulci, labia minora, clitoral hood, clitoris and perineal body. Genital mucosal involvement does not occur, the vagina and cervix always being spared (by contrast with LP). However, there may be some mucosal involvement at the edge of mucocutaneous junctions, which may lead to introital narrowing. Perianal lesions occur in women in 30% of cases. Itch is the main symptom but pain occurs if there are erosions or fissures. The itch is worse at nights and may be so severe as to disturb sleep. Dyspareunia occurs in the presence of erosions, fissures or introital narrowing.

Some women are asymptomatic and the LS is only discovered when they are being examined for another reason. Most of these patients have inactive disease, which may have occurred in childhood, and the changes seen are the long-standing atrophic changes that persist. However, some of these individuals have changes of active disease with hyperkeratosis and ecchymosis, and should therefore receive treatment.

Female anogenital: child

The lesions are similar to those in adult women but ecchymosis may be very striking and potentially mistaken as evidence of sexual abuse.[20] There has been a tendency to exclude a diagnosis of sexual abuse if LS has been confirmed; however, as LS exhibits the Koebner phenomenon at sites of trauma, some cases of LS may in fact be caused or aggravated by sexual abuse.[21] Suspicious features include LS in older prepubertal girls, the presence of associated infection (especially infections that are characteristically sexually transmitted), or other symptoms or signs of abuse.

Perianal LS with or without vulval involvement occurs in young girls, who commonly present with constipation because of painful fissuring in this area.

Male genital: adult

The lesions appear most commonly on the prepuce, coronal sulcus and glans penis. More rarely lesions may be found on the shaft of the penis. The presenting complaint is usually tightening of the foreskin, which may lead to phimosis and painful erections. One report documented that 40% of phimosis occurring in adults was due to LS,[22] although another study of 75 subjects with severe phimosis only identified LS in eight (11%).[23] In contrast to women, men commonly present with the consequences of scarring. The perimeatal area may be involved and postinflammatory

scarring may lead to stenosis and obstruction causing dysuria and poor urinary stream.

Other presenting complaints are due to the appearance of lesions, decreased penile sensitivity and soreness rather than itch. Circumcision does not necessarily ensure protection against further flares of the disease and one series showed that 50% of men requiring circumcision continued to have lesions of LS.[19] Perianal disease is extremely rare in males.

Male genital: child

The disease usually affects the prepuce and can lead to phimosis. The incidence of phimosis caused by LS in children is difficult to determine as not all surgical specimens are assessed histologically. One study documented the presence of LS in 14 of 100 prepubertal boys having elective circumcision for disease of the foreskin;[24] a similar figure of 14% was recorded in a French series.[22] A more recent study of 100 children with phimosis documented that all of them had LS.[25] Perianal involvement occurs rarely, if ever.

Extragenital

The classical extragenital sites are the upper trunk, axillae, buttocks and lateral thighs. Extragenital lesions in men are uncommon and usually do not occur in association with genital lesions. The face and scalp in both sexes are other sites that may rarely be involved.

Oral lesions of LS are extremely rare and many of the cases reported in the literature have not been substantiated with histological evidence and may well have been examples of LP or morphoea.[26] In the rare instances of oral LS these are recorded at sites in the mouth where there is cornified stratified squamous epithelium, i.e. tongue, gingiva and hard palate.

Investigations

The diagnosis in most patients is usually made clinically, but a confirmatory biopsy is helpful in cases where there is some clinical doubt about the diagnosis and to document any atypical features. The main differential diagnoses include LP, mucous membrane pemphigoid and genital psoriasis. A skin biopsy is not always practical in children and it is preferable to initiate their treatment without histological confirmation. A biopsy is essential in all cases that fail to respond to adequate treatment.

Histology

The classical histological features of uncomplicated LS include a thinned epidermis with hyperkeratosis, a wide band of homogenized collagen below the dermoepidermal junction and a lymphocytic infiltrate beneath the homogenized area. There may be small focal areas where the inflammatory infiltrate is close to the dermoepidermal junction, similar to LP.[27] A few patients may have a thickened epidermis; these patients tend to have complicated disease that is not so responsive to treatment and may have a higher risk in the long term of developing an associated squamous cell carcinoma (SCC).

The length of time that LS has been present cannot be determined accurately using histological parameters.[28]

Other investigations

Other investigations that might be indicated include a screen for other autoimmune diseases, in particular thyroid disease in women.

Complications

Malignancy

SCC, discussed below, is the commonest malignancy described in association with anogenital LS. Interestingly, SCC has not been recorded in LS at sites other than the anogenital area. Verrucous carcinomas also appear to occur on a background of LS.[29,30] There have also been reports of basal cell carcinoma[31] and melanoma occurring in cases of vulval LS.[32,33]

Squamous cell carcinoma in women with genital lichen sclerosus. SCC arising within LS only occurs in lesions affecting the anogenital area; in practice, this risk is extremely small. Two studies each of over 200 women with LS under regular review have shown a small but definite increased incidence of invasive SCC.[17,34] The magnitude of this risk is about 5% or less lifelong in known patients with LS[17,30] (and is therefore probably a significant overestimate in view of the likely high prevalence of undiagnosed cases of LS). However, histopathological examination of vulval SCCs indicates that about 60% occur on a background of LS.[35–38] A clinical study of anogenital SCC presenting to a vulval clinic demonstrated that 14 of 23 cases occurred on a background of LS.[30] The role of human papillomavirus (HPV) as a possible aetiological agent in the

progression to malignancy in LS has not been clearly established, although recent evidence suggests that there may be two distinct aetiologies for vulval SCC. One type occurs in older women with a chronic dermatosis such as LS, the other in younger women without LS but with evidence of the same oncogenic HPV types that are linked to cervical SCC.[39] Although evidence for an important role of HPV in LS-associated SCC is scanty, there is a remote theoretical risk that topical corticosteroid use might induce oncogenic HPV types that may be cause for concern because, as found in the normal population, up to 20% of cases of LS may incidentally carry the oncogenic HPV 16.[40]

SCC of the vulva should be managed by gynaecologists experienced in this field as surgery has to be individualized according to the tumour size and location, particularly in early invasive disease.[41]

Squamous cell carcinoma of the penis associated with lichen sclerosus. An association between LS and penile SCC has also been reported.[42,43] The magnitude of this association is probably less than 4%, which was the case in a retrospective series of 86 histologically confirmed cases of LS.[44] There is probably poor recognition of the association, as a review of LS in 1995 was only able to document nine reported cases.[44] The role of HPV in inducing malignant change is again unproven, but there is documentation in the literature showing a high incidence of HPV 6 (in six of 23 patients) using polymerase chain reaction (PCR) technology in childhood penile LS and another four of 23 patients with HPV 16 or 18.[45] Another recent therapeutic study suggested that three of 22 men had evidence of HPV after use of corticosteroids for LS[46] (in one case by penoscopy, and in the other two on histological criteria), and studies also using PCR documented HPV in one of 25[47] and none of 24[48] patients. Oncogenic HPV types do not appear to be commonly associated with penile LS.[48]

Scarring

Introital narrowing. Infrequently, some women may have narrowing of the introitus. This can present problems with dyspareunia and/or difficulties micturating. If surgery has to be considered to widen the introitus it is important to use part of the posterior vaginal wall in the reconstruction to prevent further adhesions and stenosis due to Koebnerization.[49]

Pseudocyst of the clitoris. Occasionally, clitoral hood adhesions seal over the clitoris and keratinous debris builds up underneath, forming a painful pseudocyst. This requires a subtotal or total circumcision.[50]

Phimosis. The most common complication in males is secondary phimosis, which may require circumcision if medical treatment fails. If the disease is still active at the time of surgery it is important to continue topical corticosteroids following the surgery to prevent Koebnerization and further scarring, particularly around the coronal sulcus.

Meatal stenosis. LS of the glans may cause meatal stenosis, which is manifest as an altered urinary stream, less commonly progressing to cause frank obstruction to urinary flow.

Sensory abnormalities: dysaesthesia

Vestibulodynia and vulvodynia. These conditions may occur after an inflammatory condition of the vulva and/or vestibule. The patient remains symptomatic despite clinical improvement or resolution of the skin lesions. This is neuropathic pain and will not respond to topical corticosteroids, so treatment must be aimed at the eradication of the neuronal sensitization. Xylocaine 5% ointment should be tried first, with progression to amitriptyline in unresponsive cases.

Penile dysaesthesia

Men may develop a similar problem, with an abnormal burning sensation on the glans or around the urethral meatus.

Psychosexual problems

Men and women who have any chronic genital disorder will often lose their interest in sexual activity, leading to problems with sexual dysfunction.[51,52] It is important to give patients the opportunity to express their concerns on their sexual function and to offer a referral to someone with the necessary expertise to address these problems.

Management

An extensive historical overview of treatment of LS is provided in the review by Meffert *et al.*[44]

Topical corticosteroids

Adult female anogenital lichen sclerosus. Ideally, all women with symptomatic or active anogenital LS should be seen at least once by a dermatologist; difficult cases with complications may be best managed in a vulval clinic with a multidisciplinary team, including a dermatologist and a gynaecologist.

The recommended and accepted treatment is the ultrapotent topical corticosteroid ointment clobetasol propionate[53,54] (*Strength of recommendation A, Quality of evidence II-ii*). There are no randomized controlled trials providing evidence for any specific corticosteroid being the most effective or documenting that one regimen is superior to another. The regimen recommended by the authors for a newly diagnosed case is clobetasol propionate initially once a night for 4 weeks, then on alternate nights for 4 weeks and, for the final third month, twice weekly. The rationale for once daily application is based on pharmacodynamic studies showing that an ultrapotent corticosteroid needs a once daily application only.[55]

If the patients' symptoms return with a drop in the schedule they are instructed to go back up to the frequency that was effective. A 30-g tube of clobetasol propionate should last 12 weeks and the patient is then reviewed. If the treatment has been successful the hyperkeratosis, ecchymoses, fissuring and erosions should have resolved but the atrophy and colour change will remain.

The clobetasol propionate is then continued and used as and when required. Most patients seem to require 30–60 g annually. Some patients go into complete remission, requiring no further treatment. Others will continue to have flares and remissions and they are advised to use clobetasol propionate as required.

A soap substitute is also recommended, and the patient is given an information sheet on LS with instructions for the safe use of the topical corticosteroid, to try to ensure compliance.

Male genital lichen sclerosus. A retrospective study of 22 men treated with clobetasol propionate documented this to be safe and effective, with significant improvement in discomfort, skin tightness, and also in urinary flow in the nine patients in whom this was affected[46] (*Strength of recommendation A, Quality of evidence II-ii*). The theoretical possibility of provoking latent HPV infection is discussed above. The use of a potent topical corticosteroid often avoids the need for circumcision.[56]

Child anogenital lichen sclerosus. There is one report of betamethasone dipropionate being used with success for vulval LS in children; all patients had improvement and eight of 11 had complete remission.[57] No maintenance therapy was required. A subsequent study of 10 girls treated with clobetasol propionate twice daily for 6–8 weeks documented similar results and lack of adverse effects during treatment or prolonged follow-up[58] (*Strength of recommendation A, Quality of evidence II-ii*).

In boys, phimosis is commonly due to LS (see above), but studies of the use of corticosteroids have not always distinguished those with LS. A prospective study of 139 boys with phimosis treated with betamethasone for 1 month documented that 80% of the 111 who completed the study had normal retractability of the foreskin after this time; 10% proceeded to circumcision as treatment failures and 10% were having ongoing topical treatment[59] (*Strength of recommendation A, Quality of evidence II-ii*).

An ultrapotent topical corticosteroid may avoid a circumcision in some cases of preputial phimosis.[60,61]

Extragenital lichen sclerosus. Clobetasol propionate, with or without occlusion, is the first-line treatment. This is used once daily, as and when required. In general, extragenital lesions are not as responsive as genital disease to the potent topical corticosteroid (*Strength of recommendation A, Quality of evidence III*).

Testosterone and other hormones

Adult female anogenital lichen sclerosus. Older studies have documented benefit from use of topical testosterone in vulval dystrophy (presumably some of these cases were LS),[62,63] including one controlled study in LS that documented greater benefit in the active treatment group.[64] However, more recent research has documented that it is not as effective as clobetasol propionate[65] and is no more effective than an emollient.[66] In the maintenance of remission after topical corticosteroid it was actually worse than an emollient control[67] (*Strength of recommendation D, Quality of evidence II-i*). Topical testosterone is expensive and with overuse can lead to virilization. This discrepancy between studies is difficult to explain, and some authors still suggest that some patients will respond; one explanation is that there may be changes in the expression of androgen receptors with disease progression, which may in turn alter the hormonal responsiveness.[68]

Topical progesterone has also been reported to be effective[69] (*Strength of evidence C, Quality of evidence IV*).

Male genital lichen sclerosus. Testosterone has also been used topically (2·5% ointment) for male genital LS[70] (*Strength of recommendation C, Quality of evidence IV*).

Child anogenital lichen sclerosus. Topical oestrogen was reported to be beneficial in four girls, improving the histological features and itch (in the three who had this symptom).[71] However, the magnitude of benefit is uncertain as this report stated that the overall clinical improvement was 20%, and no comparative trials are available.

Surgery, laser, photodynamic therapy and cryotherapy

Adult female anogenital lichen sclerosus. There is no indication for removal of vulval tissue in the management of uncomplicated LS, and surgery should be used exclusively for malignancy and postinflammatory sequelae.

In one study, nine of 12 patients with severe itch due to vulval LS unresponsive to topical treatment responded to cryotherapy, 50% for 3 years[72] (*Strength of recommendation C, Quality of evidence III*).

In an open study of photodynamic therapy for vulval LS (topical 5-aminolaevulinic acid, argon laser light, one to three treatments), 10 of 12 patients had significant improvement.[73] Laser treatment has also been used with some success[74] (*Strength of recommendation C, Quality of evidence III*).

Male genital lichen sclerosus. The role of surgery is better documented for penile LS, either to improve symptoms due to phimosis, which has failed to respond to a trial of an ultrapotent topical corticosteroid, or symptoms due to meatal stenosis. Two reviews (52 patients in total) document satisfactory results from circumcision for LS of the foreskin, and meatal dilatation, meatotomy or meatoplasty for meatal stenosis.[75,76]

Laser treatment has generally employed the carbon dioxide laser, and may have a role in the treatment of meatal stenosis[74,77] (*Strength of recommendation B, Quality of evidence III*).

Child anogenital lichen sclerosus. Surgical treatment of childhood phimosis by circumcision has demonstrated the presence of LS in a high proportion of cases, but topical corticosteroids should be used first.

Extragenital lichen sclerosus. Shave (tangential) excision has been used,[78] and carbon dioxide laser has been reported to produce an improvement in symptoms and appearance of lesions.[76]

A case of extragenital LS in a child has been successfully treated with low-dose ultraviolet (UV) A1 phototherapy.[79]

Other treatments

Ciclosporin. A pilot trial of topical ciclosporin failed to have any beneficial effect clinically or histologically on five cases of vulval LS[80] (*Strength of recommendation D, Quality of evidence III*).

Retinoids. There is no evidence that these are particularly effective in uncomplicated LS but there is some evidence that they may have a role in complicated disease that does not respond to an ultrapotent corticosteroid,[81–83] including one long-term placebo-controlled study. However, this study only documented benefit in 14 of 22 evaluable patients as well as in six of 24 controls, and only 46 of 78 patients could be evaluated. Use of topical retinoids is accompanied by the problem of irritancy (*Strength of recommendation C, Quality of evidence I*).

Potassium para-*aminobenzoate.* A report of five patients with LS at various sites, and resistant to numerous other therapies, documented good improvement in all five (dose 4–24 g daily in divided doses)[84] (*Strength of recommendation C, Quality of evidence III*).

Others. There are reports of benefits from psoralen plus UVA treatment, stanozolol,[85] antimalarials, antipruritic and antihistamine agents such as oxatomide, and various antibiotics (for which the main rationale is the uncertain link with *Borrelia* infection). These and others are summarized elsewhere,[44] but must all be viewed as less well proven or as anecdotal.

Treatment failure

If treatment with topical corticosteroids fails to bring LS under control then it is important to consider the following:

1 Non-compliance. Sometimes patients may be alarmed at the warnings on the package insert warning against the use of a topical corticosteroid in the anogenital area and they will then not use the

preparation. Also, very elderly patients disabled with poor eyesight and limited mobility may not be able to apply the medication appropriately.

2 Is the diagnosis correct, or is there an added problem such as the development of a contact allergy to the medication or is there another superimposed condition, e.g. secondary candidiasis, intraepithelial neoplasia, malignancy, psoriasis or mucous membrane pemphigoid?

3 Is the LS in fact treated, but the patient is still symptomatic because they have developed a secondary sensory problem, dysaesthetic vulvodynia or are experiencing problems with intercourse that they may feel too shy to discuss?

4 Is the problem mechanical due to scarring, e.g. severe phimosis or meatal stenosis in males, in which case surgery may be indicated?

Follow-up

The risk of malignancy in uncomplicated genital LS that has been diagnosed and treated appropriately is very small. If malignancy occurs it does so rapidly. Early detection would require 3-monthly follow-up consultations; this is generally impossible in the U.K. due to the constraints of the National Health Service system.

The authors suggest two follow-up visits after the initial consultation: (i) at 3 months to assess response to treatment and to ensure that the patient is using the topical corticosteroid appropriately and judiciously, and (ii) if response has been satisfactory, a final assessment 6 months later to ensure that the patient is confident in treating their problem and to take the opportunity to discuss any residual problems that the patient might have before discharge back to the care of their primary physician. If patients continue to use a topical corticosteroid it is suggested that they see their primary care physician once yearly. Instruction should be given to the patient at the time of their discharge from the clinic warning them that any persistent ulceration or new growth must be reported to their family practitioner who will then make an urgent referral back to an appropriate specialist.

Long-term follow up is, however, required for patients with LS that continues to be poorly controlled. These patients usually have LS with a histological pattern that has features of both LS and LP with squamous cell hyperplasia. Clinically, these patients seem to have an overlap syndrome and their disease runs a relentless course despite trials of various therapies, and a small percentage does go on to develop one or more SCCs.

It is important to biopsy persistent ulcers, erosions, hyperkeratosis and erythematous zones, whether present at initial presentation or subsequently, to exclude intraepithelial neoplasia or invasive SCC.

Recommendations and conclusions

An ultrapotent topical corticosteroid is the first-line treatment for LS in either sex at any site, but there are no randomized controlled trials comparing corticosteroid potency, frequency of application and duration of treatment.

Asymptomatic patients with evidence of clinically active LS, i.e. ecchymosis, hyperkeratosis and progressing atrophy, should be treated.

Anogenital LS is associated with SCC but the development of this complication is rare in clinical practice (5% or less). It is not yet known whether treatment will lessen the long-term risk of malignant change.

Long-term follow up in a specialized clinic is unnecessary for uncomplicated disease that is well controlled clinically using small amounts of a topical corticosteroid, and follow up should be reserved for patients with complicated LS that is unresponsive to treatment and those patients who have persistent disease with history of a previous SCC.

Surgical intervention is indicated only for the complications of scarring or the development of malignancy.

Any psychosexual issues should be addressed if appropriate and referral made to practitioners experienced in this field if indicated.

Audit points

- Has a biopsy been performed in patients with clinically active disease that is unresponsive to adequate treatment with an ultrapotent topical corticosteroid?
- Are follow-up arrangements in place for patients with ongoing symptomatic disease?
- Are patients with genital LS aware that any persistent ulcer, erosion or new growth within the affected skin needs to be reported?
- Has a topical corticosteroid of adequate potency and duration been used prior to surgery in males with symptomatic preputial tightening?

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Appendix 1

The consultation process for British Association of Dermatologists (BAD) guidelines has been published elsewhere.[86] Evidence is searched from Medline and other medical databases, from reviews and references in publications. There is a 3-month consultation process with the entire BAD membership. Updates are made at intervals according to new evidence and will appear on the BAD website and as single-sheet summary documents.

Strength of recommendations

A There is good evidence to support the use of the procedure.
B There is fair evidence to support the use of the procedure.
C There is poor evidence to support the use of the procedure.
D There is fair evidence to support the rejection of the use of the procedure.
E There is good evidence to support the rejection of the use of the procedure.

Quality of evidence

I Evidence obtained from at least one properly designed, randomized controlled trial.
II-i Evidence obtained from well-designed controlled trials without randomization.
II-ii Evidence obtained from well-designed cohort or case–control analytical studies, preferably from more than one centre or research group.
II-iii Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.
III Opinions of respected authorities based on clinical experience, descriptive studies or reports of expert committees.
IV Evidence inadequate owing to problems of methodology (e.g. sample size, or length of comprehensiveness of follow-up or conflicts in evidence).