British Journal of Dermatology 2002; **147:** 214–221.

GUIDELINES

Guidelines for the management of bullous pemphigoid

F.WOJNAROWSKA, G.KIRTSCHIG, A.S.HIGHET,* V.A.VENNING† AND N.P.KHUMALO

Department of Dermatology, Oxford Radcliffe Hospital, The Churchill, Old Road, Headington, Oxford OX3 7LJ, U.K.
**Department of Dermatology, York District Hospital, York YO3 7HE, U.K*
†Department of Dermatology, North Hampshire Hospital, Basingstoke, RG24 9NA, U.K.

Accepted for publication 9 January 2002

Summary These guidelines 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. The guidelines reflect data available from Medline, Embase, the Cochrane library, literature searches and the experience of the authors of managing patients with bullous pemphigoid in special and general clinics for over 10 years. However, caution should be exercised in interpreting the data obtained from the literature because only six randomized controlled trials are available involving small groups of patients.

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 of this report. It may be necessary or even desirable to depart from the guidelines in the interests of specific patients or special circumstances. Just as adherence to these guidelines may not constitute a defence against a claim of negligence, so deviation from them should not be deemed negligent.

Definition

Bullous pemphigoid (BP) is an acquired autoimmune subepidermal bullous disease in which autoantibodies are directed against components of the basement membrane zone of the skin. Mainly IgG (rarely IgA, IgM and IgE) autoantibodies bind to components of the hemidesmosome adhesion complex, the BP230 and BP180 antigens. The antigen–antibody interaction has been demonstrated to result in subepidermal blister formation in animal models.

Epidemiology

BP is the most common autoimmune blistering disease in the West with an estimated incidence of six to seven cases per million population per year in France and Germany.[1,2] The figures in the U.K. are unknown, but are probably similar or higher. It occurs equally in both sexes and is usually a disease of the elderly (> 70 years) but can also affect younger patients and children. BP has been reported in association with malignancies; however, most large series have concluded that there is no increased incidence of malignancy in patients with BP in western countries compared with age- and sex-matched controls.[3]

Clinical presentation

BP is a non-scarring blistering disease, typically with a flexural distribution of skin lesions. However, the disease may be generalized or may be localized to one site. Mucous membranes are involved in about 50% of

Correspondence: Prof. Fenella Wojnarowska.
E-mail: Fenella.Wojnarowska@orh.nhs.uk

These guidelines were prepared for the British Association of Dermatologists Therapy Guidelines and Audit subcommittee. The members are N.H.Cox (Chairman), A.V.Anstey, C.B.Bunker, M.J.D.Goodfield, A.S.Highet, D.Mehta, R.H.Meyrick Thomas and J.K.Schofield.

patients, with the oral mucosa most frequently affected. Tense blisters arise on either erythematous or normal-appearing skin. Oral lesions consist of small blisters or erosions and are found mainly on the palatal mucosa. The blister formation may be preceded by an urticarial or eczematous rash. The degree of itch varies from none to intense and may precede the appearance of blisters by weeks, months or occasionally years.

Laboratory diagnosis of bullous pemphigoid

The diagnosis is established clinically, histologically and immunopathologically (direct and/or indirect immunofluorescence, IF). All these investigations can be done after treatment has been started,[4] although prolonged treatment will reduce the number of positive IF results.

Biopsy of a fresh blister shows a subepidermal cleft with a mixed dermal inflammatory infiltrate often containing numerous eosinophils. Direct IF of perilesional skin shows linear deposits of IgG and/or C3 at the basement membrane zone (other immunoglobulins may also be present). Indirect IF using serum (blister fluid or urine if no serum can be obtained) demonstrates circulating IgG (sometimes with other immunoglobulins) or C3 binding in a linear pattern at the basement membrane of squamous epithelia (normal skin or monkey oesophagus substrates).

The class of immunoglobulin bound to the basement membrane zone on direct IF distinguishes linear IgA disease (LAD) (only IgA on direct IF) from BP. Indirect IF performed on salt-split skin will differentiate BP from epidermolysis bullosa acquisita (EBA) and from a subgroup of cicatricial pemphigoid (CP). The antibodies are detected at the roof of the artificial blister in BP and at the base in laminin 5-CP and in EBA. However, this is not relevant to most clinical practice, as both CP and EBA are far rarer diseases and none of the published controlled clinical trials in BP has used this method to classify patients.

Differential diagnosis

Other subepidermal autoimmune bullous diseases such as CP, EBA and LAD are the most difficult to differentiate and this is usually done on the combination of the clinical picture (which may evolve with time), direct IF and indirect IF on salt-split skin.

Erythema multiforme, generalized fixed drug eruption, impetigo and acute viral infections (particularly chickenpox in adults) can all be confused with BP on first presentation. The clinical course, bacterial and viral studies, histopathology and IF studies will all help to achieve a diagnosis.

Treatment

The aim of treatment is to suppress the clinical signs of BP sufficiently to make the disease tolerable to an individual patient (reduction of blister formation, urticarial lesions and pruritus).

The disease is self-limiting and usually remits within 5 years. The mortality rate prior to the use of oral corticosteroids was reported by Lever in 1953 to be 24%;[5] the mortality rates today vary between 6% and 41%.[6] Patients with BP are usually elderly, often on multiple therapies and at high risk of adverse drug reactions and side-effects. High doses of immunosuppressants may put these patients at risk of life-threatening adverse effects more dangerous than the BP.

The treatments available work via different mechanisms. Some aim to suppress the inflammatory process, e.g. corticosteroids, antibiotics (e.g. tetracyclines, sulphones) and other anti-inflammatory drugs. Other immunosuppressive treatments aim to suppress the production of the pathogenic antibodies, e.g. high-dose corticosteroids, azathioprine, methotrexate, cyclophosphamide and cyclosporin. Plasmapheresis removes pathogenic antibodies and inflammatory mediators. Immune-modulating treatments include intravenous immunoglobulins.

There are two approaches to the initial control of the disease, and currently there is insufficient evidence to reject either approach. Some clinicians favour the use of minimum doses of systemic therapy to control the disease, individualizing treatment and accepting that in the occasional patient more aggressive therapy may be needed. Other clinicians believe in controlling all patients with high-dose initial therapy. Treatment is tapered once control of the disease has been achieved. During prolonged maintenance treatment the occasional blister is not an indication for increasing the dose of treatment or changing it. The treatment should be reduced whenever the disease has been well controlled for a month or more. In this way it is possible to ensure that the patient is not being over-treated.

A systematic review of treatments for BP searching Medline, Embase and the Cochrane library identified only six randomized controlled trials (RCTs) with a total of 293 patients.[7] The characteristics and major outcomes of the five relevant studies[8–12] are summarized in Table 1.

Table 1. Randomized controlled trials for the treatment of bullous pemphigoid

First author (follow-up), number of patients treated/randomized, interventions (dose)	Number of patients	Equivalent prednisolone dose in mg daily for a 70-kg patient	Major outcome
Morel[8] 1984 (51 days) 24/26 Pred (0·75 mg kg^{-1}) 22/24 Pred (1·25 mg kg^{-1})	50	52·5 vs. 87·5 mg daily	No significant difference in effectiveness but more side-effects on the higher dose
Burton[9] 1978 (3 years) 13/13 Pred (30–80 mg) 12/12 Azath (2·5 mg kg^{-1} + Pred (30–80 mg)	25	30–80 mg daily (dose per kg body weight not specified)	Lower total dose steroids (45% reduction) in the Azath group
Roujeau[10] 1984 (6 months) 15/17 Pred (0·3 mg kg^{-1}) 22/24 Plasma ex + Pred (0·3 mg kg^{-1})	41	21 mg daily	Lower total dose steroids: 1240 ± 728 mg in the plasma exchange group vs. 2770 ± 1600 mg
Guillaume[11] 1993 (6 months) 31/32 Pred (1 mg kg^{-1}) 36/36 Azath (1·7–2·4 mg kg^{-1}) + Pred (mg kg^{-1}) 31/32 Plasma ex + Pred (mg kg^{-1})	100	70 mg daily	Similar effectiveness in all three groups; severe complications more often noted in the Azath group
Fivenson[12] 1994 (2 & 10 months) 6/6 Pred 40–80 mg 14/14 nicotinamide + tetracycline	20	40–80 mg daily (dose per kg body weight not specified)	Very small numbers, no difference in effectiveness but more severe side-effects and disease recurrence in the Pred group

Pred, prednisolone; Azath, azathioprine; Plasma ex, plasma exchange.

From a systematic review of treatment of BP we can draw three conclusions. Firstly, prednisolone doses higher than 0·75 mg kg^{-1} daily (52·5 mg daily for a 70-kg patient) do not seem to confer additional benefit; doses of systemic corticosteroids greater than 0·75 mg kg^{-1} or prednisolone 30 mg or more daily were all associated with significant mortality.[8,9,11,12] Secondly, the effectiveness of azathioprine and plasma exchange is difficult to assess. Thirdly, tetracyclines and nicotinamide may be effective, but larger trials are needed.

Systemic corticosteroids

The efficacy of systemic corticosteroid treatment in BP was demonstrated in uncontrolled clinical studies and is well established in clinical experience.[13–15] However, few studies are directly comparable because patients differ in severity of disease and there are also differences between treatment regimens, therefore optimum dosage schedules remain a subject for debate.

The corticosteroids most commonly used are prednisolone and prednisone, and dosages relate to these drugs unless otherwise stated. Typical recommendations for widespread disease are for a starting daily dose of about 1 mg kg^{-1} continued until cessation of new blister formation, then gradually decreased according to clinical course.[11,16,17] However, many studies do not closely relate corticosteroid dose to body weight, and tend to use a uniform starting dose, usually ranging between 40 and 80 mg daily, typically 60 mg daily.[14] More recently, lower starting doses of 20–40 mg daily have been recommended.[18]

It is common clinical experience that there is a correlation, albeit approximate, between disease severity and the amount of systemic corticosteroid required for control.[15,19,20] A retrospective study of 23 patients treated with prednisone 1 mg kg^{-1} daily showed a significant correlation between the pretreatment number of blisters and the time needed to achieve control.[16] Aggressive treatment in eight elderly patients with intravenous methylprednisolone 750–1800 mg daily reduced blistering within 24 h, although subsequent morbidity was severe.[21] Systemic corticosteroid therapy seems the best established initial treatment for BP (*Strength of recommendation A, Quality of evidence II*; see Appendix 1).

The introduction of measures for prevention of corticosteroid-induced osteoporosis (guidelines produced by the Bone and Tooth Society of Great Britain and the Royal College of Physicians, 2000) must be considered at the outset of systemic corticosteroid treatment in all patients, and implemented whenever practicable.

Topical corticosteroids

In a study of 10 patients with extensive and generalized BP, treatment with 0·05% clobetasol propionate cream achieved complete healing in all patients within

17 days of treatment. Seven of the 10 patients remained in remission at the time of reporting (1–10 months).[22] Twenty patients with BP (involvement of less than 60% body surface) in a second study were treated with very potent topical corticosteroids: in seven patients BP was completely suppressed and the same number obtained remission with an 11-month follow-up. There were mild side-effects of cutaneous infection and skin atrophy.[23] The use of topical corticosteroids has also been reported in a large number of case reports and smaller series of fewer than five patients.[23–26]

It would seem therefore that topical corticosteroids alone are likely to be most useful for localized and mild to moderate disease (*Strength of recommendation A, Quality of evidence* III). They may be a useful adjunct to systemic treatment.[27] A recent publication by Joly *et al.*[28] also supports the use and benefits of topical corticosteroids as a sole treatment in moderate and severe disease, and highlights the mortality associated with high-dose oral corticosteroids.

Antibiotics and nicotinamide

There is some evidence, one small RCT[12] (Table 1), small uncontrolled trials, and case reports that antibiotics and nicotinamide (niacinamide) should be considered as the first line of treatment for both localized and mild to moderate disease (*Strength of recommendation B, Quality of evidence* II-ii/iii). There are 38 reports (183 patients) of BP treated with tetracycline or erythromycin, often in combination with nicotinamide and sometimes with topical or even oral corticosteroids. Occasional blister formation was accepted in most reports.

There are only two case series involving 11 and 15 patients, and many case reports, of the beneficial effect of erythromycin in children and adults.[29–31] Erythromycin should be considered for treatment, particularly in children (adult dose 1000–3000 mg daily), and perhaps in combination with topical corticosteroids. A beneficial effect may be seen within 1–3 weeks after commencing treatment (*Strength of recommendation B, Quality of evidence* II-iii).

There are several case reports and small series that describe the beneficial effect of tetracyclines, usually in combination with nicotinamide. It was helpful in the majority within 1–3 weeks; however, some patients received topical or even systemic corticosteroids in addition.[12,32–36] There is a small RCT supporting this treatment (see Table 1) and emphasizing the reduction in side-effects compared with systemic corticosteroids.[12] Tetracyclines and nicotinamide should be considered for treatment in adults, perhaps in combination with topical corticosteroids (*Strength of recommendation B, Quality of evidence* II-ii). The optimum doses are not established. Tetracycline has been used at doses of 500–2000 mg daily, doxycycline at 200–300 mg daily, and minocycline at 100–200 mg daily. Tetracycline should be avoided in renal impairment and doxycycline and minocycline in patients with hepatic impairment. Minocycline should be stopped if hyperpigmentation occurs. A few cases of minocycline-associated pneumonia and eosinophilia are described, necessitating immediate withdrawal of minocycline. Nicotinamide has been used at doses of 500–2500 mg daily; it should be started at 500 mg daily and then gradually increased to 1500–2500 mg daily. When blister formation is suppressed sufficiently the antibiotics and nicotinamide must be reduced slowly, one at a time, over several months to avoid relapse.

Azathioprine

After systemic corticosteroids, azathioprine in doses of up to 2·5 mg kg^{-1} daily is the most commonly used drug in BP. It is mostly employed as an adjunct to systemic corticosteroids for its presumptive 'steroid-sparing' effect. However, the efficacy of azathioprine as a steroid-sparing agent in BP has been addressed in only two RCTs, with conflicting results (Table 1). One RCT reported a 45% reduction in cumulative prednisolone dosage over a 3-year period.[9] Conversely, a larger RCT found no difference in remission rates at 6 months in patients treated with corticosteroids only compared with those receiving combination treatment with prednisolone and azathioprine[11] (*Quality of evidence* IV).

As a sole therapeutic agent, azathioprine has also been reported in very small uncontrolled series to be effective in inducing remission and in maintaining a corticosteroid-induced remission (*Quality of evidence* IV).

Azathioprine dose should be optimized both with regard to efficacy and myelosuppression risk by prior measurement of thiopurine methyltransferase (TMPT) activity, although this test is not universally available. In view of its side-effect profile, it is recommended that azathioprine is only considered as a second-line treatment to prednisolone where response has been inadequate and either the disease is not suppressed or the side-effects are troublesome and unacceptable (*Strength of recommendation B, Quality of evidence* IV).

Dapsone and sulphonamides

There are no RCTs with respect to the use of either dapsone or sulphonamides either as sole treatments or as adjuncts in the management of BP. Four retrospective series covering a total of 110 patients have reported experience with dapsone 50–200 mg daily or (rare cases) with either sulfapyridine or sulfmethoxypyridazine 1–1·5 g daily. These were employed either as sole treatments or in combination with topical corticosteroids. The response rate was around 45% in three series,[37–39] but only 15% in the fourth.[40] Response was slower in onset than with systemic corticosteroids (2–3 weeks) (*Quality of evidence* IV). A single small uncontrolled series reported a possible steroid-sparing effect in patients in whom dapsone was added to existing treatment with prednisolone and azathioprine[41] (*Quality of evidence* IV).

Glucose-6-phosphate dehydrogenase deficiency predisposes to haematological side-effects and should be excluded in predisposed races. The side-effect profile of dapsone and sulphonamides is potentially hazardous in the elderly. These treatments should be considered only if other treatments are ineffective or contraindicated (*Strength of recommendation B, Quality of evidence* III).

Other immunomodulatory treatments

The following treatments may be useful in individual resistant cases.

Cyclophosphamide

Published experience with cyclophosphamide is very limited. In three individual cases, oral and/or intravenous cyclophosphamide was combined with pulsed intravenous dexamethasone and was reported to be of benefit in otherwise extremely resistant BP. Treatment with oral cyclophosphamide 100 mg daily in a small series of 10 patients gave no steroid-sparing effect and an unacceptably high drug-related mortality and morbidity.[42] Cyclophosphamide should be considered only if other treatments have failed or are contraindicated (*Strength of recommendation D, Quality of evidence* IV).

Methotrexate

There are no controlled trials. In one small series methotrexate in low dosage (5–10 mg weekly) permitted reduction of concomitant oral prednisolone. In a prospective open study of 11 patients with BP unresponsive to topical corticosteroids alone, methotrexate (dose range 5–12·5 mg weekly) as the only systemic treatment successfully controlled their disease for periods of 3 months to 2 years.[43] Methotrexate should be considered in patients with concomitant psoriasis and BP (*Strength of recommendation B, Quality of evidence* IV).

Cyclosporin

Experience with cyclosporin is limited to five individual case reports and a small series of seven patients. The evidence for benefit is conflicting, even with relatively high dosage, > 6 mg mg kg^{-1} daily, and responses mainly occurred in patients treated with concomitant oral corticosteroids[44] (*Strength of recommendation D, Quality of evidence* IV).

Mycophenolate mofetil

Mycophenolate mofetil is an inhibitor of purine synthesis in activated T and B cells and is a generally well-tolerated immunosuppressive agent used since 1997 in the prevention of renal graft rejection. It has been used successfully at doses of 0·5–1 g twice daily to control BP in six individual cases, in three cases as an adjunct to oral prednisolone. Further evidence is needed for its role in BP.

Intravenous immunoglobulin

The total published experience of intravenous immunoglobulin in BP amounts to five small series that suggest that it is of limited value. Used mainly at a dose of 0·4 mg kg^{-1} polyvalent immunoglobulin daily for 5 days, either as a sole treatment or with oral prednisolone, it produced some occasional dramatic but unfortunately very transient responses that were too short-lived to be useful[45,46] (*Strength of recommendation D, Quality of evidence* III).

Chlorambucil

In an open study of 26 patients with BP, treatment was started with prednisolone 40–60 mg daily and chlorambucil at approximately 0·1–0·15 mg kg^{-1} daily.[47] After 2 weeks the doses of both drugs were gradually reduced; the maintenance dose of chloram-

bucil was usually 2 mg daily. The mean duration of therapy and the mean total corticosteroid requirement were both lower than in other studies using corticosteroids plus azathioprine.

Chlorambucil should be considered as an alternative to other more established immunosuppressants if these have failed or are poorly tolerated or contraindicated. Careful monitoring is required for possible haematological toxicity (*Strength of recommendation B, Quality of evidence* III).

Plasmapheresis (plasma exchange)

There have been only two RCTs[10,11] (Table 1), several small series and a number of case reports (100–150 patients) of the use of plasmapheresis (plasma exchange) in the treatment of BP. The regimens used, the additional therapy, and the results have been very variable. There is no evidence to support the use of plasmapheresis in routine treatment of BP, although at low corticosteroid doses a steroid-sparing effect was seen (*Strength of recommendation D, Quality of evidence II-i*). There may be a limited role for plasmapheresis in resistant cases of BP where side-effects are a major issue or the disease is uncontrolled[48] (*Strength of recommendation B, Quality of evidence* III).

Follow-up

BP is a long-term disease, and ideally all patients should be followed until they are in complete remission and off all treatment. They should be regularly reviewed to ensure that they are not being continued on higher doses of topical or systemic treatment than are necessary to provide sufficient control of their disease. The occasional urticated lesion or blister is acceptable, and indicates that the patient is not being over-treated. We suggest attempted reduction of medication every 1–2 months in stable patients; this should be done on clinical rather than IF criteria.

Audit

There is no established optimum treatment for BP, and thus no gold standard against which to audit clinical practice.

Suggested audit points:

- Evidence of a clear management strategy
- Scrutiny of prednisolone dosage used
- Implementation of measures to minimize and reduce corticosteroid dosage
- Indications for use of azathioprine and other immunosuppressants
- Monitoring of drug therapy
  - Corticosteroid side-effects in relation to dose
  - Implementation of osteoporosis prophylaxis
  - TMPT screening prior to the use of azathioprine
  - Drug monitoring of dapsone, sulphonamide or immunosuppressant treatment.

Recommendations

BP is a common disease of the elderly. With our ageing population it will become increasingly frequent, and the age of the patients will add to the complexity of treatment. There is a clear need to determine how to stratify patients clinically, and to ascertain the optimum regimens for treating mild, moderate and severe BP.

- Systemic corticosteroids are the best established treatment. Recommended initial doses of prednisolone are 20 mg or 0·3 mg kg^{-1} daily in localized or mild disease, 40 mg or 0·6 mg kg^{-1} daily in moderate disease, and 50–70 mg or 0·75–1 mg kg^{-1} daily in severe disease. Measures to prevent osteoporosis must be implemented from the start of systemic corticosteroid therapy, whenever practicable.
- For localized BP, very potent topical corticosteroids are worth trying first.
- For mild to moderate disease tetracycline and nicotinamide should be considered.
- Immunosuppressants cannot be recommended routinely from the outset but should only be considered if the corticosteroid dose cannot be reduced to an acceptable level. Azathioprine is the best established; methotrexate may be considered in patients with additional psoriasis.
- Topical corticosteroids should be considered in any patient with BP; they may help to achieve control if this is only borderline using systemic agents. The aim of treatment is to suppress the clinical signs of BP sufficiently to make the disease tolerable to an individual patient. We recommend to aim for reduction, but not complete suppression, of blister formation, urticarial lesions and pruritus.

References

1 Bernard P, Vaillant L, Labeille B *et al.* Incidence and distribution of subepidermal autoimmune bullous skin diseases in three French regions. *Arch Dermatol* 1995; **131**: 48–52.

2 Zillikens D, Wever S, Roth A *et al.* Incidence of autoimmune subepidermal blistering dermatoses in a region of Central Germany. *Arch Dermatol* 1995; **131**: 957–8.
3 Venning VA, Wojnarowska F. The association of bullous pemphigoid and malignant disease: a case control study. *Br J Dermatol* 1990; **123**: 439–45.
4 Anstey A, Venning VA, Wojnarowska F *et al.* Determination of the optimum site for biopsy for direct immunofluoresence in bullous pemphigoid. *Clin Exp Dermatol* 1990; **15**: 438–41.
5 Lever WF. Pemphigus. *Medicine* 1953; **32**: 2–123.
6 Korman NJ. Bullous pemphigoid. The latest in diagnosis, prognosis and therapy. *Arch Dermatol* 1998; **134**: 1137–41.
7 Khumalo NP, Murrell DF, Wojnarowska F, Kirtschig G. A systematic review of treatments for bullous pemphigoid. *Arch Dermatol* 2002; **138**: 385–9.
8 Morel P, Guillaume J-C. Treatment of bullous pemphigoid with prednisolone only: 0.75 mg/kg/day versus 1.25 mg/kg/day. A multicenter randomized study. *Ann Dermatol Venereol* 1984; **111**: 925–8.
9 Burton JL, Harman RR, Peachey RD, Warin RP. Azathioprine plus prednisone in treatment of pemphigoid. *Br Med J* 1978; **ii**: 1190–1.
10 Roujeau JC, Guillaume J-C, Morel P *et al.* Plasma exchange in bullous pemphigoid. *Lancet* 1984; **ii**: 486–8.
11 Guillaume J-C, Vaillant L, Bernard P *et al.* Controlled trial of azathioprine and plasma exchange in addition to prednisolone in the treatment of bullous pemphigoid. *Arch Dermatol* 1993; **129**: 49–53.
12 Fivenson D, Breneman D, Rosen G *et al.* Nicotinamide and tetracycline therapy of bullous pemphigoid. *Arch Dermatol* 1994; **130**: 753–8.
13 Stevenson CJ. Treatment in bullous diseases with corticosteroid drugs and corticotrophin. *Br J Dermatol* 1960; **72**: 11–19.
14 Church R. Pemphigoid treated with corticosteroids. *Br J Dermatol* 1960; **72**: 434–41.
15 Downham TF, Chapel TA. Bullous pemphigoid. *Arch Dermatol* 1978; **114**: 1639–42.
16 Chosidow O, Saada V, Diquet B *et al.* Correlation between the pretreatment number of blisters and the time to control bullous pemphigoid with prednisone 1 mg/kg/day. *Br J Dermatol* 1992; **127**: 185–95.
17 Fine J-D. Management of acquired bullous skin diseases. *N Engl J Med* 1995; **333**: 1475–84.
18 Wojnarowska F, Eady RAJ, Burge SM. Bullous eruptions. In: *Textbook of Dermatology* (Champion RH, Burton JL, Burns DA, Breathnach SM, eds.), 6th edn. Oxford: Blackwell Science, 1998; 1817–98.
19 Venning VA, Wojnarowska F. Lack of predictive factors for the clinical course of bullous pemphigoid. *J Am Acad Dermatol* 1992; **26**: 585–9.
20 Person JR, Rogers RS, Perry HO. Localised pemphigoid. *Br J Dermatol* 1976; **95**: 531–3.
21 Siegel J, Eaglstein WH. High-dose methylprednisolone in the treatment of bullous pemphigoid. *Arch Dermatol* 1984; **120**: 1157–65.
22 Westerhof W. Treatment of bullous pemphigoid with topical clobetasol propionate. *J Am Acad Dermatol* 1989; **20**: 458–61.
23 Zimmermann R, Faure M, Claudy A. Prospective study of treatment of bullous pemphigoid by a class I topical corticosteroid. *Ann Dermatol Venereol* 1999; **126**: 13–16.
24 Muramatsu T, Iida T, Shirai T. Pemphigoid and pemphigus foliaceus successfully treated with topical corticosteroids. *J Dermatol* 1996; **23**: 683–8.
25 Spuls PI, Brakman M, Westerhof W, Bos JD. Treatment of generalized bullous pemphigoid with topical corticosteroids. *Acta Derm Venereol (Stockh)* 1995; **75**: 89 [Letter].
26 Paquet P, Richelle M, Lapiere CM. Bullous pemphigoid treated by topical corticosteroids. *Acta Derm Venereol (Stockh)* 1991; **71**: 534–5.
27 Loche F, Bazex J, Giard A *et al.* Efficacy and tolerability of topical corticosteroid treatment in the initial phase of bullous pemphigoid: an open study of 13 cases. *J Dermatol Treat* 1995; **6**: 69–72.
28 Joly P, Roujeau JC, Benichou J *et al.* A comparison of oral and topical corticosteroids in patients with bullous pemphigoid. *N Engl J Med* 2002; **346**: 321–7.
29 Fox BJ, Odom RB, Findlay RF. Erythromycin therapy in bullous pemphigoid: possible anti-inflammatory effects. *J Am Acad Dermatol* 1982; **7**: 504–10.
30 Altomare G, Capella GL, Fracchiolla C, Frigerio E. Treatment with erythromycin: a reappraisal. *Eur J Dermatol* 1999; **9**: 583–5.
31 Mensing H, Kraußе S. Therapie des bullösen Pemphigoids mit Erythromycin. *Med Klin* 1990; **85**: 481–4.
32 Thomas I, Khorenian S, Arbesfeld DM. Treatment of generalized bullous pemphigoid with oral tetracycline. *J Am Acad Dermatol* 1993; **28**: 74–7.
33 Kawahara Y, Hashimoto T, Ohata Y, Nishikawa T. Eleven cases of bullous pemphigoid treated with a combination of minocycline and nicotinamide. *Eur J Dermatol* 1996; **6**: 427–9.
34 Kolbach DN, Remme JJ, Bos WH *et al.* Bullous pemphigoid successfully controlled by tetracycline and nicotinamide. *Br J Dermatol* 1995; **133**: 88–90.
35 Hornschuh B, Hamm H, Wever S *et al.* Treatment of 16 patients with bullous pemphigoid with oral tetracycline and niacinamide and topical clobetasol. *J Am Acad Dermatol* 1997; **36**: 101–3.
36 Depaire-Duclos F, Dandurand M, Basset-Seguin N *et al.* Treatment of bullous pemphigoid with tetracyclines and topical corticosteroids. *Eur J Dermatol* 1997; **7**: 570–3.
37 Phiamphonsongant T. Dapsone for the treatment of bullous pemphigoid. *Asian Pacific J Allergy Immunol* 1983; **1**: 19–21.
38 Venning VA, Millard PR, Wojnarowska F. Dapsone as first line therapy for bullous pemphigoid. *Br J Dermatol* 1989; **120**: 83–92.
39 Bouscarat F, Chosidow O, Picard-Dahan C *et al.* Treatment of bullous pemphigoid with dapsone: retrospective study of thirty-six cases. *J Am Acad Dermatol* 1996; **34**: 683–4.
40 Person J, Rogers R. Bullous pemphigoid responding to sulfapyridine and the sulfones. *Arch Dermatol* 1977; **113**: 610–15.
41 Jeffes EW, Ahmed AR. Adjuvant therapy of bullous pemphigoid with dapsone. *Clin Exp Dermatol* 1989; **14**: 132–6.
42 Itoh T, Hosokawa H, Shirai Y, Horio T. Successful treatment of bullous pemphigoid with pulsed intravenous cyclophosphamide. *Br J Dermatol* 1996; **134**: 931–3.
43 Heilborn JD, Stahle-Backdahl M, Albertioni F *et al.* Low-dose oral pulse methotrexate as monotherapy in elderly patients with bullous pemphigoid. *J Am Acad Dermatol* 1999; **40**: 741–9.
44 Barthelemy H, Thivolet J, Cambazard F *et al.* Cyclosporin in the treatment of bullous pemphigoid: preliminary study. *Ann Dermatol Venereol* 1986; **113**: 309–13.
45 Tappeiner G, Steiner A. High-dosage intravenous gamma globulin: therapeutic failure in pemphigus and pemphigoid. *J Am Acad Dermatol* 1989; **20**: 684–5.
46 Harman KE, Black MM. High-dose intravenous immune globulin for the treatment of autoimmune blistering diseases: an evaluation of its use in 14 cases. *Br J Dermatol* 1999; **140**: 865–74.

47 Milligan A, Hutchinson PE. The use of chlorambucil in the treatment of bullous pemphigoid. *J Am Acad Dermatol* 1990; **22**: 796–801.
48 Egan CA, Meadows KP, Zone JJ. Plasmapheresis as a steroid saving procedure in bullous pemphigoid. *Int J Dermatol* 2000; **39**: 230–5.

Appendix 1

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 due to problems of methodology (e.g. sample size, or length of comprehensiveness of follow-up or conflicts of evidence).