British Journal of Dermatology 2003; **149:** 926–937.

GUIDELINES

Guidelines for the management of pemphigus vulgaris

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Accepted for publication 15 May 2003

Summary These guidelines for management of pemphigus vulgaris 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, immunosuppression, management, pemphigus vulgaris, therapy, treatment

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 patients and special circumstances. Just as adherence to guidelines may not constitute a defence against a claim of negligence, so deviation from them should not necessarily be deemed negligent.

Introduction

Pemphigus vulgaris (PV) is an acquired autoimmune disease in which IgG antibodies target desmosomal proteins to produce intraepithelial, mucocutaneous blistering. Desmoglein (Dsg) 3 is the major antigen but 50–60% of patients have additional antibodies to Dsg1, the antigen in pemphigus foliaceus (PF).[1–3] The underlying antibody profile is a major determinant of the clinical phenotype of PV.[3–5]

The mortality of PV was 75% on average before the introduction of corticosteroids (CS) in the early 1950s.[6] This figure may be an underestimate due to lack of diagnostic criteria, inclusion of all subtypes of pemphigus and inclusion of other blistering disorders, such as bullous pemphigoid, which have a better prognosis. However, not all cases of PV have such a dismal prognosis. Studies differentiating according to clinical phenotype have shown a lower mortality in patients with predominantly mucosal PV (1–17%) compared with those with mucocutaneous PV (34–42%).[7,8]

Clinical presentation

The diagnosis of PV should be suspected in any patient with mucocutaneous erosions or blisters. The oral mucosa is the first site of involvement in the majority of cases and PV may remain confined to the mucosal surfaces or extend to involve the skin (average lag period 4 months). A minority will present with cutaneous erosions but oral erosions occur in (almost) all cases. PV presents across a wide age range with peak frequency in the third to sixth decades.

Laboratory diagnosis

A skin or mucosal biopsy should be taken for histology and direct immunofluorescence (DIF), the latter requiring perilesional, intact skin or clinically uninvolved

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These guidelines were commissioned by the British Association of Dermatologists Therapy Guidelines and Audit subcommittee. Members of the committee are N.H.Cox (Chairman), A.S.Highet, D.Mehta, R.H.Meyrick Thomas, A.D.Ormerod, J.K.Schofield, C.H.Smith and J.C.Sterling.

skin.[9] Suprabasal acantholysis and blister formation is highly suggestive of PV but the diagnosis should be confirmed by the characteristic deposition of IgG in the intercellular spaces of the epidermis. Indirect immunofluorescence (IIF) is less sensitive than DIF[10–12] but may be helpful if a biopsy is difficult, e.g. children and uncooperative adults. Enzyme-linked immunosorbent assays (ELISA) are now available for direct measurement of Dsg1 and Dsg3 antibodies in serum. They offer advantages over IIF and may supersede this technique.[13,14] Five millilitres of blood is sufficient for IIF and ELISA.

In patients with oral pemphigus, an intraoral biopsy is the optimum but IIF or DIF on a skin biopsy may suffice. One study showed that the sensitivity of DIF was 71% in oral biopsies compared with 61% in normal skin taken from 28 patients with oral PV.[15] Another study reported that the sensitivity of DIF was 89% in oral biopsies compared with 85% for IIF.[16]

Baseline investigations

The following investigations are suggested prior to commencing treatment: biopsy (or IIF) as above, full blood count and differential, urea and electrolytes, liver function tests, glucose, antinuclear antibody (differential of pemphigus erythematosus), thiopurine methyltransferase (TPMT) levels (if azathioprine is to be used), chest X-ray, urinalysis and blood pressure. Current guidelines on osteoporosis should be followed, so a bone density scan early in the course of treatment may be recommended.

Evaluating therapies in pemphigus vulgaris

In general, the quality of published data concerning the therapy of PV is poor. There are few controlled trials, partly reflecting the rarity of PV. The majority of data is confined to case reports and small case series with short follow-up periods in which PV cases of variable severity are included, often with other subtypes of pemphigus. Drugs are often used in combination, particularly adjuvant drugs given concurrently with steroids, and dosing schedules vary widely. Controls are often indirect, involving comparisons of remission and mortality rates with historical controls or comparison of maintenance steroid doses before and after the addition of a given therapy. Therefore, in most studies, it is difficult to judge the effect of individual drugs and make firm treatment recommendations. In these guidelines, we have listed the highest ranking level of evidence and given an overall recommendation for each therapy. A summary of treatment options is given in Table 1.

General principles of management

The initial aim of treatment is to induce disease remission. This should be followed by a period of maintenance treatment using the minimum drug doses required for disease control in order to minimize their side-effects. Occasional blisters are acceptable and indicate that the patient is not being overtreated. The ultimate aim of management should be treatment withdrawal and a recent study reported complete remission rates of 38%, 50% and 75% achieved 3, 5 and 10 years from diagnosis.[17]

Most patients are treated with systemic corticosteroids (CS), which are effective. Adjuvant drugs are commonly used in combination with the aims of increasing efficacy and of having a steroid-sparing action, thereby allowing reduced maintenance CS doses and reduced CS side-effects. Although mortality and complete remission rates have improved since the introduction of adjuvant drugs, this is in comparison with historical controls; a more recent study of PV patients treated with CS alone demonstrated outcomes comparable with studies using adjuvants.[18] There are no prospective, controlled studies that conclusively demonstrate the benefits of adjuvant drugs in PV. Therefore, some respected authorities do not use adjuvant drugs unless there are contraindications or side-effects of CS, or if tapering the CS dose is associated with repeated relapses.[6] However, most centres do use adjuvant drugs as standard practice. In general, adjuvant drugs are slower in onset than CS and are therefore rarely used alone to induce remission in PV.

Oral corticosteroids

Systemic CS are the best established therapy for the management of PV (*Strength of recommendation A, Quality of evidence II-iii*; see Appendix 1). Their introduction in the early 1950s resulted in a dramatic fall in mortality to an average of 30%[6] with complete remission rates of 13–20%.[6,19] Outcomes have continued to improve and in a recent study, the mortality was zero and the complete remission rate was 29% in 17 patients treated with steroids alone and followed for 4–6 years.[18]

Clinical improvement may be seen within days of starting CS. On average, cessation of blistering takes 2–3 weeks[20–22] and full healing may take 6–8 weeks.[23]

Table 1. Summary of treatment options

Drug	Strength of recommendation; Quality of evidence	Evidence and *indication(s)*	Principal side-effects	Advantages	Disadvantages
Oral steroids	A; II-iii	The cornerstone of therapy; effective; optimum dosing schedule not known	Diabetes; osteoporosis; adrenal suppression; peptic ulceration; weight gain; increased susceptibility to infection; mood changes; proximal myopathy; Cushing's syndrome; cataracts	Effective; rapid onset; oral administration; inexpensive	Side-effect profile
Pulsed i.v. steroids	C; IV	Few studies;[27,28] aims are theoretical. *Consider for remission induction in severe or recalcitrant disease, particularly if unresponsive to high oral doses*	Mood changes; flushing	Rapid onset; inexpensive	i.v. administration
Adjuvant drugs		Generally slower in onset than steroids, so rarely used alone to induce remission. *Commonly used in conjunction with CS for their steroid-sparing actions; may be used alone to maintain remission after CS withdrawal*			
Azathioprine	B; II-iii	Reports show steroid-sparing action;[29–33] complete remission rates 28–45%;[6,19,31] mortality rates 1·4–7%;[7,19,31] consider measuring TPMT activity for dose.[35–37] *Commonly used in combination with oral CS for steroid-sparing effect; monotherapy possible for mild disease.*	Myelosuppression and nausea (related to TPMT activity); hepatotoxicity and hypersensitivity reactions (unrelated to TPMT activity); increased susceptibility to infection	Oral administration; inexpensive	Slow onset; side-effect profile
Oral cyclophosphamide	B; III	Five small studies.[39–43] *Could be considered as an alternative to azathioprine if secondary infertility is not a concern*	Neutropenia; alopecia; GI disturbances; raised transaminases; thrombocytopenia; secondary infertility	Inexpensive; oral administration	Potential risk of haemorrhagic cystitis and carcinoma of bladder
Pulsed cyclophosphamide and dexamethasone or methylprednisolone	B; II-iii	Large series of 300 patients.[45] *Consider for severe or recalcitrant PV; repeated courses; may not be practical*	Alopecia, infections; amenorrhoea; ovarian/testicular failure; haemorrhagic cystitis; acne; hiccup	Possibly fewer steroid side-effects than conventional CS therapy;	i.v. administration; labour-intensive
Mycophenolate mofetil	B; III	Several reports;[38,49,50] largest series 12 patients;[49] two reports of monotherapy.[51,52] *Could be considered for recalcitrant cases or if azathioprine/cyclophosphamide unsuitable; may supersede azathioprine as adjuvant of choice in future*	GI disturbances; lymphopenia; anaemia; thrombocytopenia; increased risk of opportunistic infections	Well tolerated and relatively less toxic compared with other immunosuppressive agents	Expensive

Table 1. Continued

Drug	Strength of recommendation; Quality of evidence	Evidence and *indication(s)*	Principal side-effects	Advantages	Disadvantages
Gold	B/C; III	Several series;[53–56] complete remission rates 15–44% but side-effects requiring drug withdrawal in 17–35%;[55,56] ineffective in up to 28% of cases. *Reports of use as monotherapy;*[53,54] *more commonly used as an adjuvant, enabling steroid dose reduction; an alternative to more established adjuvant drugs*[56]	Rashes; nephrotic syndrome; myelosuppression; hypersensitivity syndromes	Inexpensive	Intramuscular administration; slow onset
Methotrexate	C; III	Early reports of high mortality;[57–60] more recent small studies show benefit[61]	Myelosuppression; hepatotoxicity; pneumonitis	Oral administration; inexpensive	Slow onset
Ciclosporin	C; I	A few small case series suggest a steroid-sparing effect[22,62,63] but a randomized controlled trial showed no additional benefit and more side-effects compared with methylprednisolone alone;[18] therefore cannot be recommended as an adjuvant drug in PV	Hypertension; renal impairment; GI disturbances; hypertrichosis; hypertrophic gingivitis		Side-effects; expensive
Tetracyclines and nicotinamide	C; IV	Some reports of benefit with nicotinamide and tetracycline[64,65] or nicotinamide, tetracycline and prednisolone[64] or tetracycline/minocycline and prednisolone.[66–68] *Tetracycline/nicotinamide could be considered as an adjuvant in milder PV*	Flushing and headaches due to vasodilation with nicotinamide; GI upset (tetracyclines); hyperpigmentation, particularly at sites of blistering (minocycline); discoloration of teeth (avoid tetracyclines in children and pregnant/lactating females)	Inexpensive	Lots of tablets
Dapsone/sulphonamides	C; IV	Very few reports and small numbers but may have a steroid-sparing action[69–71]	Haemolysis; methaemoglobinaemia; hypersensitivity reactions	Inexpensive	Minimal data
Chlorambucil	C; IV	One case series only, suggesting steroid-sparing effect[72]	Myelosuppression	Oral administration; inexpensive	Minimal data
IVIG	B; III	Reports of 48 patients treated;[73–83] most beneficial when used as adjuvant when improvement may be rapid but transient unless repeated.[75,81,82] *Possible adjuvant maintenance agent for recalcitrant PV failed on other regimens; could be considered in severe cases to induce remission while slower-acting drugs take effect*	During infusion, chills, tachycardia, hypertension, muscle pains, pyrexia, nausea and headache are common, self-limited and respond to slowing the infusion; anaphylaxis is rare	Rapid action reported in some cases	i.v. administration; expensive; labour-intensive; theoretical risk of blood-borne virus infections

Table 1. Continued

Drug	Strength of recommendation; Quality of evidence	Evidence and *indication(s)*	Principal side-effects	Advantages	Disadvantages
Plasma exchange	C; I	One randomized study showed no benefit over and above steroids;[84] some case reports suggest steroid- sparing effect/ clinical benefit.[85–96] *Not recommended as routine; may be considered for difficult cases if combined with steroids and immunosuppressants*	Septicaemia; fluid and electrolyte imbalance	Direct and immediate removal of IgG and therefore removal of PV antibodies	Central venous access; specialist equipment; trained staff; limited availability; labour-intensive; expensive rebound production of PV antibodies after PE
Extracorporeal photopheresis	B; III	Nine patients with recalcitrant PV improved allowing reduced steroid/immunosuppressive doses.[101–104] *Could be considered in recalcitrant disease where conventional treatment has failed*	Symptoms of hypovolaemia during procedure	Can be performed via peripheral venous access	Specialist equipment; trained staff; labour-intensive; expensive; limited availability; limited data; UV protective sunglasses on the day of treatment; venous access can be a problem

CS, corticosteroids; GI, gastrointestinal; i.v. intravenous; IVIG, intravenous immunoglobulin; PE, plasma exchange, UV, ultraviolet; PV, pemphigus vulgaris; TPMT, thiopurine methyltransferase.

IIF titres fall with CS treatment but lag behind clinical improvement.[24]

The optimum CS dosing schedule is not known and dosing schedules are largely empirical and based on practical experience. Early studies advocated high doses, e.g. initial doses of 120–180 mg prednisolone daily.[23] However, CS side-effects were common and dose related[25,26] and one study estimated that up to 77% of deaths were CS related.[25] Therefore, a more moderate approach to CS therapy has been advocated. However, only one controlled trial has compared dosing schedules; initial therapy with low-dose prednisolone (45–60 mg day^{-1}) was compared with high-dose prednisolone (120–180 mg day^{-1}) in patients with severe pemphigus (19 with PV, three with PF) affecting more than 50% of their body surface. There was no significant difference in the duration to achieve remission and in relapse rates at 5 years, and there were no deaths.[21]

A tailored dosing schedule has been advocated according to disease severity[6,23] and a modified regimen is suggested here. Patients with mild disease are treated with initial prednisolone doses of 40–60 mg day^{-1} and in more severe cases, 60–100 mg day^{-1}. If there is no response within 5–7 days, the dose should be increased in 50–100% increments until there is disease control, i.e. no new lesions and healing of existing ones. If doses above 100 mg day^{-1} are required, pulsed intravenous CS could be considered.

Once remission is induced and maintained with healing of the majority of lesions, the dose of CS can be cautiously tapered. A 50% reduction every 2 weeks has been suggested.[6] In our own practice, we initially reduce by 5–10 mg of prednisolone weekly and more slowly below 20 mg prednisolone daily.

It is strongly recommended that guidelines for the prevention of CS-induced osteoporosis are followed.

Pulsed intravenous corticosteroids

This refers to the intermittent administration of high doses of intravenous CS, usually methylprednisolone (250–1000 mg) or equivalent doses of dexamethasone given on one to five consecutive days. The theoretical aims of pulsing are to achieve more rapid and effective disease control compared with conventional oral dosing, thus allowing a reduction in long-term maintenance CS doses and CS side-effects. This has yet to be demonstrated conclusively. One small retrospective study concluded that pulsed intravenous methylpred-

nisolone (one course of 250–1000 mg day^{-1} for 2–5 days in eight cases, two courses in one case) resulted in increased complete remission rates (44% vs. 0%) and lower mean maintenance oral CS doses in nine patients with recalcitrant PV compared with six controls.[27] One report records disease control in 7–10 days in five of nine patients given pulsed methylprednisolone.[28]

Pulsed CS could be considered in severe or recalcitrant PV to induce remission, particularly if there has been no response to high oral doses (*Strength of recommendation C, Quality of evidence IV*).

Adjuvant drugs

Azathioprine

Azathioprine is a commonly prescribed adjuvant drug in PV and small case series report a steroid-sparing effect.[29–33] The complete remission rates of 28–45%[6,19,31] and mortality rates of 1·4–7%[6,7,19,31] exceed those seen in historical controls treated with CS alone.

In three cases, azathioprine was successfully used as a monotherapy to induce and maintain clinical remission with a fall in antibody titre.[30,34] However, there is a latent period of at least 6 weeks before the effects of azathioprine are seen[29–31,34] and its use as monotherapy to induce remission should be reserved for mild cases only.

Azathioprine doses of 1–3 mg kg^{-1} have been used in previous studies but ideally should be titrated according to the individual activity of TPMT. Azathioprine is best avoided in patients with very low TPMT levels (1 : 200–300 of the general population[35]), and should be used at reduced doses, e.g. 0·5 mg kg^{-1}, in those with low levels ($\approx$ 10%[35]). Patients with high levels ($\approx$ 10%[35]) are at risk of undertreatment using standard doses.[36,37] The dose should be titrated upwards according to clinical response and side-effects, and doses up to 3·5–4 mg kg^{-1} may be required.[38]

Azathioprine is a well-established choice as an adjuvant drug for the management of pemphigus (*Strength of recommendation B, Quality of evidence II-iii*).

Oral cyclophosphamide

Several authors have reported the steroid-sparing effects of cyclophosphamide at doses of 50–200 mg day^{-1} in case series of up to six patients.[39–43] In some cases, prolonged remission with cessation of all therapy was possible.[40] In a randomized study, the efficacy of prednisolone (40 mg day^{-1}) alone was compared with prednisolone/cyclophosphamide (100 mg) and prednisolone/ciclosporin (5 mg kg^{-1}) in 28 patients with oral pemphigus.[15] There was no significant difference in the duration to achieve remission or in relapse rates between the three groups. However, cyclophosphamide and ciclosporin were given for a brief period of only 2–3 months.[15]

Oral cyclophosphamide could be considered as an alternative to azathioprine (*Strength of recommendation B, Quality of evidence III*).

Pulsed intravenous cyclophosphamide with dexamethasone or methylprednisolone

This refers to the intermittent administration of high doses of intravenous CS and cyclophosphamide, usually three daily doses of dexamethasone (100 mg) or methylprednisolone (500–1000 mg) and a single dose of cyclophosphamide (500 mg) given monthly. Pasricha and Ramji first described this therapy for PV.[44] Doses and frequency are arbitrary.

A large case series of 300 Indian patients with pemphigus (255 with PV) treated with dexamethasone–cyclophosphamide pulse (DCP) therapy at 4-weekly intervals has been reported.[45] Low-dose daily oral cyclophosphamide (50 mg) was administered between pulses. Pulsing continued until clinical remission and was followed by a consolidation phase of a further six DCP courses. Oral cyclophosphamide was then continued alone and if there were no relapses after 1 year all treatment was withdrawn. The number of DCPs required to induce clinical remission was variable, with 49% requiring six pulses or fewer but 11% needing more than 2 years of pulsing. Overall, 190 patients (63%) achieved complete remission, 123 (41%) for more than 2 years and 48 (16%) for more than 5 years. The overall mortality rate was 4%. The authors report relative freedom from steroid side-effects but 62% of menstruating females (18 of 29) developed amenorrhoea and azoospermia was also noted. Haemorrhagic cystitis occurred in 0·6%[46] and pituitary–adrenal suppression in 55% of patients (17 of 33).[47]

Another study of 50 Indian patients (45 PV) reported DCP therapy to be effective in most and ineffective in 12%. The mortality was 6% compared with an estimated 25–30% mortality in historical cohorts on conventional CS therapy at the same institute.[48]

Pulsed CS cyclophosphamide therapy could be considered in severe or recalcitrant cases of PV.

However, it may not be practical to administer repeated courses (*Strength of recommendation B, Quality of evidence II-iii*).

Mycophenolate mofetil

Mycophenolate mofetil (MMF) is a relatively new agent in PV therapy. Total daily doses of 2–2·5 g are typically given in two divided doses with prednisolone.[38,49,50] In a series of 12 patients who had relapsed on CS/azathioprine, 11 improved on MMF (2 g day^{-1}) and prednisolone (2 mg kg^{-1}), allowing a reduction in the prednisolone dose to 5 mg day^{-1} or less during the follow-up of 1 year. The patients responded rapidly, with a fall in IIF titres, and were free of lesions within 8 weeks of initiating MMF.[49] However, based on nine patients, Nousari and Anhalt commented that higher doses of MMF (2·5–3 g day^{-1}) were often required to induce remission in PV and at least 8 weeks' treatment was necessary before clinical and immunological improvement was observed.[38]

MMF given as monotherapy has been reported to be beneficial in two cases.[51,52]

On the basis of current evidence, MMF could be considered in recalcitrant cases or when azathioprine and cyclophosphamide cannot be used (*Strength of recommendation B, Quality of evidence III*). However, as experience increases, it may supersede other agents as the adjuvant drug of choice in view of its efficacy and more favourable side-effect profile.

Gold

Most studies have used intramuscular gold, initially at a dose of 50 mg $week^{-1}$ if test doses were tolerated. It was used successfully as monotherapy in five patients,[53,54] with an associated fall in IIF titre.[53] However, it has more commonly been used as an adjuvant drug and steroid-sparing effects are reported. The two largest reported case series are of 18 and 26 patients.[55,56] Complete remission occurred in 15–44% and there were no deaths. The average dose of prednisolone was reduced from 55 mg pregold to 9 mg at the end of the study.[56] However, gold was considered ineffective in 15–28% and side-effects necessitated stopping the drug in 17–35% of patients.

Gold could be considered as an alternative to more established adjuvant drugs if they cannot be used (*Strength of recommendation B/C, Quality of evidence III*).

Methotrexate

High mortality and morbidity rates were attributed to methotrexate in studies from the late 1960s and early 1970s[57–60] and for this reason it has not been a commonly used adjuvant drug for PV. For example, three of four patients cited in one report died, but high doses of methotrexate had been used (125–420 mg $week^{-1}$) in combination with 40–240 mg of prednisolone daily.[59] However, a recent study of nine patients with recalcitrant PV on CS reports favourable outcomes and few side-effects in response to the addition of a mean dose of 12 mg of methotrexate weekly. CS were completely withdrawn within 6 months in six patients (67%) compared with an estimated 5–7% of similar patients treated previously at the same centre with CS alone.[61]

Methotrexate could be considered as an adjuvant drug if more established drugs cannot be used (*Strength of recommendation C, Quality of evidence III*).

Ciclosporin

Initial small case series reported that ciclosporin was a useful adjuvant with steroid-sparing effects in PV.[22,62,63] However, a single randomized, prospective, controlled trial of 33 patients comparing oral methylprednisolone 1 mg kg^{-1} alone vs. methylprednisolone with ciclosporin 5 mg kg^{-1} found no statistically significant difference in outcome measures such as time to healing, complete remission rate and cumulative CS dose.[18] More side-effects were encountered in the ciclosporin group during a mean follow-up period of 5 years.[18] There were no deaths and 10 patients (five from each group) were in complete remission, off all therapy, while the others were taking an average of prednisone 2·5 mg day^{-1}.[18]

On the basis of current evidence, ciclosporin cannot be recommended as an adjuvant drug in PV (*Strength of recommendation C, Quality of evidence I*).

Tetracyclines/nicotinamide

Variable combinations of tetracyclines with or without nicotinamide have been described in PV. Sixteen patients were given nicotinamide 1·5 g and tetracycline 2 g daily. In 12, no systemic steroids were given and of these only three cleared and three improved.[64,65] Of the four patients given additional prednisolone, there was clearance in one, partial improvement in two and no response in another.[64]

Thirteen new patients with PV were given tetracycline 2 g daily in combination with oral prednisolone. They had a faster response rate and reduced prednisolone requirement compared with seven historical CS-treated controls.[66]

Two studies using minocycline 50–200 mg day^{-1} as an adjuvant drug reported improvement and a steroid-sparing effect in seven of 13 patients.[67,68]

Tetracyclines with or without nicotinamide could be considered as adjuvant treatment, perhaps in milder cases of PV (*Strength of recommendation C, Quality of evidence IV*).

Dapsone/sulphonamides

Dapsone was reported to be beneficial as an adjuvant drug in four cases of PV.[69–71] However, in two of these cases, it was started either with or shortly after prednisolone and in two cases, it was started after the long-standing prednisolone was increased to high doses. Therefore, it is difficult to be certain if dapsone had a significant role and there is little evidence to recommend the use of dapsone in PV (*Strength of recommendation C, Quality of evidence IV*).

Chlorambucil

Seven patients with PV who had failed to respond to other steroid/immunosuppressive combinations were given oral chlorambucil 4 mg day^{-1} titrated upwards according to clinical response. There was improvement or remission in five patients and a steroid-sparing effect was reported. A fall in IIF titres was reported in three of four cases.[72] Chlorambucil could be considered as an adjuvant drug if more established options cannot be used but there are limited data to support its use (*Strength of recommendation C, Quality of evidence IV*).

Intravenous immunoglobulin

Several reports describe a total of 48 patients with PV who have been treated with intravenous immunoglobulin (IVIG).[73–83] Doses of 1·2–2 g kg^{-1} divided over 3–5 days were infused every 2–4 weeks for 1–34 cycles. It was beneficial and steroid-sparing in 44 cases,[74–79,81–83] with falls in IIF titres.[77,79,81–83] Clinical improvement was rapid in some cases[75,81,83] but may be transient unless repeated courses of IVIG are given.[75,81,82] In all cases where beneficial, IVIG was initially given as an adjuvant therapy. Of the four treatment failures, three were given one course of IVIG as monotherapy.[73]

The largest series is of 21 patients with recalcitrant PV who were given 2 g kg^{-1} of IVIG divided over 3 days monthly. Improvement was noted after 4·5 months on average. A mean of 18 cycles was given (range 14–34). It was possible to withdraw all other therapies including CS, then reduce the frequency and finally stop IVIG infusions. All patients have been in complete remission for an average of 20 months (range 13–73).[82]

Repeated courses of IVIG could be considered as an adjuvant, maintenance agent in patients with recalcitrant disease who have failed more conventional therapies. In view of reports of a rapid action in some cases, it could be used to help induce remission in patients with severe PV while slower-acting drugs take effect (*Strength of recommendation B, Quality of evidence III*).

Plasma exchange

One randomized study of patients with newly diagnosed pemphigus treated with oral CS with ($n = 19$) or without ($n = 15$) additional plasma exchanges (PEs, 10 over 4 weeks) failed to demonstrate any additional clinical benefit of PE. Cumulative steroid doses and changes in IIF titre in the two groups were similar. Furthermore, there were four deaths from sepsis in the PE group.[84] This is in contrast to case reports and small case series which have reported clinical benefit, short-term falls in IIF titres and a steroid-sparing effect of PE.[85–96] In general, these were 'problem' patients with either steroid side-effects, poorly controlled disease on conventional therapy or life-threatening disease. In most cases, PEs were combined with both CS and immunosuppressive drugs and it is thought that the latter is necessary for clinical effect in order to prevent the rebound production of autoantibodies stimulated by PE.[85,88,93,94,97–100]

PE cannot be recommended as a routine treatment option in newly presenting patients with PV. However, it could be considered in difficult cases if combined with CS and immunosuppressant drugs (*Strength of recommendation C, Quality of evidence I*).

Extracorporeal photopheresis

Nine patients with recalcitrant PV were treated with extracorporeal photopheresis (ECP), 2-day cycles given every 2–4 weeks for a minimum of two cycles. In all cases, there was clinical improvement and it was

possible to taper the concurrent doses of prednisolone and immunosuppressant drugs.[101–104] Two reports documented a fall in IIF titre[101,103] while another showed no change.[102]

ECP could be considered in recalcitrant cases of PV where there has been failure to improve with more conventional therapy (*Strength of recommendation B, Quality of evidence III*).

Topical therapy

PV is largely managed with systemic therapy but adjuvant topical therapy may be of additional benefit, although there are no controlled studies to confirm this. Rarely, patients with mild disease, particularly if confined to the mucosal surfaces, can be managed on topical therapy alone. Huilgol and Black have reviewed topical therapy for pemphigus and pemphigoid in detail.[105,106]

For oral pemphigus, measures such as soft diets and soft toothbrushes help minimize local trauma. Topical analgesics or anaesthetics, for example benzydamine hydrochloride 0·15% (Difflam Oral Rinse®), are useful in alleviating oral pain, particularly prior to eating or toothbrushing. Oral hygiene is crucial otherwise PV may be complicated by dental decay; toothbrushing should be encouraged and antiseptic mouthwashes may be used, such as chlorhexidine gluconate 0·2% (Corsodyl®), hexetidine 0·1% (Oraldene®), or 1 : 4 hydrogen peroxide solutions. Patients are susceptible to oral candidiasis, which should be treated. Topical CS therapy may help reduce the requirement for systemic agents.[105,106] For multiple oral erosions, mouthwashes are most practical, for example, soluble betamethasone sodium phosphate 0·5 mg tablet dissolved in 10 mL water may be used up to four times daily, holding the solution in the mouth for about 5 min. Isolated oral erosions could be treated with application of triamcinolone acetonide 0·1% in adhesive paste (Adcortyl in Orabase®), 2·5 mg hydrocortisone lozenges or sprayed directly with an asthma aerosol inhaler, for example beclomethasone dipropionate 50–200 μg or budesonide 50–200 μg. Topical ciclosporin (100 mg mL^{-1}) in oral pemphigus has been described and may be of some benefit but is expensive.[107,108]

Follow-up

Once remission is induced, there should follow a period of maintenance treatment using the minimum drug doses required for disease control and during which occasional blisters are acceptable. Drug doses should be slowly reduced and patients should remain under follow-up while they remain on therapy. Ultimately, treatment may be withdrawn if there has been prolonged clinical remission. This decision should largely be clinical but the chances of relapse are reduced if immunofluorescence studies are negative, e.g. the risk of relapse is 13–27% if DIF is negative, 44–100% if DIF is positive, 24% if IIF is negative, and 57% if IIF is positive.[109,110] However, DIF can occasionally remain positive in patients who are in remission and off all treatment.[11]

Suggested audit topics

- Measurement of baseline parameters prior to starting treatment
- Appropriate investigations to establish diagnosis
- Evidence of appropriate drug monitoring
- Adherence to guidelines for prophylaxis and management of steroid-induced osteoporosis.

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Appendix 1

The consultation process and background details for the British Association of Dermatalogists guidelines have been published elsewhere[111,112]

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 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, of length or comprehensiveness of follow–up or conflicts of evidence).