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Guidelines for management of Bowen's disease: 2006 update

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Summary

This article represents a planned regular updating of the previous British Association of Dermatologists (BAD) guidelines for management of Bowen's disease. They have been prepared for dermatologists on behalf of the BAD. They present evidence-based guidance for treatment, with identification of the strength of evidence available at the time of preparation of the guidelines.

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Conflicts of interest
A statement is provided at the end of these guidelines.

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Disclaimer

These guidelines have been prepared for dermatologists on behalf of the British Association of Dermatologists (BAD) and are based on the best data available at the time the report was prepared. Caution should be exercised when interpreting data where there is a limited evidence base; 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 guidelines may not constitute defence against a claim of negligence, so deviation from them should not necessarily be deemed negligent.

Definition and introduction to the guideline

The scope, aims and methodology of the BAD guidelines process have been published elsewhere;[1,2] these references should be consulted for guideline validation purposes.

This article represents a planned regular updating of the previous BAD guidelines for management of Bowen's disease (BD).[3] Those guidelines included discussion of epidemiology, predisposing factors, disease associations and risk of malignancy as well as the local treatment options for the disease itself. New information in these areas, other than that pertaining to issues that influence therapeutic decisions, will only be briefly summarized in this update. Similarly, detailed evidence for therapies discussed in the previous paper will not be repeated except where comparison with other evidence is necessary. It should be recognized that this may entail a disproportionate weight being given to referencing newer therapies. Where there are direct comparisons between therapies, these are generally discussed in the section relating to those deemed to be most efficacious. Recommendations take into account simplicity, cost and healing as well as the type and validity of the published evidence base; for any treatment, there may be site-specific differences in the recommended option. The abbreviation RCT is used for randomized controlled trial throughout.

BD is a form of intraepidermal (in situ) squamous cell carcinoma (SCC), originally described in 1912.[4] Genital lesions which have the histology of BD include erythroplasia of Queyrat (males), some vulval intraepithelial neoplasia (VIN) and

bowenoid papulosis (either sex). There is a strong association of genital or perianal intraepithelial neoplasia in either sex with human papillomavirus (HPV) infection, although many such cases do not have the clinical morphology of BD. The association between BD and HPV is briefly discussed and we have included some brief comments in relation to therapy and outcomes (especially for erythroplasia of Queyrat, as this is often referred to as penile BD), but a detailed therapeutic review of HPV-related epidermal dysplasia, VIN, vaginal intraepithelial neoplasia and penile intraepithelial neoplasia (PIN) is beyond the scope of this guideline. Perianal BD is not commonly treated by dermatologists but is briefly discussed as its therapy and outcome also often differ from those of BD at extragenital sites.

Clinical description, demographics and variants

Typical BD presents as a gradually enlarging well-demarcated erythematous plaque with an irregular border and surface crusting or scaling.[3,5,6] An annual incidence of 15 per 100 000 has been suggested in the U.K.;[6] however, this figure was derived from an American study that primarily examined internal neoplasia associated with BD,[7] and was the annual incidence rate for the 1980 U.S. white population – this may not be the same as in the less sun-exposed U.K. population.

In the U.K., the peak age group for BD is the seventh decade, it occurs predominantly in women (70–85% of cases), and about three-quarters of patients have lesions on the lower leg (60–85%).[8,9] Lesions are usually solitary but are multiple in 10–20% of patients. Less common sites or variants include pigmented BD, subungual/periungual, palmar, genital and perianal (see above) and verrucous BD.

The age group, number and size of lesions, and site(s) affected may all influence therapeutic choice.

Aetiology

Reported relevant aetiological factors were discussed in the 1999 guidelines,[3] but are briefly listed here in order to update the roles of HPV and immunosuppression. Aetiologies include:

1 Irradiation – solar, photochemotherapy, radiotherapy.

2 Carcinogens – arsenic.

3 Immunosuppression – therapeutic,[10,11] AIDS. For example, one study demonstrated that 23% of skin cancers in renal transplant recipients were BD.[11] This would suggest that educating immunosuppressed patients about sun exposure is important.

4 Viral – oncogenic HPV types such as HPV 16 are strongly implicated in the aetiology of VIN, but are also common in perianal BD, and in PIN. However, HPV DNA has also been demonstrated in some extragenital BD. A report of 28 biopsies from extragenital sites demonstrated *in situ* hybridization evidence of oncogenic HPV types in eight of 28 (29%); all had HPV 16/18 and two of these also had HPV 31/33/51. Of note, this study had a higher than average proportion of lesions on hands and feet (eight of 28 cases) and these accounted for 50% of the positive results.[12] A further study of HPV in extragenital cutaneous BD detected HPV DNA in 58% of 69 samples from 50 patients, the percentage of HPV detection being similar in exposed (55%) and unexposed areas (65%), and also between immunosuppressed and immunocompetent patients.[13] A study of the cell proliferation activity between HPV-positive and HPV-negative BD showed similar results in each, suggesting that HPV infection alone does not induce cell proliferation in those lesions.[14] HPV 16 has been implicated in 60% of palmoplantar and periungual lesions.[15] Multiple lesions of BD may occur on the distal digits ('polydactylous BD'), consistent with aetiological involvement of HPV. This has therapeutic implications, as HPV-induced BD should be responsive to agents that have a combined antiviral and antitumour effect.

5 Others – chronic injury or dermatoses, pre-existing skin lesions such as seborrhoeic keratoses (rarely).

Association with other malignancy

Internal neoplasia

Several larger studies and meta-analysis of the association between BD and internal cancers were summarized in our previous guideline.[3] A further study of 1147 patients found the overall incidence of internal cancers in patients with BD to be slightly increased [115 cancers vs. 103 expected, the standardized incidence ratio (SIR) of 1·1 not being statistically significant].[16] However, there was an SIR of 3·2 for leukaemia in men and of 4·6 for lung cancer in men with BD before age 60 years (the overall lung cancer SIR for both sexes and all ages was 1·3). There are various sources of potential bias in many studies of this type, and available evidence would still suggest that routine investigation for internal malignancy in patients with BD is not justified (*Strength of recommendation E*, *Quality of evidence I*; Appendix 1).

Skin malignancy

Previous studies suggested that about 30–50% of subjects with BD may have previous or subsequent nonmelanoma skin cancer (NMSC), mainly basal cell carcinoma.[17,18] The NMSC risk after an index BD is probably similar to the overall risk of NMSC following any index NMSC (overall 35–60% 3-year risk[19]). In the study by Jaeger *et al.*, NMSC had an SIR of 4·3, and lip cancer of 8·2, in patients with BD.[16] These increased risks of further BD or of other NMSC probably reflect a common solar aetiology.

Risk of progression to squamous cell carcinoma

There is no new literature to inform this debate in terms of the overall risk – *ex vivo* research studies to identify individual lesional risk and differentiation from other NMSC are beyond the scope of this guideline.

Most studies suggest a risk of invasive carcinoma of about 3–5% for 'ordinary' BD[20,21] and perhaps 10% for erythroplasia of Queyrat.[3] Perianal BD also has higher risk of invasion and recurrence (*Quality of evidence II-ii*), and an association with cervical and vulval dysplasia.[22–24] However, these estimates are drawn from retrospective case series, may be biased by different referral patterns of lesions to different disciplines (dermatologists, surgeons etc.), and do not take account of subjects with BD who have either not requested medical advice or who have been treated in primary care. Indeed, it is unlikely that this question can be accurately answered as any group of patients who could be followed up without intervention are likely to be unrepresentative individuals (for example, elderly patients with small lesions). Risks of cervical intraepithelial carcinoma in affected women or in female sex partners of affected men with bowenoid papulosis, and of oral papillomas and tumours in association with HPV 16-positive bowenoid papulosis, were discussed previously.[3]

Treatments

Evaluation of treatment studies of BD is difficult due to potential selection bias to specific forms of treatment. Similarly, healing and success rate may vary with body site. Earlier studies used clinical appearance rather than histological assessment to determine the end-point of lesion clearance. Even for the same treatment modality, there is difficulty in directly comparing studies due to different lesion sites, sizes of lesions, and use/availability of different types of equipment and treatment regimens.[25] Retrospective studies in particular may have several inherent problems – in 'real world' treatment of BD, dermatologists may select several different types of treatment,[26] decisions potentially being influenced by several factors such as lesion size and thickness, equipment available, and the perceived potential for poor wound healing (e.g. at sites such as the lower leg[27]). Even in recent controlled trials in which older treatments are compared with newer modalities, the regimen for the established treatment or the site at which it is applied may not concur with the approach used by all dermatologists.

Other than a small number of anecdotal or single series reports considered at the end of the therapeutic list, the therapeutic options have been listed in a sequence to include observation alone, topical treatments and surgical treatments; within this sequence, longer-established or less interventional treatments are considered first. This sequence does not necessarily reflect the frequency of use, importance, availability or strength of evidence for any treatment option – a summary of advice incorporating these issues and related to lesion sites and sizes is provided in Table 1. Current U.K. product licences for many drugs listed do not include treatment of BD; all recommendations in this guideline are extrapolated from literature on BD and knowledge of other neoplastic skin lesions, and are presented on the understanding that neither the authors nor the BAD can formally recommend an unlicensed treatment.

Treatments are presented in a sequence that discusses the least invasive and topical therapies first, surgical approaches, and finally treatments that require more complex or expensive equipment or that are not as widely available.

No treatment

In some patients with slowly progressive thin lesions, especially on the elderly lower leg where healing is poor, there is an argument for observation rather than intervention.

5-Fluorouracil (*Strength of recommendation B, Quality of evidence II-i*)

5-Fluorouracil (5-FU) has been used topically for treatment of BD in several studies as previously summarized.[3] Most of these are open trials or small case series; several used concentrations that are not commercially available in the U.K., and some do not specify the concentration or schedule. These suggest cure

Table 1 Summary of the main treatment options for Bowen's disease. The suggested scoring of the treatments listed takes into account the evidence for benefit, ease of application or time required for the procedure, wound healing, cosmetic result and current availability/costs of the method or facilities required. Evidence for interventions based on single studies or purely anecdotal cases is not included

Lesion characteristics	Topical 5-FU	Topical imiqumod[a]	Cryotherapy	Curettage	Excision	PDT	Radiotherapy	Laser[b]
Small, single/few, good healing site[c]	4	3	2	1	3	3	5	4
Large, single, good healing site[c]	3	3	3	5	5	2	4	7
Multiple, good healing site[c]	3	4	2	3	5	3	4	4
Small, single/few, poor healing site[c]	2	3	3	2	2	1–2	5	7
Large, single, poor healing site[c]	3	2–3	5	4	5	1	6	7
Facial	4	7	2	2	4[d]	3	4	7
Digital	3	7	3	5	2[d]	3	3	3
Perianal	6	6	6	6	1[e]	7	2–3	6
Penile	3	3	3	5	4[d]	3	2–3	3

5-FU, 5-fluorouracil; PDT, photodynamic therapy; 1, probably treatment of choice; 2, generally good choice; 3, generally fair choice; 4, reasonable but not usually required; 5, generally poor choice; 6, probably should not be used; 7, insufficient evidence available. [a]Does not have a product licence for Bowen's disease. [b]Depends on site. [c]Refers to the clinician's perceived potential for good or poor healing at the affected site. [d]Consider micrographic surgery for tissue sparing or if poorly defined/recurrent. [e]Wide excision recommended.

rates of 90–100%. In current clinical use, 5-FU is usually applied once or twice daily as a 5% cream for a variable period of time (between 1 week and 2 months in most studies using this concentration) to achieve disease control, and repeated if required at intervals. Lower concentrations are less effective.

Efficacy may be increased by application under occlusion, use of dinitrochlorobenzene as a vehicle (both previously referenced[3]), iontophoresis[28] (to improve follicular penetration) or pretreatment with a laser (to ablate the stratum corneum and thereby enhance penetration of 5-FU).[29] In the study of iontophoresis,[28] only one of 26 patients had histological evidence of residual disease at 3 months after eight treatments. More recently, the erbium:YAG laser was used as a pretreatment measure on half of each lesion in three lesions from a patient with multiple BD, who was subsequently treated with twice-daily application of 5-FU cream to both sides. The response (clinical and histological) was accelerated on the side pretreated with laser.[29]

Few studies provide details of the success rate for the currently available preparation in the U.K. (5% cream to be used once or twice daily for 3–4 weeks) as a first-line option for unselected lesions. However, in an RCT comparing 5-FU with photodynamic therapy (PDT) the initial response rate in the 5-FU limb, after one (or two if required) cycles of once-daily application for 1 week then twice daily for 3 weeks, repeated at 6 weeks if clinically indicated, was 67%, with only 48% remaining clear at 12 months.[30] (The comparative results are discussed in the section on PDT, below). By contrast, in a follow-up study (26 patients, clinical follow up of 2·4–204 months), recurrences had occurred at some point in just two patients (8%).[31] This study used 5% 5-FU twice daily for a planned 9 weeks (actual 3–13 weeks), with a repeat cycle for recurrences, and biopsy to confirm clearance in most cases, but is a small number collected given the 10-year overall period.

As 5-FU can be very irritant, less aggressive regimens have been used for disease control rather than cure. Two applications of 5% 5-FU on a single day of each week for 3 months improved lesions in 24 of 26 patients (92%) with BD of the leg (lesions were flat with less or no erythema, and with minor or absent scaling), although long-term clearance was achieved only in a minority with this regimen.[32]

Formal comparison with other modalities is limited to RCTs of PDT vs. 5-FU, only one of which is currently published and which showed that PDT was the more effective[30] (see section on PDT below).

In erythroplasia of Queyrat, application of 5% 5-FU cream twice daily for 4–5 weeks has been recommended but inflammation frequently limits this treatment regimen.

Imiquimod (*Strength of recommendation B, Quality of evidence I*)

Imiquimod is a topical immunomodulatory heterocyclic imidazoquinoline amide that has become available since the earlier BAD guideline.[3] It has been used as a 5% cream to treat BD, including larger diameter lesions, lower leg lesions and erythroplasia of Queyrat. It has both anti-HPV and antitumour effects, and is therefore potentially useful for HPV-associated BD/bowenoid papulosis as well as for non-HPV-associated BD. The evidence base consists of a single small RCT, one open study plus some small case series (most two or three patients) and individual case reports.[33–40] The regimen used varies between reports. Such reports are not referenced at length as it is felt that stronger evidence is required before firm conclusions can be drawn. At the time of writing, the product licence for topical imiquimod in the U.K. is for small superficial basal cell carcinomas; it is not currently licensed for use in BD.

The best evidence currently available is a single small RCT that demonstrated 73% histologically proven resolution with imiquimod (once daily for 16 weeks; lesions untreated for at least a month) vs. zero response in the placebo group.[33] This study acknowledged that the ideal dosing regimen and cost-effectiveness require further investigation. An earlier 16-patient open study (15 having lower leg lesions; once daily application for up to 16 weeks; previously untreated lesions) documented that 14 of 15 patients (93%) who completed the study had clinical and pathological resolution of BD 6 weeks after the treatment period (one patient died of unrelated causes and was not analysed).[34] Five lesions had an area of 5 cm^2 or greater.

Single cases or small case series suggest that different regimens such as cyclical treatment[35] might be useful, and also that imiquimod may be useful for large facial lesions.[36] The latter, together with lower leg lesions,[34] are typically those that pose the greatest therapeutic challenge. Some studies suggest that shorter treatment periods may be adequate.[34,35] In the open study discussed above,[34] six of 16 patients discontinued treatment early due to side-effects but still had lesion clearance, and in the placebo-controlled trial, three of 15 in the active limb dropped out (two being withdrawn by the investigators due to local side-effects).[33] A few anecdotal reports and small open-label case series suggest that there may be a role for imiquimod in treatment of erythroplasia of Queyrat[37] and in basaloid VIN.

Benefit has also been reported in the treatment of BD in immunosuppressed patients,[38–40] although combining it with other modalities such as oral sulindac[39] or 5-FU[40] makes interpretation of the relative roles of the pairs of agents used difficult. Five renal transplant patients with BD have been treated with a combination of a local immune therapy, imiquimod cream, and a topical chemotherapeutic agent, 5% 5-FU, with clearing of the areas of SCC *in situ*. In addition, there is evidence that cytokines induced by imiquimod may improve the therapeutic efficacy of topical 5% 5-FU in BD.[40]

Cryotherapy (*Strength of recommendation B, Quality of evidence II-i*)

The results reported vary, probably reflecting differences between studies in the techniques and regimens used. As previously summarized,[3,6] the failure rate varies from zero to about 35%, the larger series suggesting a failure or recurrence rate in the order of 5–10% provided that adequate cryotherapy is used [e.g. liquid nitrogen (LN_2) cryotherapy, using a single

freeze-thaw cycle (FTC) of 30 s, two FTCs of 20 s with a thaw period, or up to three single treatments of 20 s at intervals of several weeks].[41–44] Such doses do, however, cause discomfort and may cause ulceration, especially on the lower leg.

In an RCT of PDT vs. cryotherapy,[44] the latter produced 100% clearance in 20 patients with one to three treatments of LN_2 using one FTC of 20 s on each occasion (50% success after a single treatment). Ulceration was observed following cryotherapy in 25% of lesions. There were two (10%) recurrences following cryotherapy in the 1-year follow-up period. A single treatment of PDT was significantly more effective than cryotherapy.

A prospective, nonrandomized study comparing curettage vs. cryotherapy found better healing, less discomfort and a lower recurrence rate with curettage,[45] and cryotherapy had more complications (discussed below).

Cryotherapy appears to have a good success rate with adequate treatment (recurrences less than 10% at 12 months) but healing may be slow for broad lesions and discomfort may limit treatment of multiple lesions. Curettage and PDT both have higher success rates and less discomfort overall, but are more time-consuming and/or expensive to perform.

Curettage with cautery/electrocautery (*Strength of recommendation A, Quality of evidence II-ii*)

Previously summarized studies[3] suggested a wide range of cure rates without recurrence, larger series suggesting a recurrence rate of 20%.[17] These studies do not give details of the treatment regimens or equipment used (cautery vs. electrodesiccation, number of cycles etc.).

In a prospective but nonrandomized trial of curettage and cautery (44 lesions) compared with cryotherapy (36 lesions) involving 67 patients, curettage was preferable in terms of pain, healing and recurrence rate.[45] Seventy-four percent of lesions were on the lower leg. Median time to healing with cryotherapy was 46 days (90 days on the lower leg) compared with 35 days (lower leg 39 days) for curetted lesions, and reported pain was significantly greater with cryotherapy. Recurrences were more likely following cryotherapy (13 of 44) compared with curettage (four of 36) during a median 2 years' follow up, although the cryotherapy regimen was less aggressive than that used by authors in most studies of this technique (see above and comment in this Journal[25]).

Curettage followed by cryotherapy has also been used, but reports are anecdotal and it is impossible to determine the relative contribution of the two treatments or whether the combination is better than either alone.

Excision (*Strength of recommendation A, Quality of evidence II-iii*)

There are no substantive new data on simple excision since the last guidelines.[3] In retrospective studies of 65 and 155 patients, the reported recurrence rates were 4·5%[17] and 19%,[46] respectively. Even higher rates are recorded in some smaller studies, and at sites such as the perianal region. While it is logical that excision should be an effective treatment, the evidence base is limited. Additionally, lower leg excision wounds may be associated with considerable morbidity.[26]

A retrospective study of 47 cases of perianal BD[24] found a lower recurrence rate for wide excision (six of 26, 23%) than for local excision (eight of 15, 53%) or laser therapy (four of five, 80%) although this series did not include patients treated with radiotherapy (which has been recommended as a first-line treatment,[47] discussed below). Wide surgical excision is the most commonly used treatment for perianal BD;[48] a survey of American colorectal surgeons found that most are performing wide local excision for both small and large perianal BD lesions (96% for patients with small lesions and 87% for patients with large lesions). Prolonged follow up is recommended as late recurrences are common at this site (see the previous guideline[3]).

Mohs micrographic surgery has become the recommended treatment for digital BD and for some cases of genital (especially penile) BD for its tissue-sparing benefits. A large retrospective series of 270 patients has reported on micrographic surgery for tissue sparing at head and neck sites (this site comprised 252 of 270 patients).[49] This study included 128 cases of previously treated head and neck BD. Among the 270 cases analysed, 94 had had previous cryotherapy, 18 curettage and cautery, 44 excision (10 incomplete) and one radiotherapy (some had been treated with more than one modality); nearly all referrals cited poorly defined tumour, recurrent or incompletely excised tumour, or tumour site as the rationale for micrographic surgery, so it cannot be assumed to be routinely necessary or cost-effective (*Strength of recommendation* B, *Quality of evidence* II-iii). The mean and median number of excision levels for clearance was 2, range 1–7. Of 95 patients who had 5-year follow-up data there were six (6%) recurrences.

Photodynamic therapy (*Strength of recommendation A, Quality of evidence I*)

This modality requires the activation of a photosensitizer, usually a porphyrin derivative, by visible light. Systemic photosensitization, with various photosensitizers, was used with excellent results in early studies summarized previously.[3] A recent report using systemic verteporfin, which has a much shorter duration of photosensitivity than agents used in earlier studies, has confirmed the efficacy of this approach.[50] It has a particular role in patients with multiple BD lesions, in whom use of topical porphyrin derivatives may be expensive and time-consuming, although topical PDT is more practical for most BD.

These guidelines refer mainly to topical PDT using topical 5-aminolaevulinic acid (ALA) or its ester, methyl aminolaevulinate (MAL). Studies have included various illumination sources (e.g. filtered xenon arc, diode, halogen, laser), wavelengths (red, green, blue/violet light) and dosing schedules (both in duration of ALA application and total light energy delivered), hence comparisons between studies may be difficult to interpret. Most studies have used one or two

treatments, depending on response (usually repeated at about 6 weeks if clinically necessary). Issues such as use of analgesia, and fluorescence detection, are not addressed here but details may be found in the British Photodermatology Group guidelines for topical PDT.[51]

The previously summarized studies[3] suggested an initial clinical clearance rate for ALA-PDT of 80–100% (most around 90%) with one or two treatments, and a recurrence rate of about 0–10% at 12 months. These figures remain valid. In a prospective open study, 44 of 50 lesions (88%) cleared after two treatments (30 of 50 after one treatment, 60%) although two patients failed to clear after four treatments; this study, which used a halogen red light source, had a 31% 12-month recurrence rate in the 48 initially responsive lesions.[52] Similarly, a departmental review documented that 117 of 129 lesions (91%) were cleared,[53] and a trial vs. 5-FU found that 29 of 33 lesions (88%) cleared after one or two treatments.[30]

An open study using ALA-PDT specifically for large diameter and multiple BD lesions showed that 35 (88%) of 40 large patches of BD, all with a maximum diameter > 20 mm, cleared following one to three treatments, although four patches recurred within 12 months. In 10 further patients with multiple (three or more) patches of BD, 44 (98%) of 45 patches cleared, although four lesions recurred over 12 months.[54]

Digital BD was treated with PDT in four patients, with good cosmetic and functional results (one recurrence at 8 months responded to retreatment);[55] the schedule was different from that in most studies (2% ALA solution, occluded for 16 h, two treatments of 240 J cm^{-2} 90 min apart using a 630-nm diode source). There are additional single case reports.

There are several comparative studies involving PDT, as follows.

Comparison with other treatments

ALA-PDT for BD has been compared with cryotherapy[45] and with 5-FU,[30] each in an RCT involving 40 patients. PDT proved superior in terms of efficacy and adverse events in comparison with 5-FU, as well as being less painful than cryotherapy. Both studies used a PDT schedule of 20% ALA applied 4 h before irradiation with narrowband red light. The cryotherapy study is discussed above and was summarized in the 1999 guideline.[3] In the comparison with 5-FU, this was applied as 5% cream once daily for a week and then twice daily for 3 weeks; either treatment was repeated at 6 weeks if necessary. Initial clearance rates (PDT vs. 5-FU) were 88% vs. 67%, and 12-month rates were 82% vs. 48%, with more short-term side-effects in the 5-FU group.[30]

Topical MAL-PDT has been compared with clinician's choice of cryotherapy or 5-FU in a 40-centre European trial of 225 patients with 275 lesions of BD:[56] MAL was applied for 3 h and sites illuminated with a broadband red light. Lesion complete response rates 3 months after last treatment were similar with MAL-PDT (107 of 124; 86%), cryotherapy (75 of 91; 82%) and 5-FU (30 of 36; 83%). PDT gave superior cosmetic results compared with cryotherapy or 5-FU. MAL-PDT is now approved in many countries for the treatment of actinic keratoses, basal cell carcinomas and BD.

Comparison between wavelengths

Green light (29 patients) was compared with red light (32 patients) in an RCT using ALA-PDT for BD but was inferior in terms of initial clearance (94% vs. 72%) and 12-month clearance (88% vs. 48%) and had no advantages in terms of pain (which was the rationale for the investigation).[57] Violet light irradiation (10–20 J cm^{-2}, after application of ALA for 8 h) was used in six patients with BD, including one with multiple lesions involving 50% of the scalp, the rationale being the lower light dose required for production of phototoxicity.[58] Despite the theoretical risk of reduced light penetration compared with red light PDT, the solitary lesions responded in all four evaluable patients (one dropped out for unrelated reasons) and the large area of scalp involvement showed a 90% response, 50% of the remaining area responding to retreatment. However, there has been no direct comparison with other wavelengths.

PDT has been used specifically in immunosuppressed subjects, in an open trial involving 20 transplant recipients and 20 immunocompetent controls with histologically confirmed actinic keratoses or BD (one or two treatments, 20% ALA for 5 h, 75 J cm^{-2} of visible light delivered at 80 mW cm^{-2}). The cure rates in both patient groups were comparable at 4 weeks (86%) but were significantly lower in transplant recipients than in controls at 12 and 48 weeks (below 50%). Despite the poor long-term response, the authors concluded that PDT is particularly useful in transplant recipients because of the possibility for repeated treatment of large lesional areas (although subsequent responsiveness was not confirmed).[59]

Successful use of PDT has also been reported in two cases of bowenoid papulosis using ALA-PDT with a diode red light source.

Radiotherapy (*Strength of recommendation overall B, Quality of evidence II-iii* for most sites; *Strength of recommendation D*, *Quality of evidence II-iii* for lower leg)

Various radiotherapy techniques and regimens have been used to treat BD. The larger studies have suggested a complete response rate to X-irradiation of 100%, for example in 77 lesions treated by Blank and Schnyder[60] (in this study, two patients with genital lesions relapsed at 8 and 16 months) and in 59 patients treated by Cox and Dyson.[43]

The patients in the latter series all had lower leg lesions; poor healing, related to age, diameter of field and radiotherapy dose, was a feature in 12 of 59 (20%) of cases. Poor healing of lower legs was supported by a more recent but smaller retrospective series of 11 patients with 16 lower leg lesions in which 100% cure was obtained but with 25% failure to heal (median follow up 27·5 months, minimum 9 months), even though the fraction sizes used were relatively low.[61] Thus the

high cure rate of radiotherapy may be offset by impaired healing on the lower leg, and it is best avoided for BD at this site (*Strength of recommendation D, Quality of evidence II-iii*).

To overcome some of the disadvantages of external beam X-irradiation, a skin patch coated with high-energy β-emitter holmium-166 (^{166}Ho patch) was used to treat 29 biopsy-confirmed BD lesions in eight patients [one with 22 sites, one with three sites but only one (palmar) treated with this method, the others solitary].[62] All lesions were 3 cm or larger (up to 7·2 cm); most lesions were on buttocks or thighs, or were acral in the patient with multiple lesions (no lower leg lesions were specifically identified in the report). The patches were applied to the surface of lesions for 30–60 min for a total radiation dose of 35 Gy. Acute radiation reactions healed within a month with mild fibrosis; there were good functional and cosmetic results with confirmed histological clearance at 5 months and without any late (10 months–2 years) recurrences or complications. This treatment may therefore be useful, at least at non-lower leg sites (*Strength of recommendation B, Quality of evidence II-ii*).

Radiotherapy has been advocated as the treatment of choice for anal margin epidermoid cancers, although without any strong evidence to support this viewpoint.[47]

Laser (*Strength of recommendation overall B, Quality of evidence II-iii* but may vary according to site)

Lasers have mainly been used to treat lesions at difficult sites such as the finger or genitalia. Results are generally stated to be good (*Strength of recommendation B, Quality of evidence II-iii*), but most published results are based on small numbers, or are considered with other epidermal neoplasia and are difficult to analyse. One retrospective review included six cases of digital BD treated with CO_2 laser, and reported good cosmetic results, no functional deficit and no recurrences (follow up 0·5–7·7 years),[63] although some failures for digital BD are reported by others (one of five cases).[64]

A study of 16 patients with 25 lower leg BD lesions treated with CO_2 laser demonstrated 100% healing at 2 months and no recurrences at 6 months. However, there was a 12% progression to invasive carcinoma within 12 months of discharge from follow up. This suggests that the depth of laser eradication may have been inadequate, and there are currently some reservations about use of this modality at this site (*Strength of recommendation C, Quality of evidence II-iii*).[65]

Results for perianal BD are poor[48] (*Strength of recommendation D, Quality of evidence II-iii*). CO_2 laser has been recommended for erythroplasia of Queyrat (*Strength of recommendation B, Quality of evidence II-iii*) but there is inadequate evidence to comment on other sites (*Quality of evidence IV*).

Other treatments

An ultrasonic surgical aspirator was used initially in an animal model (grafted areas of BD onto immunodeficient mice) and subsequently for 20 human lesions of BD where surgery had been considered inappropriate.[66] The rationale is that the aspirator removes epidermis but not dermis. It has a 2-mm diameter probe, and up to 300 μm oscillation at 28 kHz. An area of about 1 cm of normal skin was included in the treatment field, treatment taking 5–10 min under local anaesthesia. Follow up was monthly for 12 months, 3-monthly thereafter, for 12–26 (mean 20) months with no recurrences. Large lesions, lower leg lesions and lesions over joints were included.

Hyperthermic treatment was performed using disposable chemical pocket warmers applied under pressure each day throughout the patient's waking hours for 4–5 months.[67] There was initial complete clinical remission in six of eight patients (and partial remission in one) but absence of residual histological evidence of BD was achieved only in three of eight. Although of some benefit, this response compares poorly with other standard therapies (*Strength of recommendation E, Quality of evidence IV*).

Acitretin has been used alone or in conjunction with 5-FU in anecdotal cases but the relative merits of each are unclear in the combination approach. The same applies to combinations of topical bleomycin with LN_2 cryotherapy in a case of digital BD and isotretinoin with interferon-α in a patient with multiple lesions.

Summary of treatment modalities

All of the above treatments have some advantages and disadvantages, which are dictated by lesional factors (size, number, site, potential for healing or functional impairment), general health issues, availability and costs (both of the equipment or agent, and of the time to deliver the treatment or its aftercare). A cost-minimization analysis showed that, at the time, curettage or excision were the cheapest options, and PDT the most expensive (other treatments considered in this study were cryotherapy, 5-FU and laser).[68] However, changing costs of PDT and laser, the likely use of (relatively expensive) imiquimod in the future, and the fact that all of these therapies may not have equivalent efficacy, means that it is difficult to make a strong and currently applicable single recommendation on the basis of this study.

The relative status of the available treatment options is summarized in Table 1. This takes into account the evidence for benefit, ease of application and time required for the technique, wound healing, cosmetic result and availability of the method or facilities required.

Follow up

The required duration of follow up remains uncertain. Some treatments may need to be repeated, for example a second PDT treatment is typically needed in about 20–30% of patients, and a second cycle of 5-FU is needed in a similar proportion (although the latter may potentially be instituted by the patient or the primary care physician). Formal studies have generally used 12-month follow-up periods and clinical assessment for detection of recurrences.

On the basis that most of the treatments have about a 10% recurrence risk, a follow-up check for possible recurrence at 6–12 months is recommended. Different arrangements may be dictated in the shorter term by a likely need for a second cycle of treatment or to check on healing (in which case review at about 2–3 months to confirm clearance and healing may be more appropriate). The requirement for subsequent review should take into account the presence of multiple lesions, previous recurrence, high-risk lesions, other skin neoplasia, background risk factors such as immunosuppression, the reliability of the patient and the degree of primary care support. For treatments that are novel, outside product licence, or have a small evidence base, we suggest that follow up should be more frequent and should continue for at least 12–24 months in order to compare results with current literature on other therapies.

As a specific follow-up issue, the higher risk and the late timing of recurrences of perianal BD should be noted. In a series of 19 patients with perianal BD[23] the recurrence rate increased from 16% at 1 year to 31% at 5 years; in another series, the median time to recurrence for 26 radically excised lesions was 41·5 months.[24] Longer follow up may therefore be appropriate for BD at less common and less visible sites, or where HPV infection is likely to have been relevant.

Tools for guideline users

We have presented here:

1 A summary of the evidence and relevant aspects of the main management options.

2 A tabular summary of appropriate treatment for different lesional types, sizes and situations.

3 Suggestions for audit.

Summary of the main management recommendations

1 Routine investigation for internal malignancy in patients with BD is not justified (*Strength of recommendation E*, *Quality of evidence I*).

2 The risk of progression to invasive cancer is about 3%. This risk is greater in genital BD, and particularly in perianal BD. A high risk of recurrence, including late recurrence, is a particular feature of perianal BD and prolonged follow up is recommended for this variant (*Strength of recommendation A*, *Quality of evidence II-ii*).

3 There is reasonable evidence to support use of 5-FU (*Strength of recommendation B*, *Quality of evidence II-i*) but its use may be limited by irritancy and it was less effective than PDT in an RCT. It is more practical than surgery for large lesions, especially at potentially poor healing sites, and has been used for 'control' rather than cure in some patients with multiple lesions.

4 Topical imiquimod is likely to be used for BD (*Strength of recommendation B*, *Quality of evidence I*), especially for larger lesions or difficult/poor healing sites. However, it is costly, currently unlicensed for this indication, and the optimum regimen has yet to be determined.

5 Topical PDT has been shown to be equivalent or superior to cryotherapy and 5-FU, either in efficacy and/or in healing, in RCTs (*Strength of recommendation A*, *Quality of evidence I*). It may be of particular benefit for lesions that are large, on the lower leg or at otherwise difficult sites, but it is costly. PDT for NMSC and premalignant skin lesions has now been approved as an interventional procedure by the National Institute for Health and Clinical Excellence in the U.K.,[69] and MAL-PDT has been approved by the European Medicines Authority for treatment of BD.

6 Curettage has good evidence of efficacy, and time to healing is faster than with cryotherapy (*Strength of recommendation A*, *Quality of evidence II-ii*).

7 Cryotherapy has good evidence of efficacy (*Strength of recommendation B*, *Quality of evidence II-i*), but discomfort and time to healing are inferior to PDT (*Strength of recommendation A*, *Quality of evidence I*) or curettage (*Strength of recommendation A*, *Quality of evidence II-ii*).

8 Excision should be an effective treatment with low recurrence rates, but the evidence base is limited and for the most part does not allow comment on specific sites of lesions (*Strength of recommendation overall A*, *Quality of evidence II-iii*). Lower leg excision may be limited by lack of skin mobility. For perianal BD treated surgically, wide excision is recommended rather than narrow excision or laser treatment (*Strength of recommendation A*, *Quality of evidence II-iii*). Micrographic surgery is logical at sites such as digits or penis where it is important to limit removal of unaffected skin (*Strength of recommendation B*, *Quality of evidence III*) and is useful for poorly defined or recurrent head and neck BD (*Strength of recommendation B*, *Quality of evidence II-iii*).

9 Radiotherapy has good evidence of efficacy but poor healing on the lower leg suggests that it should be avoided at this site (*Strength of recommendation generally B*, *Quality of evidence II-iii*; for lower leg lesions *Strength of recommendation D*, *Quality of evidence II-iii*).

10 There is limited evidence on laser treatment, suggesting that it is a reasonable option for digital or genital lesions (*Strength of recommendation B*, *Quality of evidence II-iii*) but probably not for other sites (*Strength of recommendation mostly C or D*, *Quality of evidence II-iii to IV*); specifically, results for perianal BD are worse than those using wide surgical excision.

All therapeutic options have failure and recurrence rates at least in the order of 5–10%, and no treatment modality appears to be superior for all clinical situations. Direct comparison between treatment modalities is difficult as there are few randomized clinical trials with comparable patient subgroups. There is now increased choice for patients between clinic-based and home-applied therapies. For individual patients, factors such as treatment-related morbidity and the ease and availability of the treatment options may be a greater issue than the cure rate. As previously, we still feel that it is important that our BAD therapeutic guidelines reflect the fact that there is no single definite 'right way' to treat all patients with BD.

Summary of appropriate treatment for different lesional types, sizes and situations

See Table 1.

Possible audit points

Is a measure of patient acceptability linked with treatment? (may be indirect, e.g. willingness to repeat treatment if necessary)
For novel, unlicensed or small evidence-base treatments, has clinical cure rate been extended to 12 months? (and what are the results?)
For destructive therapies, has the dose, frequency etc. been recorded where applicable?

Conflicts of interest

Relevant product details are given in brackets for the first citation of any pharmaceutical company below.
N.H.C. has received support for attendance at non-product-related educational meetings from Valeant Pharmaceuticals (5-fluorouracil cream); has acted as an advisor regarding development of pathways of care for basal cell carcinoma, sponsored by 3M Pharmaceuticals (imiquimod); and has a performed a sponsored clinical trial for Photocure of photodynamic therapy (PDT) using methyl aminolaevulinic acid for Bowen's disease. He has performed unsponsored research on cryotherapy and radiotherapy for Bowen's disease.
D.J.E. has received fees for speaking and chairing meetings for 3M Pharmaceuticals, travelling expenses from Leo Pharmaceuticals and is an advisor to Novartis (U.K.).
C.A.M. has received sponsorship for speaking and chairing meetings from Galderma (Metvix®, a brand of methyl aminolaevulinic acid), and sponsorship from 3M and Leo Pharmaceuticals. He has performed sponsored as well as unsponsored research to evaluate the potential of topical PDT using various photosensitizers in dermatological indications.

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Appendix 1 Strength of recommendations and quality of evidence[a]

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)

[a]A different system of evidence grading and recommendations has been adopted for new guidelines,[70] but the Therapy Guidelines and Audit Committee has recommended use of the original grading system in this guideline update.