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## Interventions for bullous pemphigoid (Review)

Kirtschig G, Middleton P, Bennett C, Murrell DF, Wojnarowska F, Khumalo NP

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**Interventions for bullous pemphigoid (Review)**

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[Intervention Review]

# Interventions for bullous pemphigoid

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## ABSTRACT

### Background

Bullous pemphigoid (BP) is the most common autoimmune blistering disease in the West. Oral steroids are the standard treatment. This is an update of the review published in 2005.

### Objectives

To assess treatments for bullous pemphigoid.

### Search methods

In August 2010 we updated our searches of the Cochrane Skin Group Specialised Register, the Cochrane Central Register of Controlled Trials (Clinical Trials), MEDLINE, EMBASE, and the Ongoing Trials registers.

### Selection criteria

Randomised controlled trials of treatments for participants with immunofluorescence-confirmed bullous pemphigoid.

### Data collection and analysis

At least two authors evaluated the studies for the inclusion criteria, and extracted data independently.

### Main results

We included 10 randomised controlled trials (with a total of 1049 participants) of moderate to high risk of bias. All studies involved different comparisons, none had a placebo group. In 1 trial plasma exchange plus prednisone gave significantly better disease control at 1 month (0.3 mg/kg: RR 18.78, 95% CI 1.20 to 293.70) than prednisone alone (1.0 mg/kg: RR 1.79, 95% CI 1.11 to 2.90), while another trial showed no difference in disease control at 6 months.

No differences in disease control were seen for different doses or formulations of prednisolone (one trial each), for azathioprine plus prednisone compared with prednisone alone (one trial), for prednisolone plus azathioprine compared with prednisolone plus plasma exchange (one trial), for prednisolone plus mycophenolate mofetil or plus azathioprine (one trial), for tetracycline plus nicotinamide compared with prednisolone (one trial). Chinese traditional medicine plus prednisone was not effective in one trial.

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There were no significant differences in healing in a comparison of a standard regimen of topical steroids (clobetasol) with a milder regimen (RR 1.00, 95% CI 0.97 to 1.03) in one trial. In another trial, clobetasol showed significantly more disease control than oral prednisolone in people with extensive and moderate disease (RR 1.09, 95% CI 1.02 to 1.17), with significantly reduced mortality and adverse events (RR 1.06, 95% CI 1.00 to 1.12).

### Authors' conclusions

Very potent topical steroids are effective and safe treatments for BP, but their use in extensive disease may be limited by side-effects and practical factors. Milder regimens (using lower doses of steroids) are safe and effective in moderate BP. Starting doses of prednisolone greater than 0.75 mg/kg/day do not give additional benefit, lower doses may be adequate to control disease and reduce the incidence and severity of adverse reactions. The effectiveness of adding plasma exchange, azathioprine or mycophenolate mofetil to corticosteroids, and combination treatment with tetracycline and nicotinamide needs further investigation.

## PLAIN LANGUAGE SUMMARY

### Treatments for bullous pemphigoid

Bullous pemphigoid (BP) is the most common autoimmune blistering disease in the West. Incidence figures are not available for most parts of the world but BP appears to be rarer in the Far East. Bullous pemphigoid is usually a disease of the elderly but it can also affect younger people and children. Both sexes are similarly affected. While BP usually resolves within five years, there is a moderate death rate associated with the disease and its treatment. Oral corticosteroid drugs are the most common treatment, but may be associated with serious adverse effects, including some deaths. The most common adverse effects of oral steroids, include weight gain and high blood pressure. Long-term use is associated with an increased risk of diabetes mellitus and decreased bone density. Topical steroids are also associated with adverse effects, such as thinning of the skin and easy bruising. The risk of experiencing adverse effects of topical steroids depends on the strength of the steroid, how long it is used for, which area of the body it is applied to, and the kind of skin problem; if a high-strength, potent steroid is used, enough may be absorbed through the skin to cause adverse effects in the rest of the body.

Other treatments include azathioprine, mycophenolate mofetil, dapson, methotrexate, cyclosporin, cyclophosphamide, plasma exchange, erythromycin, and tetracycline and nicotinamide. Some of these drugs or interventions have the potential for severe adverse effects such as increased susceptibility to serious infections, liver and kidney damage, and bone marrow suppression; and many are very expensive.

Three new studies were included in this update of the review published in 2005 making a total of 10 randomised controlled trials with a total of 1049 participants. All studies involved different comparisons, none had a placebo group. Different doses and formulations of corticosteroids plus azathioprine showed no significant differences in disease control, although azathioprine reduced the amount of prednisone required for disease control. There were no significant differences in healing or disease-free intervals in participants taking azathioprine compared with mycophenolate mofetil, or in disease response comparing tetracycline plus nicotinamide with prednisolone. One small study using Chinese traditional medicine, 'Jingui Shenqi Pill' (JSP), plus prednisone did not show any benefit in favour of adding this traditional Chinese herbal remedy. Most of the deaths were in participants taking high doses of oral corticosteroids.

The review of trials concluded that lower doses of oral steroids and strong steroid creams seem safe and effective. However, the use of steroid creams in extensive disease may be limited by side-effects and the practicality of applying creams to large areas of the skin. Milder regimens of topical steroids are safe and effective in moderate BP. More research is needed on treatments for BP, in particular, the effectiveness of adding plasma exchange, azathioprine or mycophenolate mofetil to corticosteroids, and the treatment with tetracyclines and nicotinamide.

## BACKGROUND

### Description of the condition

#### Definition and epidemiology

Bullous pemphigoid (BP) is an acquired autoimmune disorder in which disease-specific autoantibodies are directed against components of the basement membrane zone of the skin (Morrison 1990; Wojnarowska 1998). It 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 (Bernard 1995; Zillikens 1995). The figures are probably similar or higher in the United Kingdom. Incidence figures are not available for most parts of the world but bullous pemphigoid appears to be rarer in the Far East (Adam 1992; Jin 1993; Tham 1998). Bullous pemphigoid is usually a disease of the elderly but it can also affect younger people and children (Kirtschig 1994; Orange 1989; Nemeth 1991). Both sexes are similarly affected.

#### Clinical picture

The characteristic clinical picture is the development of tense blisters, which may arise on inflamed skin or skin of normal appearance. This may be heralded by an urticarial or eczematous rash. The degree of itch varies from none to intense and may precede the appearance of blisters, which contain either clear or bloodstained fluid. The blisters are usually generalised on the body with a tendency to appear on the creases of the limbs. Localised forms also occur. Bullous pemphigoid may affect mucosal surfaces such as the mouth; scarring is usually not observed.

#### Investigation and diagnosis

The most reliable test to achieve a diagnosis is a skin biopsy for immunopathological investigation. A direct immunofluorescence technique (IF) (on skin) demonstrates deposits of IgG autoantibodies and complement (C3) at the dermo-epidermal junction. Indirect IF (using serum) demonstrates circulating autoantibodies directed against basement membrane proteins (Morrison 1990; Wojnarowska 1998). When skin tissue is incubated in one molar sodium chloride, separation of the dermis from the epidermis occurs within the lamina lucida level of the basement membrane (visualised on electron microscopic examination). Immunofluorescence techniques performed on such split skin was first shown in the late 1980s to result in a more precise localisation of the antigen-antibody-binding site. This helps to separate other autoimmune bullous diseases such as epidermolysis bullosa acquisita and bullous systemic lupus erythematosus (in which fluorescence is at the floor of the blister: dermal binding) from BP (in which fluorescence is usually at the roof: epidermal binding) (Logan 1987). Immunoelectron microscopy and immunoblotting are more specific investigations and in some cases can lead to a change in the diagnosis (Kirtschig 1994). The latter investigations are not yet available for routine clinical use, being largely limited to research centres.

#### Natural history

The natural history of both treated and untreated BP is of a persistent disease with eventual remission occurring in the majority of cases. Remission is likely to occur within five years, although relapses and exacerbations may occur (Ahmed 1977; Hadi 1988; Nemeth 1991; Person 1977). The mortality rate in the initial 30 cases reported by Lever was 24% at 1 year. This was

prior to the use of oral corticosteroids (Lever 1953). The mortality rate in other studies ranges from about 10% to 40% at 1 year (Colbert 2004; Venning 1992; Savin 1979; Savin 1987; Roujeau 1998; Gudi 2005), despite the use of topical and systemic treatments. This might suggest that treatment is at best suppressive (without really altering the prognosis of the disease) or at worst contributes to mortality (e.g. from sepsis secondary to immunosuppression) whilst relieving itch and preventing blisters. Savin suggested that death seemed to be more commonly related to underlying illness in the elderly, debilitation associated with severe illness, or the adverse effects of treatment. The study by Parker et al supports this view, they evaluated 223 participants with pemphigoid and compared mortality data with the general population in the United States (Parker 2008). There was no difference between pemphigoid participants and age-matched controls in expected mortality. They conclude that mortality of participants with bullous pemphigoid is more likely related to advanced age and associated medical conditions than disease-specific factors and treatment will not alter the natural disease history but the quality of life.

#### Description of the intervention

Current treatments include oral steroids (e.g. prednisone or prednisolone), azathioprine, mycophenolate mofetil, dapsone, methotrexate, cyclosporin, cyclophosphamide, plasma exchange, erythromycin, and tetracycline and nicotinamide. Some of these drugs or interventions have the potential for severe adverse effects such as increased susceptibility to serious infections, liver and kidney damage, and bone marrow suppression; and some are very expensive.

High-potency topical steroids (clobetasol propionate cream) have been demonstrated to improve survival in patients with bullous pemphigoid (Joly 2002). These topical steroids may be safer and more effective than high-dose oral corticosteroids for controlling BP and therefore may be suitable for treating those patients, often the elderly, who have a poor prognosis because they are at high risk of developing adverse effects with systemic treatments. Topical steroids are not without risk of adverse effects, both locally (increased susceptibility of the skin to damage like skin atrophy and bruising and infections of the skin) and systemically if enough steroid is absorbed through the skin, leading, for example, to Cushing syndrome with fluid retention, increased blood pressure and diabetes mellitus, and adrenal gland suppression.

Prednisone is an inactive drug precursor that is metabolised by the liver and converted to biologically active prednisolone. The two forms are virtually identical therapeutically and can be used interchangeably in many situations. As prednisone is rapidly converted to prednisolone, prednisolone may be preferred in some patients who have liver disease or some other metabolic disorder. There are some differences in the appearance and taste of the two formulations: prednisolone sodium phosphate is very soluble with a not unpleasant taste, whereas prednisone is bitter and poorly soluble. Some reports have suggested that the use of prednisone is preferable to prednisolone in the treatment of BP (Lebrun-Vignes 1999) and this may account for differences in use of the drug, for example, in France. For the purposes of this review, prednisone and prednisolone are regarded as bio-equivalent, however, for each of our included studies we have used the drug name which was quoted in the report of the study.

#### Interventions for bullous pemphigoid (Review)

There are emerging reports of some BP cases being treated with biological therapies, in particular, anti-CD20 monoclonal antibodies (rituximab) (Hertl 2008). CD20 is a molecule which is expressed on the surface of B lymphocytes (the immune cells which produce antibodies) including the autoantibodies which are directed at the skin in BP. Rituximab, a monoclonal antibody, binds specifically to this transmembranous CD20 antigen and the resulting lysis (breaking down) of the B lymphocyte is induced via a number of immune pathways. This limits the immune system's attack by depleting the number of B lymphocytes available to produce antibodies. Rituximab could be used either as an alternative to standard treatments for bullous pemphigoid, in patients that are refractory to standard treatment (Reguiñi 2009) or if the patient is unable to tolerate other treatments.

### Why it is important to do this review

Mortality figures, based on uncontrolled studies, have not improved much since the introduction of systemic treatments. This may suggest that BP is a self-limiting condition (occurring in older people with a higher mortality than the general population) and that the prognosis is not altered by treatment. It is also possible that improved skin care and medical support currently available, compared with the times of Lever (Lever 1953) do significantly lower the mortality rate and that this benefit is masked by the adverse effects of systemic treatments. However, this does not tell us about morbidity and the quality of life of these affected people and whether treatment alters the duration of the lesions. There is also variation in the long-term toxicity of systemic agents ranging from very little (e.g. antibiotics) to a lot (e.g. prednisolone or cyclophosphamide). Use of very potent topical steroid treatment may be adequate in localised disease and has minimal side-effects. There is wide variation in practice among clinicians as to which drugs or interventions are used and in what order or combinations.

This review aims to establish:

1. which are the most effective drugs or interventions, with the least adverse effects;
2. whether combination therapy (e.g. azathioprine plus steroids) offers any advantages over single drugs (e.g. oral steroids alone);
3. whether antibiotics such as tetracyclines, erythromycin, dapson, or sulphonamides are useful; and
4. whether systemic treatment is better than topical or no treatment.

## OBJECTIVES

To assess the effects of treatments for bullous pemphigoid.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

Randomised controlled trials.

#### Types of participants

People of any age who have received treatment for a diagnosis of bullous pemphigoid, confirmed by immunofluorescence studies.

#### Types of interventions

Any therapeutic intervention used to treat bullous pemphigoid.

#### Types of outcome measures

##### Primary outcomes

(a) Regression or healing of the skin lesions at time periods specified by individual trials.

##### Secondary outcomes

(a) Effect on the quality of life, e.g. relief of soreness or itching.

(b) Duration of remissions after stopping treatment.

(c) Complications of the primary disease (BP), e.g. localised skin infection.

(d) Systemic infection.

(e) Adverse effects of treatment:

i) organ failure

ii) allergic reactions.

f) Mortality.

### Search methods for identification of studies

#### Electronic searches

We searched the following databases up to 10th August 2010:

- The Cochrane Skin Group Specialised Register using the search terms in [Appendix 1](#); and
- The Cochrane Central Register of Controlled Trials (Clinical Trials) within *The Cochrane Library* using the search strategy in [Appendix 2](#); and
- MEDLINE and EMBASE using the strategies in [Appendix 3](#) and [Appendix 4](#) respectively.

#### Ongoing Trials

We searched the following Ongoing Trials registers in August 2010 using the term 'bullous pemphigoid'.

- The metaRegister of Controlled Trials [www.controlled-trials.com](http://www.controlled-trials.com).
- The U.S. National Institutes of Health ongoing trials register [www.clinicaltrials.gov](http://www.clinicaltrials.gov).
- The Australian and New Zealand Clinical Trials Registry [www.anzctr.org.au](http://www.anzctr.org.au).
- The World Health Organization International Clinical Trials Registry platform [www.who.int/trialsearch](http://www.who.int/trialsearch).
- The Ongoing Skin Trials Register on [www.nottingham.ac.uk/ongoingskintrials](http://www.nottingham.ac.uk/ongoingskintrials).

#### Searching other resources

#### References from published studies

We searched the bibliographies from identified studies.

## Data collection and analysis

### Selection of studies

We screened the abstracts of potentially relevant studies and obtained full articles if necessary. We assessed articles that were possible RCTs for eligibility using inclusion criteria outlined in the protocol. This was done independently by at least two authors (NP, PM, and GK).

### Data extraction and management

We extracted details of eligible studies and summarised them using a data extraction sheet that was based on the outcome measures. Two authors (GK, PM) extracted data independently and subsequently checked for discrepancies. The data of the Chinese article was kindly extracted by Dr Ching-Chi Chi from Taiwan. We had planned to resolve disagreements by discussion with the other authors (DM and FW), but this was not necessary because there were very few small studies.

### Assessment of risk of bias in included studies

Risk of bias for the new studies identified by the updated search was independently assessed by two authors (CB and GK) and we resolved any differences by consensus.

We made an assessment of the risk of bias which includes an evaluation of the following components for each included study, using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008) (details are available in the [Characteristics of included studies](#) ('Risk of bias') for each study):

- (a) the method of generation of the randomisation sequence;
- (b) the method of allocation concealment - it was considered 'adequate' if the assignment could not be foreseen;
- (c) who was blinded or not blinded (participants, clinicians, outcome assessors); and
- (d) how many participants dropped out of the study overall, and whether participants were analysed in the groups to which they were originally randomised (intention-to-treat analysis).

The original protocol of this review stated that the Jadad quality assessment scale would be used, which also similarly assesses randomisation, blinding, withdrawals, and dropouts (Jadad 1996). We assessed all these aspects but reported them individually (see [Characteristics of included studies](#)) rather than as a summary score.

### Measures of treatment effect

We presented dichotomous measures as risk ratios (RR) with 95% confidence intervals (CI); and continuous measures were presented as mean differences with 95% CI.

### Dealing with missing data

We contacted trial investigators to obtain missing data and clarify the specifics of the trial conditions when this was not clear to us from the published report of the trial.

### Assessment of heterogeneity

For an assessment of heterogeneity we used the  $I^2$  statistic. If we found moderate to high levels of heterogeneity ( $I^2 > 50\%$ ) for the primary outcomes, we explored the possible sources of heterogeneity.

## Data synthesis

We had planned to divide data analysis into two groups:

- (a) trials where the diagnosis of BP was confirmed by immunofluorescence (IF) using intact skin; and
- (b) trials where split skin was used for IF (this procedure helps, although not completely, to distinguish true BP participants from those with other subepidermal immunobullous diseases), however, this was unnecessary as only one of the studies used IF on split skin (Beissert 2007).

We conducted a narrative synthesis of included trials, and present the characteristics of the trials and results in tables and figures. We were unable to pool data in a meta-analysis as the studies were heterogenous especially in terms of the treatments used. We did, however, present some of the data in Review Manager 5 (RevMan) in the form of risk ratios and 95% confidence intervals for the results of single trials.

The adverse events are summarised in a separate table "Adverse events in the included studies; [Table 1](#)"; some columns are left empty, it would have been misleading to enter "zero" when a paper was silent about a particular adverse event, because we are not sure that all adverse events have been reported.

## RESULTS

### Description of studies

#### Results of the search

We identified 73 abstracts from MEDLINE, 27 from EMBASE, and 7 from the Cochrane Central Register of Controlled Trials (Clinical Trials) at our initial searches. For this update we searched the Cochrane Skin Group Specialised Register, *The Cochrane Library* (Issue 1, 2009), MEDLINE, and EMBASE on 16th March 2009 and 31 abstracts were identified. Prior to publication we ran another search on 10th August 2010 of the listed databases but found no potentially eligible studies. We assessed 28 of these for eligibility and they were clearly either not RCTs or the participants did not have a diagnosis of bullous pemphigoid. Therefore as none of the studies appeared to meet the eligibility criteria on the surface, no studies appear in the excluded studies table. We included 3 new RCTs in this update (Beissert 2007; Joly 2009; Liu 2006), therefore there are 10 completed RCTs with a total of 1049 participants included in this review; details of all the studies are included in the [Characteristics of included studies](#).

We identified seven ongoing trials from the above mentioned Ongoing Trial registers. We are aware that two of these are ongoing RCTs (ISRCTN13704604; NCT00809822). The remaining five trials will be assessed for eligibility when more details become available.

### Included studies

#### Design

Six of the studies in this review were multicentre French studies (Dreno 1993; Guillaume 1993; Joly 2002; Joly 2009; Morel 1984; Roujeau 1984). Morel was a co-author in two (Morel 1984; Roujeau 1984), Guillaume in three (Guillaume 1993; Roujeau 1984; Joly 2009), three trial authors (Crickx, Labeille, and Guillot) were in the same two trials (Roujeau 1984; Guillaume 1993), Dreno in three (Dreno 1993; Joly 2002; Joly 2009), and Roujeau in four studies



(Guillaume 1993; Joly 2002; Roujeau 1984; Joly 2009). It is not clear if any of the studies included the same groups of participants.

### Sample sizes

There were 1049 participants in total. There were 8 small studies (between 20 and 100 participants in each) and 2 larger RCTs including more than half of the participants (653) in this review (Joly 2002; Joly 2009).

### Setting

Only four studies in this review were done in centres outside France. Burton 1978 was conducted in the UK, Fivenson 1994 in the USA, Liu 2006 in China, and Beissert 2007 in Germany. The studies were carried out in hospital settings, although it is unclear what the setting was in Liu 2006.

### Participants

All participants had confirmed bullous pemphigoid (confirmed by immunofluorescence, except Liu 2006, in which this is unclear). The participants were older men and women (range of mean ages at baseline quoted in the included studies was 65.4 to 84.8 years of age).

### Interventions

None of the studies included a placebo group. The interventions tested in the included studies included, oral steroids, with or without other interventions, topical steroids, and tetracycline and nicotinamide (versus prednisolone). All used different interventions with only five studies overlapping; therefore classification by intervention is intended to assist the reader, rather than to attempt to fit different interventions in to broad classification groups. A brief summary of the type of interventions used is presented below. Full details of each trial are given in the [Characteristics of included studies](#).

#### Oral steroid with or without other interventions, including plasma exchange

Beissert 2007 used oral methylprednisolone plus azathioprine versus (vs) oral methylprednisolone plus mycophenolate mofetil; and Dreno 1993 administered prednisolone versus methylprednisolone. Morel 1984 looked at prednisolone at two doses (0.75 mg/kg versus 1.25 mg/kg). Liu 2006 compared a traditional Chinese medicine, 'Jingui Shenqi Pill' (JSP), plus prednisone (0.5 to 1.0 mg/kg/day) to prednisone alone (0.5 to 1.0 mg/kg/day). In Guillaume 1993 participants received prednisolone versus prednisolone and azathioprine, versus plasma exchange and prednisolone, and Roujeau 1984 also investigated plasma exchange and prednisolone. Burton 1978 compared azathioprine plus prednisone versus prednisone alone. We have used the drug names as reported in the included studies (i.e. prednisone or prednisolone); for the purposes of this review, prednisone and prednisolone are regarded as bio-equivalent.

#### Topical steroid treatment

Joly 2002 used topical clobetasol propionate versus oral prednisolone, and in Joly 2009 investigated 2 different regimens of topical clobetasol propionate cream: 40 g clobetasol propionate cream/day versus a mild regimen of 10 to 30 g/day, depending on the body weight, were compared in a large, randomised study. The regimen was chosen according to disease severity.

### Tetracycline and nicotinamide

Fivenson 1994 used prednisolone versus nicotinamide and tetracycline.

### Outcomes

We specified a number of outcomes of interest for this review in [Types of outcome measures](#). Our primary outcome of regression or healing of skin lesions was reported in all the included studies. Effects of the interventions on quality of life were reported in Dreno 1993, Guillaume 1993, and Roujeau 1984. The duration of remission after stopping treatment was reported in Beissert 2007 and Joly 2009.

Adverse effects were recorded in Beissert 2007, Joly 2002, and Joly 2009, while mortality was reported in Burton 1978, Joly 2002, and Joly 2009. The remaining review outcomes of complications of the primary disease and systemic infection were not reported in any of the included studies.

The reports of the included studies focused on a variety of outcomes, including disease control, survival, and cumulative steroid doses which are summarised as follows:

- The outcomes reported in Beissert 2007 were complete healing (complete re-epithelialisation of all lesions), and cumulative steroid dose. Secondary outcomes were duration of remission (disease-free interval) and safety.
- Dreno 1993 reported the number of blisters, intensity of erythema, and the intensity of pruritus (itch) at days five and ten.
- Fivenson 1994 reported the number of bullous, crusted, urticarial lesions as the total highest score possible on each visit per participant.
- Only Burton 1978 did not have clearly stated outcome measures. The following outcome measures were obtained from the published report, and include cumulative dose of prednisone in both groups necessary for disease control, mortality, and adverse effects, including whether azathioprine and prednisolone (synergistic immunosuppression) was associated with increased risk of malignancy.
- Guillaume 1993 reported disease control in terms of blister formation, resolution of erythema, and no more than minimal pruritus at four weeks and six months after starting treatment.
- Joly 2002 and Joly 2009 both reported survival after one year, disease control at three weeks, and occurrence of severe adverse events during the follow-up year; Joly 2009 also reported occurrence of relapses during follow-up and cumulative doses of steroid cream.
- Liu 2006 reported complete healing at four weeks; Morel 1984 assessed new blister formation at days 21 and 51, and Roujeau 1984 assessed the cumulative and daily corticosteroid dose to achieve disease control in terms of blister formation. Other parameters of disease control were intensity of pruritus and extent of erythema and urticarial lesions.

### Excluded studies

A search of the abstracts of potential RCTs for the initial published version of this review and for this update indicated that there were no studies that should be listed in the Characteristics of excluded studies table, e.g. no RCTs that dealt with closely related conditions.

## Risk of bias in included studies

### Allocation

Some attempt at randomisation was made in all of the studies. Randomisation was not described in detail by [Burton 1978](#), [Fivenson 1994](#), or [Liu 2006](#).

Only [Joly 2009](#) was assessed as having adequate randomisation as both sequence generation and allocation concealment were adequate.

It was not explicitly stated in [Burton 1978](#) that the 25 participants were initially randomised, but this was implied in other sections of the article in that each participant was described as being assigned to treatment by the ward sister who drew a marked paper from an envelope. Since there are no details about how the envelopes were marked, the sequence generation was rated as unclear.

[Morel 1984](#) randomised 50 participants using a table of numbers, but allocation concealment was unclear.

The study reported by [Dreno 1993](#) was randomised, but the method was not described.

Similarly, in [Fivenson 1994](#) randomisation was mentioned but the method used was not explained. A full translation of the study of [Liu 2006](#) provided no details about the randomisation method used.

The prednisolone and plasma exchange versus prednisolone-only study ([Roujeau 1984](#)) had an adequate method of sequence generation (computer-generated), but allocation was unclear.

The [Joly 2002](#) study on topical versus oral corticosteroids studies ([Joly 2002](#)), had an adequate sequence generation method, but seemed marginal for allocation concealment therefore we coded it as unclear.

A three-arm study ([Guillaume 1993](#)) comparing the efficacy of azathioprine or plasma exchange when added to prednisolone used an adequate method of sequence generation (pre-established lists). But [Guillaume 1993](#) was also marginal regarding allocation concealment as it was not clear if the study co-ordinator was or was not involved in the allocation process; therefore we have coded it as unclear.

[Beissert 2007](#) had adequate sequence generation by centrally-generated random numbers to receive oral methylprednisolone plus azathioprine or mycophenolate mofetil.

### Blinding

Most of the studies had no blinding of either participants or outcome assessors (see [Figure 1](#)). [Dreno 1993](#) employed a double-blind method although the two products used as interventions were of a different appearance, the supply of the products to the participants was made by a person other than the investigator. Additionally clinical follow-up after the end of the study was done by a blinded investigator.

**Figure 1. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.**

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Beissert 2007	+	?	-	+	+	+
Burton 1978	?	?	?	?	?	?
Dreno 1993	?	?	+	+	+	?
Fivenson 1994	?	?	-	?	+	?
Guillaume 1993	+	?	-	?	?	?
Joly 2002	+	?	-	+	+	?
Joly 2009	+	+	-	?	+	+
Liu 2006	?	?	-	+	+	?
Morel 1984	+	?	-	-	+	?
Roujeau 1984	+	?	-	?	+	+

Two regimens of very potent topical corticosteroids, a standard regimen of 40 g clobetasol propionate cream/day versus a mild regimen of 10 to 30 g/d depending on the body weight, were compared in a large, randomised study (Joly 2009). Blinding was

not deemed necessary as the primary outcome was event-free survival.

The studies by [Burton 1978](#), [Guillaume 1993](#), [Fivenson 1994](#), [Liu 2006](#), and [Roujeau 1984](#) were also not blinded. In [Guillaume 1993](#) blinding could be considered by some as unethical (this was given as a reason for not blinding in one study) because it would mean an invasive procedure (intravenous line) in the control group as well. [Joly 2002](#) was not blinded, however, the primary outcome was survival at one year which was unlikely to be biased by lack of blinding (this was given as the reason for not blinding). However, assessments for disease control and complications were also made which might potentially have been biased by the lack of blinding. In [Beissert 2007](#) complete healing defined as complete re-epithelialisation of the lesions and cumulative steroid dose at complete healing were primary end points, judgement may have been biased because of the lack of blinding.

### Incomplete outcome data

There was one dropout in [Dreno 1993](#): treatment was stopped after eight days of treatment as the participant was in a coma unrelated to treatment.

In [Morel 1984](#) four participants were excluded from the analysis, two because they did not fit the inclusion criteria and two due to protocol deviation.

[Burton 1978](#) and [Liu 2006](#) seemed to have no dropouts but the reports were short and no details were given.

In [Roujeau 1984](#) the number and reasons for dropouts, two from each arm of the study, were listed.

In the prednisone (6 participants) versus tetracycline and nicotinamide (14 participants) trial, the report of the trial states that 18 of 20 participants enrolled in the study were treated, the 2 that were unavailable for follow up at 8 weeks were both in the tetracycline/nicotinamide group. The reasons for dropout were not given ([Fivenson 1994](#)).

[Guillaume 1993](#) had 3 arms, prednisolone-only (32 participants with 1 dropout), prednisolone and azathioprine (36 participants, no dropouts) and prednisolone and plasma exchange (32 participants with 1 dropout), the reasons for the 2 dropouts were not given.

[Joly 2002](#) stated reasons for dropouts. This study was the largest study including 341 participants.

In [Joly 2009](#) the intention-to-treat analysis was not fulfilled, as only 150 of 153 randomised participants of the standard regimen were analysed, however, this is only a small deviation.

In [Beissert 2007](#) one participant was lost. Two died of causes not related to the treatment, they were included in the intention-to-treat analysis.

### Selective reporting

All the prospectively stated outcomes were reported in all of the studies except for [Burton 1978](#) and [Guillaume 1993](#). In [Burton 1978](#) the prospectively stated outcome measures were unclear. In [Guillaume 1993](#) outcome measurements of controlled disease were stated to be no more than one new blister occurring four weeks after starting treatment, resolution of erythema, and no more than minimal pruritus. However, only the composite measure of controlled disease was reported.

### Other potential sources of bias

[Dreno 1993](#) only had a very short (10 days) follow-up, which limits the applicability of results to clinical practice, especially in a chronic disease such as BP.

Initial diagnosis confirmed by immunofluorescence was performed in all but one study (a pathological test was mentioned but not described further in [Liu 2006](#)).

More participants in the azathioprine group in [Beissert 2007](#) had severe disease; 53% had  $\geq 20\%$  body surface area involvement compared to only 27% in the mycophenolate mofetil (MMF) group, and more participants had raised liver enzyme tests. However, a test to check for thiopurinemethyltransferase activity was not performed. Additionally, only those participants who were likely to attend for follow up were recruited. Eligibility was also determined by the consultant doctor after baseline testing.

In [Fivenson 1994](#) the study was originally designed to randomise 96 participants, but enrolment was terminated when 20 participants were enrolled. No reasons were given for this.

The [Guillaume 1993](#) study was stopped after the interim analysis became available; this showed no appreciable benefit resulting from the addition of azathioprine or plasma exchange to prednisolone.

### Effects of interventions

The assessment and reporting of disease control, symptoms, and adverse effects of medication were recorded in varying detail in the different trials. Mortality is the only outcome measure documented in all the studies, however, this was not a stated outcome of interest in most studies and it is not always clear whether the deaths were related to treatment.

The following effects of interventions section is organised by comparison, followed by the primary and secondary outcomes stated in the [Methods](#) section of this review ([Types of outcome measures](#)).

#### Higher versus lower doses of prednisolone

##### Primary outcome

##### Regression or healing of skin lesions

The study [Morel 1984](#) comparing the starting dose of prednisolone 0.75 mg/kg (26 participants) versus prednisolone 1.25 mg/kg (24 participants) reported that 51% versus 64% of participants were clear of skin lesions at day 21 and 33% versus 55% at day 51 (no significant difference in effectiveness, comparing each dose at 21 days and 51 days, data not shown). This was the case for analyses based on completers only as well as on an intention-to-treat basis (assuming unknown = not healed). There were no significant differences between doses of prednisolone at 21 days in terms of disease control (healing of skin lesions) (RR 1.20, 95% CI 0.77 to 1.87), or 51 days (RR 1.38, 95% CI 0.69 to 2.79, [Analysis 1.1](#)).

##### Secondary outcomes

##### Mortality

At day 51, there were 3 deaths out of 22 participants in the higher dose compared to 2 deaths out of 24 participants in the lower dose (RR 1.64, 95% CI 0.30 to 8.90, [Analysis 1.2](#)) ([Morel 1984](#)).

## Methylprednisolone versus prednisolone

### Primary outcome

#### Regression or healing of skin lesions

The study comparing different formulations of steroids, methylprednisolone (n = 28) with prednisolone (n = 29) (Dreno 1993), found a large reduction in the number of blisters in both groups. At day 10 the mean number of blisters was 6.0 (SD 19) for methylprednisolone and 13.0 (SD 35) for prednisolone (mean difference -7.00) (95% CI -21.55 to 7.55, Analysis 2.1).

Collective figures of overall improvement (22 of 28 participants in the methylprednisolone group, 78.6%, versus 18 of 29 participants in the prednisolone group, 62.1%) were reported (RR 1.27, 95% CI 0.90 to 1.79, Analysis 2.2). This was not statistically significant.

### Secondary outcomes

#### Effect on the quality of life

Erythema and pruritus (itch) were each measured by the participant on a scale from zero (absent) to three (severe). No significant difference was seen between the groups for either score: erythema 0.59 (SD 0.69) versus 0.93 (SD 0.72), mean difference -0.34 (95% CI -0.71 to 0.03, Analysis 2.3), and pruritus 0.59 (SD 0.8) versus 0.86 (SD 0.8), mean difference -0.27 (95% CI -0.69 to 0.15, Analysis 2.4). The study investigators report that the only statistically significant result was a reduction in pruritus; the statistical significance for this outcome (pruritus) was given as 0.042 by the study investigators, but it was unclear which statistical test they used.

#### Mortality

There were no deaths recorded in this study, but the follow-up period was only 10 days.

### Prednisone plus azathioprine versus prednisone

This comparison was evaluated in two small studies, Burton 1978 with a three-year follow-up, and Guillaume 1993 with a six-month follow-up.

### Primary outcome

#### Regression or healing of skin lesions

The Guillaume 1993 study failed to show improvements in disease control (14/36 vs 13/31; RR 0.93, 95% CI 0.52 to 1.66, Analysis 3.1).

In Burton 1978, the prednisone plus azathioprine group, 9/12 participants had their disease controlled at 3 years (7 participants off treatment and 2 still on treatment), and 9/13 participants in the prednisone-only group had their disease controlled (4 participants off treatment and 5 still on treatment) (RR 1.08, 95% CI 0.67 to 1.76, Analysis 3.1) (P = 0.75: not statistically significant). This study found a 45% reduction in the amount of prednisone required for disease control by the azathioprine group over a 3-year period (mean total dose 3688 mg in the azathioprine group versus 6732 mg in the prednisone-only group), which was statistically significant (P < 0.01). The statistical test that was used was not reported.

### Secondary outcomes

#### Adverse effects

In Burton 1978 one of the off-treatment participants who was originally assigned to the prednisone-only group withdrew from the prednisone group due to adverse effects and was subsequently successfully treated with azathioprine. In Guillaume 1993 severe complications were more often noted in the azathioprine group (RR 1.29, 95% CI 0.68 to 2.45, Analysis 3.2) (not statistically significant). Unfortunately, the adverse effects were not given in detail for each group (see Adverse Events; Table 1). The study investigators stated that "most of the adverse events could be attributed to corticosteroids". The chief adverse effect associated with azathioprine was a reduction in the white cell count (2 of 12 participants in the Burton 1978 trial and 4 of 36 participants in the Guillaume 1993 trial).

#### Mortality

There was no statistical significance in mortality at 6 months between the prednisone and the prednisone plus azathioprine group in Guillaume 1993 (RR 1.03, 95% CI 0.35 to 3.06, Analysis 3.3). The Burton 1978 study had the longest follow-up (3 years) and an overall mortality of 7/25 participants (28%). There were 3 deaths in the prednisone plus azathioprine group (n = 12) and 4 in the prednisone-only group (n = 13) (RR 0.81, 95% CI 0.23 to 2.91, Analysis 3.3) (P = 0.75) after 3 years of treatment.

### Prednisolone plus plasma exchange versus prednisolone

### Primary outcome

#### Regression or healing of skin lesions

This comparison was evaluated in two small studies: Roujeau 1984 with a one-month follow-up, and Guillaume 1993 with a six-month follow-up.

In the study comparing prednisolone versus prednisolone and plasma exchange (Roujeau 1984), all participants were started on a low dose of prednisolone (0.3 mg/kg/day) which was increased (max 2 mg/kg/day methylprednisolone intramuscular + 2 mg/kg/day oral cyclophosphamide) until disease control was achieved. The addition of plasma exchange appeared to reduce the amount of prednisolone required to achieve disease control. Disease control was achieved with a dose of 0.3 mg/kg/day in 13/22 participants in the prednisolone plus plasma exchange group but in none of the 15 participants in the prednisolone-only group (risk ratio in favour of prednisolone plus plasma exchange: RR 18.78, 95% CI 1.20 to 293.70, Analysis 4.1) (P = 0.04). This is statistically significant, although the confidence intervals are very wide.

Significantly more participants also achieved disease control with prednisolone doses less than or equal to 1 mg/kg: 21/22 for prednisolone plus plasma exchange and 8/15 for prednisolone-only (RR 1.79, 95% CI 1.11 to 2.90, Analysis 4.1) (P = 0.02). Disease control was achieved with less than half the total prednisolone dose in the plasma exchange group; significantly lower doses of prednisolone were required to achieve disease control, both in terms of the cumulative dose (mean difference -1.53 g: 95% CI -2.40 to -0.66, Analysis 4.2) and the average daily dose: 0.52 (SD 0.28) mg/kg in the plasma exchange group versus 0.97 (SD 0.33) mg/kg in the prednisolone-only group. They found a similar side-effect profile in both groups and the disease was controlled within about four weeks in both groups.

However, this favourable effect of adding plasma exchange was not seen in the [Guillaume 1993](#) study for disease control at 6 months: 9/31 prednisolone plus plasma exchange vs 13/31 prednisolone (RR 0.69, 95% CI 0.35 to 1.38, [Analysis 4.1](#): see [Analysis 4.1.3](#)). The report of the study indicates that the trial was "interrupted after the interim analysis showed no appreciable benefit resulting from the addition of azathioprine or plasma exchange to prednisolone" at four weeks or at six weeks follow-up.

### Secondary outcomes

#### Mortality and adverse effects

In [Guillaume 1993](#) mortality at 6 months was assessed as mortality alone (3/31 vs 5/31, RR 0.60, 95% CI 0.16 to 2.30, [Analysis 4.4](#): see [analysis 4.4.3](#)), or total adverse events including mortality (10 major adverse events including 5 deaths in the prednisolone, versus 6 major adverse events including 3 deaths in the plasma exchange group) (RR 0.60, 95% CI 0.25 to 1.45, [Analysis 4.3](#)) ([Guillaume 1993](#)).

In [Roujeau 1984](#) no deaths occurred during the treatment period ([Analysis 4.4](#)). There were only 25 of the participants available for follow up, that is after the initial treatment period which included 41 original participants, of which only 37 were analysed by the trial authors because they were lost early in the treatment period. Of those 25 participants available for follow up, 2 participants died in the prednisolone group, and 1 in the prednisolone plus plasma exchange group (the calculation for the worst case scenario includes the 4 lost participants, 2 in each group).

### Prednisolone plus azathioprine versus prednisolone plus plasma exchange

#### Primary outcome

##### Regression or healing of skin lesions

Comparing the prednisolone plus azathioprine group with the prednisolone plus plasma exchange group ([Guillaume 1993](#)), no significant differences were found for disease control at 6 months: 14/36 and 9/31 respectively (RR 1.34, 95% CI 0.67 to 2.66, [Analysis 5.1](#)).

### Secondary outcomes

#### Mortality and adverse effects

Mortality at 6 months in [Guillaume 1993](#) was 6/36 (azathioprine) versus 3/31 (plasma exchange) (RR 1.72, 95% CI 0.47 to 6.32, [Analysis 5.2](#)). Total adverse events including deaths were more often noted in the azathioprine group (15/36 total adverse effects (including 6 deaths) versus 6/31 (including 3 death) in the plasma exchange group). The results almost reach statistical significance with regard to total adverse events, including mortality at 6 months in favour of the plasma exchange plus prednisolone group (RR 2.15, 95% CI 0.95 to 4.87, [Analysis 5.3](#)).

### Prednisone versus tetracycline and nicotinamide

#### Primary outcome

##### Regression or healing of skin lesions

Comparing prednisone with tetracycline and nicotinamide ([Fivenson 1994](#)), 1 complete and 5 partial responders were reported in the steroid group (n = 6), compared with 5 complete, 5 partial responders, 1 non-responder, and 1 disease progression in the tetracycline group (n = 12). Two participants in the tetracycline

group were unavailable for follow-up at 8 weeks (together n = 14). The results are not statistically significant for either complete response (RR 2.50, 95% CI 0.37 to 16.89, [Analysis 6.1](#)) or complete and/or partial response (RR 0.87, 95% CI 0.62 to 1.22, [Analysis 6.1](#)). The data for the non-responder (n = 1), the participant whose disease progressed (n = 1), and the two participants that were lost to follow up (n = 2) in the tetracycline group are not shown in the table.

### Secondary outcomes

#### Duration of remissions

Of the participants available for long-term follow-up in [Fivenson 1994](#), all 5 in the tetracycline group remained disease-free (mean 17.5 weeks) while 2 of the 3 in the steroid group had repeated flare-up with tapered off treatment (mean 21.3 weeks). Unfortunately, this trial included very few participants, two thirds of whom were in the tetracycline group (14 of 20 participants). The randomisation in this study was unclear and there was a high dropout rate (2/20 at 8 weeks and a further 10 participants at the end of study). At 10 months there were only 3 participants left in the steroid group (2 of whom had multiple recurrences with tapering of medication), and only 5 participants remained in the nicotinamide plus tetracycline group, all of whom remained disease-free during medication tapering.

#### Adverse effects

The report of the study states that "fewer short-term and long-term adverse effects occurred in the participants treated with the nicotinamide/tetracycline combination compared with prednisone therapy" (there was also one death due to sepsis in the prednisone group ([Analysis 6.2](#))). Most of the side-effects in the tetracycline/nicotinamide group in [Fivenson 1994](#) were mild (two participants developed gastrointestinal symptoms which resolved after substitution of tetracycline with minocycline, one of them developed tinnitus on minocycline which resolved despite continuing treatment. One participant in the latter group developed severe tubular necrosis. He had been enrolled in the study with elevated serum creatinine (159 which peaked at 654 micromol/L: normal 60 to 120 micromol/L) and was also taking nonsteroidal anti-inflammatory drugs (ibuprofen and aspirin). This participant's renal function returned to normal within two weeks of stopping treatment.

### Very potent topical steroids (clobetasol propionate) versus prednisone

The largest study had two study groups with the study stratified by severity of disease ([Joly 2002](#)):

1. Moderate disease (less than 10 new blisters a day): topical steroids (initial dose of 40 g of 0.05% clobetasol propionate twice daily applied to entire body surface) (77 participants), and oral prednisone 0.5 mg/kg (76 participants).
2. Extensive disease (more than 10 new blisters a day): topical steroids (93 participants), and oral prednisone 1 mg/kg (95 participants).

#### Primary outcome

##### Regression or healing of skin lesions

In the moderate disease group differences were seen between the topical steroid and 0.5 mg/kg oral steroid groups in terms of rate of

disease control at 3 weeks: 100% vs 94% (RR 1.06, 95% CI 1.00 to 1.12, [Analysis 7.1](#); see [Analysis 7.1.1](#)) ( $P = 0.07$ ).

Both interventions resulted in nearly 100% of participants experiencing disease control. The disease was controlled in 99% of the participants with extensive disease using topical steroids versus 91% of those on oral steroids at 3 weeks. This reached statistical significance (RR 1.09, 95% CI 1.02 to 1.17, [Analysis 7.1](#); see [Analysis 7.1.2](#)) ( $P = 0.01$ ), although this outcome was not assessed blindly, and therefore the possibility of bias exists.

### Secondary outcomes

#### Adverse effects

The incidence of severe complications was reported for people with extensive disease: 29% for topical steroids versus 54% for oral steroids (RR 0.54, 95% CI 0.37 to 0.78,  $P = 0.001$ ), which is statistically significant, i.e. there were fewer adverse events due to clobetasol ([Analysis 7.2](#); see [analysis 7.2.2](#)). But this was not statistically significant in the moderate disease group (32% vs 38%, RR 0.85, 95% CI 0.55 to 1.31, [Analysis 7.2](#)) ( $P = 0.46$ ) ([Joly 2002](#)).

#### Mortality (survival)

The major outcome in this study was survival, the study being designed to have 80% power to detect a reduction in the 1-year mortality rate for both moderate and extensive bullous pemphigoid. To achieve this power, 75 participants were needed in each treatment group, which was accomplished.

In the extensive disease group, those using topical steroids had a better survival rate at 1 year compared to those on oral steroids (76% versus 58%, RR 0.58, 95% CI 0.37 to 0.89, [Analysis 7.3](#); see [analysis 7.3.2](#)) (statistically significant:  $P = 0.01$ ). This was consistent with the incidence of severe complications in the people with extensive disease. In the moderate disease group no significant differences were seen between the topical steroid and 0.5 mg/kg oral steroid groups in terms of overall survival (30% vs 30%, RR 0.99, 95% CI 0.61 to 1.60, [Analysis 7.3](#)) ([Joly 2002](#)).

### Standard dose (40 g/day) of very potent topical steroids versus mild dose (10 to 30 g/day)

A second large study from the same French group was recently published to compare two different regimens of topical steroids ([Joly 2009](#)). In the mild regimen of [Joly 2009](#), participants received different amounts of clobetasol propionate cream depending on their body weight and severity of the disease (moderate disease ( $\leq 10$  new blisters/day): 69 participants received 20 g/day if their body weight was  $> 45$  kg and 10 g/day if  $< 45$  kg) (severe disease ( $> 10$  new blisters/day): 90 participants received 30 g/day if their body weight was  $> 45$  kg and 20 g/day if  $< 45$  kg), in the standard regimen all participants received 40 g of the cream/day (moderate disease  $n = 65$ , severe disease  $n = 88$ ).

#### Primary outcome

##### Regression or healing of skin lesions

The report of the study has a discrepancy in the number of participants who were evaluated at 21 days and states that 150/153 participants were evaluable, as 3 included participants were lost to follow up early after the initiation of treatment and were not available for evaluation of efficacy at day 21. However, disease control rates at 21 days are given for 153/153 participants. We

wrote to the study investigator for clarification ([Joly 2010](#)), who confirmed that the published report contains a typographical error. The correct figures are: 153 participants randomised, 150 analysed. We carried out an analysis of the results using the randomised number of participants ( $n = 153$ ). In the mild regimen 156/159 participants were controlled by day 21 and in the standard regimen 150/153 (RR 1.00, 95% CI 0.97 to 1.03, [Analysis 8.1](#); see [Analysis 8.1.1](#)) (not statistically significant  $P = 0.96$ ).

In the report of the study, participants and their responses to the treatment regimens were stratified by severity of disease. Using the correct figures supplied by the study investigator ([Joly 2010](#)), of those with moderate disease, disease control was achieved in 68/69 using the mild regimen, and with the standard regimen 63/65 were controlled (RR 1.02, 95% CI 0.97 to 1.07, [Analysis 8.1](#); see [Analysis 8.1.2](#)). Of those with extensive disease, 88/90 achieved disease control in the mild regimen and 87/88 were controlled with the standard regimen (RR 0.99, 95% CI 0.95 to 1.03, [Analysis 8.1](#); see [Analysis 8.1.3](#)).

The median cumulative doses of cream used during the study period were 5760 g in the standard regimen versus 1314 g (mild regimen), which is a 70% reduction in cumulative doses of corticosteroid.

### Secondary outcomes

#### Duration of remissions

There were 67 relapses in 159 participants in the mild regimen and 52 in 153 participants in the standard regimen (RR 1.24, 95% CI 0.93 to 1.65, [Analysis 8.2](#)). This was not significantly different between the two groups. There is insufficient evidence to say that one treatment regimen is different from the other in terms of effectiveness.

#### Adverse effects

Eighty-nine participants in each group had severe adverse events. This consisted of 194 events in 89 participants in the mild regimen group and 227 in the standard regimen group. There were 42 life-threatening adverse effects in 33 participants. The main severe side-effects in both groups were diabetes mellitus ( $n = 34$  standard,  $n = 18$  mild), cardiovascular and neurovascular disorders in  $n = 35$  (standard) and  $n = 21$  participants (mild), and severe infections in 32 and 27 participants, in the standard and mild regimen groups respectively. There were also cutaneous side-effects which included purpura, severe skin atrophy, and striae.

#### Mortality

In the mild regimen 60/159 participants had died by year 1 (moderate disease 19/69, severe disease 41/90) and in the standard regimen 58/153 (moderate disease 21/65, severe disease 37/88). This was not statistically significant between the 2 groups for those participants with moderate (RR 0.85, 95% CI 0.51 to 1.43) or extensive (RR 1.08, 95% CI 0.78 to 1.51) disease ([Analysis 8.3](#)).

The report of the study gives an adjusted analysis (Cox model adjusted for age and Karnofsky score), after which a beneficial effect of the mild regimen was observed in participants with moderate BP, with an almost twofold decrease in the risk of death or life-threatening adverse events relative to the standard regimen (hazard ratio = 0.54, 95% confidence interval, 0.30 to 0.97;  $P = 0.039$ ).

## Jingui Shenqi Pill (JSP) 1# bid plus prednisone versus prednisone

The Jingui Shenqi Pill (JSP) 1# bid plus prednisone 0.5 to 1.0 mg/kg/day was compared to prednisone alone 0.5 to 1.0 mg/kg/day in a small trial ([Liu 2006](#)). Thirty participants with bullous pemphigoid were included, the primary clinical outcome was healing of the skin lesions after 4 weeks treatment.

A cure was defined as > 90% of the total number of lesions being healed, moderate healing if only 60% to 89% of the affected area had healed, improved if 30% to 59% of the lesions had healed, and not effective if less than 30% of the lesions had healed.

### Primary outcome

#### Regression or healing of skin lesions

Complete healing of the lesions at 4 weeks was achieved in 1 participant receiving the Jingui Shenqi Pill (1/15) and none in the prednisone group (0/15) (RR 3.00, 95% CI 0.13 to 68.26, [Analysis 9.1](#)). Partial healing was achieved in 13 of 15 with JSP treatment compared with 11 of 15 participants with prednisone-only treatment (RR 1.18, 95% CI 0.82 to 1.70, [Analysis 9.1](#)).

Overall, the treatment was effective (some degree of healing) in 14/15 participants (93.33%) of the treatment group compared to 11/15 (73.33%) of the prednisone group (RR 1.27, 95% CI 0.91 to 1.78, [Analysis 9.1](#)). None of the results were statistically significant.

### Secondary outcomes

#### Mortality

No deaths were reported during the four-week follow-up ([Liu 2006](#)).

## Azathioprine plus corticosteroid versus mycophenolate mofetil plus corticosteroid

### Primary outcome

#### Regression or healing of skin lesions

Comparing azathioprine (2 mg/kg/day) and mycophenolate mofetil (MMF) (2000 mg twice/day) both in addition to oral methylprednisolone (0.5 mg/kg/day), all participants achieved some degree of healing (either partial or complete).

In this trial complete healing and disease remission was defined as complete re-epithelialisation of all lesions. 35/38 of the azathioprine group and 35/35 of the MMF group showed complete healing (92% vs 100%) (RR 0.92, 95% CI 0.83 to 1.03, [Analysis 10.1](#)) ([Beissert 2007](#)). Participants showed complete healing after 23.8 ± 18.9 days and 42.0 ± 55.3 days for azathioprine and mycophenolate mofetil respectively, but this difference was not statistically significant (unpaired t-test).

Three participants in the azathioprine group showed partial healing (RR 6.46, 95% CI 0.35 to 120.81, [Analysis 10.1](#)) (not statistically significant), 2 of whom died of unrelated cause, leading to premature discontinuation of the treatment, and 1 was lost to follow up before treatment was completed.

### Secondary outcomes

#### Duration of remissions (weeks)

The disease-free interval between complete remission and recurrence of lesions (new blister formation) was 23.5 weeks ± 19.4

weeks for azathioprine and 18 weeks ± 12.8 weeks for MMF, that is 5.50 more weeks of remission for those participants treated with azathioprine, but this difference was not statistically significant (unpaired t-test).

### Adverse effects

Nine (24%) grade 3/4 adverse effects are described in the azathioprine group, and 6 (17%) in the MMF group. There were more elevated liver function tests in the azathioprine group (6/37 vs 1/35), however, participants were not checked for thiopurinemethyltransferase activity prior to treatment. There was no statistical difference between treatments for any of the outcomes.

### Mortality

There were two deaths in the azathioprine group, described as not treatment-related.

## DISCUSSION

### Summary of main results

Ten studies were included in this review (7 studies were previously included; in this updated review 3 new studies were found and included: [Beissert 2007](#), [Joly 2009](#), and [Liu 2006](#)). The studies in this review used oral prednisolone or prednisone in the control group (there were no comparisons with placebo) and were all small trials apart from two studies comparing different amounts of topical steroids and oral steroids ([Joly 2002](#); [Joly 2009](#)). For the purposes of this review prednisone and prednisolone are regarded as bio-equivalent.

No meta-analysis was possible because of the clinical heterogeneity of the studies in terms of interventions, measures of disease control, and follow-up. The three studies that had overlapping treatments compared prednisone versus prednisone plus azathioprine ([Burton 1978](#)), prednisolone versus prednisolone plus plasma exchange ([Roujeau 1984](#)), and prednisolone alone, with azathioprine and with plasma exchange ([Guillaume 1993](#)), but they were heterogenous especially in terms of the doses of treatment used.

### Overall completeness and applicability of evidence

The outcome measures in these studies are very varied, as can be seen when looking at the definition of disease control and the interventions used (see [Characteristics of included studies](#)). Our primary outcome was regression or healing of skin lesions; we did not pre-specify the follow-up times in our protocol as there is no established optimum treatment for BP ([Wojnarowska 2002](#)) and we did not want to exclude potentially effective therapies from our analyses because they did not meet strict inclusion criteria in relation to follow up times. We found that there were relatively few reports of trials for this rare disease and that there is variation in the time points reported.

Some of the included studies reported short follow-up periods (only 10 days in [Dreno 1993](#)), which makes judgment of the practical significance of the results difficult, especially in view of the chronic nature of this disease. One study ([Morel 1984](#)) compared the starting dose of prednisolone, and reported results at 21 and 51 days, so perhaps the follow-up of 51 days may be more reasonable. We reported the results of that study at both



time points in this review, although there were no significant differences in healing when the length of time or the dose given were compared. The [Burton 1978](#) trial had the longest follow-up period but unfortunately details on how disease control was evaluated are not given and few clinical data were available. Participants with contraindications to oral steroids or azathioprine and those "unlikely to attend follow-up" were excluded from the trial.

The [Fivenson 1994](#) study had an unclear method of randomisation, a high dropout rate, and small numbers, but may suggest some merit in the use of tetracycline and nicotinamide. However, further study is needed to confirm these findings.

Probably the most interesting feature of the [Roujeau 1984](#) study was the lower doses of prednisolone used in both treatment groups. Strict measures of disease control were used (complete disappearance of blisters, pruritus, and erythema) and in both groups the disease was controlled within about 4 weeks in all participants; however, higher doses than the initial low dose of 0.3 mg/kg prednisone were needed in all participants of the prednisolone-only group and in two thirds of the participants in the plasma exchange group to achieve disease control. There were no deaths during the study but this may be partly because of the exclusion of participants older than 80 years of age. This study found that the plasma exchange group required much less prednisolone than the prednisolone-only group. This benefit was, however, not confirmed by [Guillaume 1993](#). This latter study also failed to confirm the benefit of the addition of azathioprine to prednisolone. [Beissert 2007](#) added either azathioprine or mycophenolate mofetil to an initial dose of 0.5 mg methylprednisolone/kg/day; there was no difference in effectiveness. The cumulative steroid dose until the end of the documentation (> 720 days) was  $4967 \pm 12191$ mg for the azathioprine group and  $5754 \pm 9693$ mg for the MMF group. The similarity between the two groups possibly reflects a comparable immunosuppressive effect of the two drugs. Interestingly, there were more participants with severe disease in the azathioprine group: 53% had  $\geq 20\%$  body surface area involvement compared to only 27% in the MMF group.

In a small, methodologically unclear trial [Liu 2006](#) added the Jingui Shenqi Pill to oral steroids and described a beneficial effect after four weeks treatment compared to the control group. They found an increased expression of glucocorticosteroid receptor (GCr)  $\alpha$  and a decreased expression of GCr  $\beta$  in skin lesions of the treatment group which may improve the sensitivity of the skin to glucocorticosteroids. However, the effectiveness of this intervention was not proven in our analyses.

As it is unlikely that future studies on interventions for bullous pemphigoid including a placebo group would be ethically justifiable, a comparison of low-dose prednisolone with tetracyclines and nicotinamide (or potent topical corticosteroids, for mild and/or localised disease) may prove a worthy alternative. Uncontrolled studies have suggested the successful use of topical steroids as first-line for the treatment of both localised and mild disease ([Garg 1994](#); [Rollin 1993](#); [Zimmermann 1999](#)), and two recent randomised controlled trials ([Joly 2002](#); [Joly 2009](#)) confirm this view. The use of potent topical steroids is favoured because they have minimal side-effects and a limited number of contraindications. [Joly 2002](#) showed a significant benefit of 40 g 0.05% clobetasol propionate cream/day over 1 mg/kg of

prednisone in extensive disease for disease control, adverse events, and mortality. No statistically significant differences between clobetasol propionate cream and 0.5 mg/kg prednisone were found in the moderate disease group for disease control, adverse events, and mortality.

However, even though there were less severe adverse effects (pneumonia, diabetes requiring insulin, myocardial infarction, psychiatric symptoms, stroke, thrombosis, bone fracture) noted in the group of participants treated with prednisone 1 mg/kg, it is not mentioned if participants in the different groups had similar adverse effects regarding, for example, blood pressure and bone mineral density. Also, the effort needed in applying the creams twice daily to the whole body is a major limitation in people with BP, who are mostly elderly and may have other co-existing disease. Another aspect is that topical preparations may be more costly than oral cortisone preparations and nursing care may be costly too.

It is likely that very potent topical corticosteroids applied in such large quantities may have systemic effects (perhaps comparable to 0.5 mg/kg/day prednisone). However, we do expect that there is also a local immunosuppressive and anti-inflammatory effect of the topically applied corticosteroids, because there are reports of participants with localised BP effectively treated with potent topical steroids only. In fact, a later trial by the same group shows that less topical steroids ( $\leq 30$  g 0.05% clobetasol propionate cream/day) are as effective in disease control after 21 days, and that the mean cumulative dose was 71% lower in a mild treatment regimen than in a standard treatment regimen. The mild regimen was associated with less severe adverse effects ([Joly 2009](#)).

An important research question for the future is to evaluate whether a lower dose of steroid (0.5 mg/kg/day) would be adequate for disease control in extensive disease when compared with standard higher doses.

### Quality of the evidence

Most of the studies were very small and of poor methodological quality because of:

- an unclear method of randomisation;
- lack of blinding in the majority of studies; and
- exclusion of dropouts from the analysis in most studies.

This is summarised in [Figure 1](#).

Some studies which did not describe the method of randomisation were published some time ago (e.g. [Burton 1978](#); [Dreno 1993](#); [Morel 1984](#)); we did not attempt to gain further information as it was unlikely that further details of the studies would be available.

The main concern with [Liu 2006](#) is that in the published report of this study it was not absolutely clear that the diagnosis of BP was confirmed by immunofluorescence. The report of the trial was translated from Chinese and refers to the confirmation of the diagnosis listing the usual clinical features, histology, direct immunofluorescence, indirect IF on salt split skin and immuno EM, using a method given in a reference. The source of the methods in the reference was translated but it was unclear which of the methods listed were used. We contacted the trial investigators on two occasions, regarding the method used to confirm diagnosis, but did not receive a reply. Given that the description of the

diagnosis of BP in the published report is not precise, it is possible that inclusion of the trial into a meta-analysis could introduce bias. However, Chinese traditional medicine plus prednisone was not shown to be effective in this single trial.

In [Burton 1978](#) there may have been selection bias, as participants were "started on oral prednisone 30 to 80 mg/day, to suppress new blisters" and only then "did the consultant decide whether to include the participant in the trial". Also [Joly 2002](#) switched three participants from one intervention group to another because of side-effects of treatment, although this was done in accordance with the study protocol.

The [Guillaume 1993](#) study was stopped after the interim analysis became available which showed no appreciable benefit resulting from the addition of azathioprine or plasma exchange to prednisolone. The trial investigators calculated that "the inclusion of 120 participants as initially scheduled, could not change these negative results". The [Fivenson 1994](#) study was terminated after 20 participants were enrolled (the study was originally designed to randomise 96 participants in 4 centres). No reasons were given for this early ending but a further randomised, double-blind, multicentre trial was mentioned as being 'underway' in the published report of the trial. We have attempted to contact the trial investigators but have been unsuccessful in obtaining any further details or data from the later study.

Overall, there were relatively few included studies of and these were of variable methodological quality, therefore some caution should be exercised in interpreting the results. Additionally no statistical pooling of the data was possible because of the clinical heterogeneity of the studies in terms of interventions, measures of disease control, and follow-up.

### Agreements and disagreements with other studies or reviews

The last published version ([Khumalo 2005](#)) of this review had seven included randomised controlled trials. The authors concluded at that time that oral corticosteroid drugs were the most common treatment, but may have been associated with serious adverse effects, including some deaths. The review concluded that more research was needed on treatments for BP; however, strong corticosteroid creams appeared safe and effective and lower doses of oral corticosteroids could be effective also in severe disease with fewer adverse effects than usual doses.

Since the review was last updated we have found and included three new RCTs but our conclusions have not changed greatly: very potent topical steroids are effective and safe treatments for bullous pemphigoid. Their use in extensive disease may be limited by side-effects and practical factors; new evidence suggests that milder regimens are safe and effective in moderate BP ([Joly 2009](#)). Starting doses of prednisolone greater than 0.75 mg/kg/day do not give additional benefit; lower doses may be adequate to control disease and reduce the incidence and severity of adverse reactions. One new included study investigated the addition of a Chinese herbal medicine (Jinqi Shui pill) to prednisone, but this was not more effective ([Liu 2006](#)). The third newly included study, [Beissert 2007](#), compared oral methylprednisolone plus azathioprine versus oral methylprednisolone plus mycophenolate mofetil, but no significant differences between the two therapies were observed. The effectiveness of adding plasma exchange, or

azathioprine to corticosteroids has therefore not been established, a conclusion which is unchanged from the previous published version of this review. There was no new information about combination treatment with tetracycline and nicotinamide to add to this review, therefore further research is needed to determine if this therapy might be helpful.

We identified seven ongoing trials from the updated searches: [ACTRN12607000104459](#) (rituximab), [NCT00286325](#) (rituximab), [NCT00472030](#) (omalizumab), [NCT00525616](#) (rituximab (Mabthéra)), [NCT00802243](#) (leflunomide), [NCT00809822](#) (NPB-01 (intravenous immunoglobulin)), and [ISRCTN13704604](#) (doxycycline versus prednisolone).

The latter study ([ISRCTN13704604](#)) investigates the effectiveness of doxycycline versus 0.5 mg/day prednisolone in the treatment of bullous pemphigoid. The primary outcomes are effectiveness measured by a blinded blister count at week six and safety, measured by the number of adverse events related to the trial medication which occur during the year of follow-up; results will be available by October 2013.

Monoclonal antibody therapies could offer alternatives to long-term steroid use, or may permit the dose of steroids or immune suppressive drugs to be reduced. Four of these ongoing studies are investigating the use of such biological agents. The use of rituximab as an adjuvant treatment in BP is being studied in [ACTRN12607000104459](#), and the efficacy and tolerance of a single cycle of rituximab in the control of bullous pemphigoid is being examined in [NCT00525616](#). The safety and efficacy of omalizumab is being tested in [NCT00472030](#), and the safety of treatment of bullous pemphigoid in participants resistant to therapy with systemic corticosteroids, with rituximab plus systemic corticosteroids in [NCT00286325](#). However, results from randomised controlled trials were not available at the time of this update, and while monoclonal antibody therapy may have a role to play in treatment of BP, it is not without adverse reactions including infusion reactions, fever, neutropenia, chills, increased risk of infection, weakness, and fatigue. Participants would potentially also require re-treatment with monoclonal antibodies, and there is a risk of neutralising antibodies that would interfere with therapeutic efficacy. Furthermore, it is a very costly treatment and will probably be reserved for treatment-resistant cases. The efficacy and safety of newer biology therapies (monoclonal antibodies) such as rituximab should be investigated in the context of randomised controlled trials.

## AUTHORS' CONCLUSIONS

### Implications for practice

- Starting doses of prednisolone greater than 0.75 mg/kg/day do not seem to give additional benefit, and it would appear that lower doses (0.5 mg/kg/day) may be adequate for disease control in more participants than was previously believed. This would be expected to reduce the incidence and severity of adverse reactions (especially death) associated with treatment.
- Very potent topical steroids (clobetasol propionate) are an effective treatment for bullous pemphigoid. They seem to have less serious adverse effects compared to high-dose systemic steroids, however, their use in extensive disease may be limited by practical factors (ability of participant or availability of carer to apply the treatment). When feasible they should

be considered for first-line treatment, especially in localised disease. However, if large quantities are needed to be applied topically, they may be associated with systemic absorption and adverse events. It would be helpful to determine serum cortisol levels with the use of topical steroid therapies.

- The effectiveness of the addition of plasma exchange, azathioprine, or mycophenolate mofetil to prednisolone or prednisone, has not been established. The addition of a Chinese traditional herbal medicine to prednisone was not beneficial.
- Combination treatment with tetracycline and nicotinamide may be useful, although this needs further validation.

### Implications for research

- Double-blind studies are needed to confirm the appropriate oral steroid doses for the treatment of bullous pemphigoid.
- Blinded RCTs comparing topical steroids with low doses of prednisolone/prednisone and with (less toxic) systemic treatments such as tetracycline and nicotinamide are needed.
- The efficacy and safety of newer biologic therapies (monoclonal antibodies) such as rituximab, should be investigated in the context of randomised controlled trials.

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Wojnarowska F, Eady RAJ, Burge SM. Bullous pemphigoid. In: Champion RH, Burton JL, Burns DA, Breathnach SM editor(s).

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#### Wojnarowska 2002

Wojnarowska F, Kirtschig G, Highet AS, Venning VA, Khumalo NP. Guidelines for the management of bullous pemphigoid. *British Journal of Dermatology* 2002;**147**(2):214-221.

#### Zillikens 1995

Zillikens D, Wever S, Roth A, Weidenthaler-Barth B, Hashimoto T, Bröcker EB. Incidence of autoimmune subepidermal blistering dermatoses in a region of central Germany (Comment). *Archives of Dermatology* 1995;**131**(1):48-52.

#### Zimmermann 1999

Zimmermann R, Faure M, Claudy A. Prospective study of treatment of bullous pemphigoid by a class I topical corticosteroid. *Annales de Dermatologie et de Vénérologie* 1999;**126**(1):13-6.

### References to other published versions of this review

#### Khumalo 2002

Khumalo NP, Murrell DF, Wojnarowska F, Kirtschig G. A systematic review of treatments for bullous pemphigoid. *Archives of Dermatology* 2002;**138**(3):385-9.

#### Khumalo 2005

Khumalo N, Kirtschig G, Middleton P, Hollis S, Wojnarowska F, Murrell DF. Interventions for bullous pemphigoid. *Cochrane Database of Systematic Reviews* 2005, Issue 3. [DOI: [10.1002/14651858.CD002292.pub3](https://doi.org/10.1002/14651858.CD002292.pub3)]

\* Indicates the major publication for the study

## CHARACTERISTICS OF STUDIES

### Characteristics of included studies [ordered by study ID]

#### Beissert 2007

Methods	Multicentre in Germany, central randomisation, not blinded  2 parallel groups; initial dose was maintained until blister formation ceased and re-epithelialisation started. Corticosteroid dose was then reduced every 2 weeks; after discontinuation of corticosteroid, azathioprine, or mycophenolate mofetil (MMF) dose was maintained for 4 more weeks, then reduced (see taper regimen page 1537)  Follow-up of 720 days
Participants	73 participants with bullous pemphigoid, confirmed by direct and indirect immunofluorescence on salt split skin
Interventions	A: 38/38 oral methylprednisolone 0.5 mg/kg/day plus azathioprine sodium 2 mg/kg/day.

**Beissert 2007** (Continued)

B: 35/35 oral methylprednisolone 0.5 mg/kg/day plus mycophenolate mofetil 2000 mg/day (tapering described on page 1537).

Outcomes	Primary: <ol style="list-style-type: none"> <li>1. Complete healing (complete reepithelialisation of all lesions)</li> <li>2. Cumulative steroid dose (until end of documentation &gt; 720 days) (Table 2)</li> </ol> Secondary: <ol style="list-style-type: none"> <li>1. Duration of remission (disease-free interval)</li> <li>2. Safety profiles</li> </ol>
Notes	Cumulative corticosteroid dose: described as primary outcome until complete healing was achieved (page 1537); on page 1539 the cumulative corticosteroid dose was defined as corticosteroid dose until the end of the documentation period (> 720 days) (Table 2, Table 3). We presumed that calculated cumulative corticosteroid dose is calculated until the end of the documentation period.

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was stratified according to the clinical centre and performed centrally with the use of random number of three for each stratum." (Page 1537)
Allocation concealment (selection bias)	Unclear risk	Allocation concealment is not well described.
Blinding (performance bias and detection bias) All outcomes	High risk	Intentionally not blinded by trial investigators.  Quote: "Since complete healing was a primary outcome measure, blinding was not considered necessary." (Page 1537)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Yes. In <a href="#">Beissert 2007</a> 1 participant was lost, 2 died of treatment unrelated causes - they were included in the intention-to-treat analysis.  The same number of participants who started the trial were analysed at the end of the trial. (Figure 1, page 1538)
Selective reporting (reporting bias)	Low risk	Outcomes reported for both outcome measures.  Primary: <ol style="list-style-type: none"> <li>1. Complete healing</li> </ol> Secondary: <ol style="list-style-type: none"> <li>1. Cumulative corticosteroid doses used</li> </ol>
Other bias	Low risk	No other bias.

**Burton 1978**

Methods	Randomised but not blind  Intervention took place over 3 years, treatment maintained at starting doses until 'rash suppressed' at which point prednisone doses were gradually reduced in both groups. If rash did not recur then also azathioprine was gradually withdrawn in the azathioprine group
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**Interventions for bullous pemphigoid (Review)**

**Burton 1978** (Continued)

Follow-up: at the end of the 3-year treatment period

Participants	25 participants with BP confirmed by IF studies
Interventions	A: 12/12 participants prednisone (30 to 80 mg/day) + azathioprine (2.5 mg/kg/day). B: 13/13 participants prednisone (30 to 80 mg/kg/day).
Outcomes	Unclear outcome measures: <ol style="list-style-type: none"> <li>1. Whether azathioprine + prednisolone (synergistic immunosuppression) associated with increased risk of malignancy</li> <li>2. Disease control</li> <li>3. Cumulative dose of prednisone in both groups</li> <li>4. Mortality</li> </ol>
Notes	After 1 week of prednisolone to suppress lesions, consultant decided whether to include in trial. Not clear how prednisolone dose decided or numbers of participants on lower or higher doses in each group

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details given.
Allocation concealment (selection bias)	Unclear risk	Quote: "Once included, each participant was randomly assigned .....by the ward sister who drew a marked paper from an envelope." (Page 1190)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Unclear. Unlikely as the intervention group (azathioprine) were monitored by frequent blood testing.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear. The results section states that 25 participants completed a 3-year follow-up, but it is unclear how many were randomised to each group at the start. Table 1 page 1190 reports outcomes over 3 years for all 25 participants.
Selective reporting (reporting bias)	Unclear risk	Outcome measures were not clearly stated.
Other bias	Unclear risk	Only those participants who were likely to attend for follow up were recruited. Eligibility was also determined by the consultant doctor after baseline testing.  Baseline imbalance: There were more participants with severe disease in the azathioprine group, 53% had $\geq 20\%$ body surface area involvement compared to only 27% in the MMF group.

**Dreno 1993**

Methods	Randomised, double-blind  Disease control = reduction of blisters, redness & itch > 50%  Follow-up: 10 days (= treatment period)
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**Dreno 1993** (Continued)

Participants	57 participants with BP confirmed by IF studies
Interventions	A: 29/29 participants prednisolone (1.16 mg/kg/day). B: 28/28 participants methylprednisolone (1.17 mg/kg/day).
Outcomes	1. Number of blisters 2. Extent of erythema scale: 0 (absent) to 3 (severe) 3. The intensity of pruritus (itch), scale 0 (absent) to 3 (severe), at days 5 and 10
Notes	Problem: 'scale' for measuring symptoms & signs. Very short study duration

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The study was randomised.
Allocation concealment (selection bias)	Unclear risk	Unclear.
Blinding (performance bias and detection bias) All outcomes	Low risk	Yes: double-blind.  Quote: "Taking into account the difference in presentation between the 2 products, the supply of the products to the participants was made by a person other than the investigator; additionally clinical follow-up after the end of the study was done by a masked (blinded) investigator." (Translation, page 518)
Incomplete outcome data (attrition bias) All outcomes	Low risk	29/29 evaluated at both time points for prednisolone group. 27/28 evaluated at both times points for the methylprednisolone group. 1 participant dropped out (ceased treatment) after 8 days of treatment, due to a coma unrelated to the treatment (page 519).
Selective reporting (reporting bias)	Low risk	All outcomes (number of blisters, itching, and redness) reported on at 5 and 10 days of treatment.
Other bias	Unclear risk	Short study duration. Non-validated assessment scales.

**Fivenson 1994**

Methods	Randomised open-label, but randomisation method not stated, not blind  Disease control after 8 weeks Rx: complete response = 100% clearing of all lesions, partial response $\geq$ 50%, no response < 25%.  Pruritus and physician's global assessment were also recorded.  Disease recurrence in the follow up period was recorded if: new blisters, urticarial lesions and/or crusts were noted.  Follow-up: 10 months (= treatment period)
Participants	20 participants with BP confirmed by IF studies
Interventions	A: 6/6 participants prednisone 40 to 80 mg/day.

**Interventions for bullous pemphigoid (Review)**

**Fivenson 1994** (Continued)

B: 14/14 participants nicotinamide 1500 mg/day in 3 divided doses + tetracycline 2 g/day 4 divided doses.

Outcomes	1. Number of bullous, crusted, urticarial lesions as follows: none = 0, 1 to 5 = 1+, 6 to 10 = 2+, 11 to 20 = 3+, 20 to 40 = 4+, more than 40 lesions = 5+. All three of these recorded as less than or more than 1 cm in size. Total highest score possible on each visit per participant. Mean scores for each group used to calculate P values
Notes	Not clear how the prednisone dose was decided or number of participants on higher or lower dose

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details given.
Allocation concealment (selection bias)	Unclear risk	Unclear; no details given.
Blinding (performance bias and detection bias) All outcomes	High risk	Not blind, described as "open-label" (page 753).
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	20 were randomised, 18 were treated.  2 were unavailable for follow up within the initial 8 weeks, both from the tetracycline/nicotinamide group. There was 1 death in the prednisone group due to sepsis complicated by aspiration pneumonia, the time point was not given but the participant was available for follow up at week 8 as the results for all 8 participants who received prednisolone is given in Table 1 (page 755).  At longer term follow-up, only n = 3 in the prednisolone group and n = 5 in the tetracycline/nicotinamide group are reported, no detail of the reasons for loss to follow up at this later follow-up were reported.
Selective reporting (reporting bias)	Low risk	All outcomes reported at each time point.
Other bias	Unclear risk	Unclear if the participant groups were equivalent with respect to disease severity or demographics at the start of the therapy.

**Guillaume 1993**

Methods	Randomised, not blind  Disease control = no new blisters for 4 weeks, prednisolone dose decreased gradually to 0.5 mg/kg at 3 months and 0.2 mg/kg at 6 months  Follow-up: 6 months (= treatment period)
Participants	100 participants with BP confirmed by IF studies
Interventions	31/32 participants prednisolone 1 mg/kg/day versus 36/36 participants azathioprine + prednisolone 1 mg/kg/day versus 31/32 participants plasma exchange + prednisolone 1 mg/kg/day.

**Guillaume 1993** (Continued)

Outcomes	1. Disease control: No more than 1 new blister in the 4 weeks after starting treatment, these participants were followed up a further 6 months. Resolution of erythema and no more than minimal pruritus
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Notes	Trial stopped at interim period due to no appreciable benefit
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**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised. Quote: "According to pre-established randomisation lists equilibrated in blocks of 3 for each center." (Page 50)
Allocation concealment (selection bias)	Unclear risk	Unclear. No details given about how the allocation was concealed from the study investigator. Quote: "After determining a patient's eligibility, the attending physician telephoned the study co-ordinator who assigned the patient." (Page 50)
Blinding (performance bias and detection bias) All outcomes	High risk	The study was not blind. See "Treatment Groups", page 50. "Technically difficult and theoretically debatable to perform 'sham' plasma exchanges".
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Reasons for 2 dropouts not clear. Quote: "unavailable for follow-up after having withdrawn their consent" (page 51) (not clear if this was before or after starting treatment). Dropouts not included in the analysis.
Selective reporting (reporting bias)	Unclear risk	Controlled disease was stated to be no more than 1 new blister occurring 4 weeks after starting treatment, resolution of erythema, and no more than minimal pruritus. Only the composite measure of controlled disease was reported (Table 2, page 52).
Other bias	Unclear risk	Trial stopped early. Quote: "Our trial was interrupted after the interim analysis showed no appreciable benefit resulting from the addition of azathioprine or plasma exchange to prednisolone in the initial (at 4 weeks) and maintenance (at 6 months) treatments of BP" (page 52).

**Joly 2002**

Methods	Randomised, not blinded  Disease control = number of new blisters after 3 weeks (21 days) of treatment. (Not clear if participant kept record of new blisters daily or if all new blisters since previous visit were averaged out to get a daily rate)
Participants	341 participants with BP confirmed by IF studies
Interventions	Moderate disease: A: 40 g topical clobetasol propionate cream twice daily to entire body 77/77 versus 0.5 mg/kg/day oral prednisone 76/76.  Extensive disease: A: topical clobetasol 93/93 versus prednisone 1 mg/kg/day 95/95.
Outcomes	1. Major outcome: survival 2. Disease control at 3 weeks

**Interventions for bullous pemphigoid (Review)**

July 2002 (Continued)

## 3. Complications

Notes Originally there were 364 participants recruited: 14 did not meet the inclusion criteria, 8 did not give consent, 1 withdrew his consent in the beginning of the study: left with 341 study participants

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed centrally with the use of random numbers in permuted blocks of four within each stratum." (Page 322)
Allocation concealment (selection bias)	Unclear risk	Allocation concealment is not well described. Probably adequate as it was done centrally.
Blinding (performance bias and detection bias) All outcomes	High risk	The study was not blinded. A nurse not otherwise associated with the study assessed the number of new bullae, daily.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants and outcomes adequately reported.
Selective reporting (reporting bias)	Low risk	Adequately reported.
Other bias	Unclear risk	Quote: "In accordance with the study protocol, the investigators switched three patients with moderate bullous pemphigoid and four with extensive bullous pemphigoid from the oral-prednisone group to the topical-corticosteroid group because of side-effects of treatment." (Page 324) 'Compliance with treatment and adverse effects'.

**July 2009**

Methods	Multicentre in France, centrally randomised; not blinded  2 different regimens were applied. In the mild regimen participants received doses depending on their body weight; follow-up of 360 days
Participants	312 participants with bullous pemphigoid; confirmed by direct immunofluorescence test
Interventions	Mild regimen: clobetasol propionate cream 10 to 30 g/day, until 15 days after disease control, thereafter corticosteroid tapering over 4 months (159)  moderate disease ( $\leq 10$ new blisters/day):  20 g/day if body weight > 45 kg, 10 g/day if < 45 kg  severe disease (>10 new blisters/day):  30 g/day if body weight > 45 kg, 20 g/day if < 45 kg.  Standard regimen: clobetasol propionate cream 40 g/day initially, until 15 days after disease control, corticosteroid tapering over 12 months (page 1686) (153 participants).
Outcomes	Primary:

July 2009 (Continued)

1. Complete healing (no new bullae for 3 consecutive days) after 21 days (moderate disease - severe disease)
2. Death/event-free survival after 1 year (moderate disease - severe disease)

Secondary end points:

1. Time to achieve disease control
2. Occurrence of severe (grade 3 or 4) side-effects (adverse events requiring hospitalisation or prolongation of hospitalisation or life-threatening events) during the follow-up year
3. Occurrence of relapses during follow-up
4. Cumulative doses of clobetasol propionate cream used during the study period

Notes

Page 1686 typing error: should be 0.05% clobetasol propionate cream, not 0.005%

Discrepancy between the numbers of participants as follows: the numbers in figure 1 (153 participants randomised, 150 participants analysed), text (153 participants randomised, 150 participants analysed), and table 2 (153 randomised and 153 analysed) for the standard regimen do not match

Clarification from the study investigator ([July 2010](#)): numbers in table 2 on page 1684, are wrong, should be 150 in the standard regimen

Only 150 were analysed, therefore intention-to-treat (ITT) analysis is not fulfilled

Worst case scenario calculation (none of the 3 missing cases in the standard group had complete healing): - 156/159 v 150/153 (ITT analysis), [Analysis 8.1](#)

### Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed centrally with the use of random numbers in permuted blocks of four within each stratum." (Page 1686)
Allocation concealment (selection bias)	Low risk	Allocation concealment is not well described. Probably adequate as it was done centrally.
Blinding (performance bias and detection bias) All outcomes	High risk	Intentionally not blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not all participants were accounted for at each stage of the trial. See Figure 1, page 1683, and Table 2, page 1686: typing error in table 2, only 150 participants were analysed.
Selective reporting (reporting bias)	Low risk	All outcomes reported adequately.
Other bias	Low risk	No other bias.

### Liu 2006

Methods	Healing of skin lesions (complete, partial, or no healing depending on the area affected) after 4 weeks treatment
Participants	30 participants with bullous pemphigoid; diagnosis confirmed by pathological tests
Interventions	A: Jingui Shenqi Pill (JSP) 1# bid plus prednisone 0.5 to 1.0 mg/kg/day (15 participants).

### Interventions for bullous pemphigoid (Review)

**Liu 2006** (Continued)

B: prednisone alone 0.5 to 1.0 mg/kg/day (15 participants).

Outcomes	<ol style="list-style-type: none"> <li>1. Complete healing after 4 weeks</li> <li>2. Partial healing</li> <li>3. No response</li> </ol>
Notes	Article in Chinese. Translation obtained

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No randomisation details in English abstract; nor in paper.
Allocation concealment (selection bias)	Unclear risk	No details in English abstract; nor in paper.
Blinding (performance bias and detection bias) All outcomes	High risk	Not blinded, no details in English abstract; nor in paper.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Adequately reported.
Selective reporting (reporting bias)	Low risk	Outcome is adequately reported.
Other bias	Unclear risk	Few details about any methods in translated paper. Precise method of diagnosis not specified (referred to as 'clinical' and 'pathological' tests). No further details available from the trial investigator.

**Morel 1984**

Methods	Randomised but not blind  Disease control = number new blisters between days 21 to 51  Follow-up: 51 days (= treatment period)
Participants	50 participants with BP confirmed by IF studies.
Interventions	A: 24/26 prednisolone 0.75 mg/kg/day.  B: 22/24 prednisolone 1.25 mg/kg/day.
Outcomes	<ol style="list-style-type: none"> <li>1. New blister formation: at day 21 and 51</li> </ol>
Notes	2 dropouts in each group, no reasons given, and not included in analysis  Erythromycin used for infection but its anti-inflammatory effect not evaluated or commented upon

**Risk of bias**

Bias	Authors' judgement	Support for judgement
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**Interventions for bullous pemphigoid (Review)**

**Morel 1984** (Continued)

Random sequence generation (selection bias)	Low risk	Quote: "using a single table of pre-established and balanced randomisation for all 8 patients." (Translation, page 926).
Allocation concealment (selection bias)	Unclear risk	No details given.
Blinding (performance bias and detection bias) All outcomes	High risk	No. No details given.
Incomplete outcome data (attrition bias) All outcomes	High risk	2 dropouts in each group, no reasons given, and not included in analysis.
Selective reporting (reporting bias)	Low risk	New blister formation at days 21 and 51 reported.
Other bias	Unclear risk	Some participants that could have been recruited were excluded on the grounds that they were able to take part in a parallel study involving plasma exchanges.

**Roujeau 1984**

Methods	Randomised but not blinded  Disease control = complete disappearance of blisters, itch, and erythema  Follow-up: 6 months (= treatment period)
Participants	41 participants with BP confirmed by IF studies, age > 80 years excluded
Interventions	A: 15/17 prednisolone 0.3 mg/kg/day.  B: 22/24 plasma exchange + prednisolone 0.3 mg/kg/day.  Both groups were treated with an identical protocol based on weekly dose adjustments according to the therapeutic results observed. Therapy was started at a dose of 0.3 mg/kg oral prednisolone daily for 1 week. If the treatment was ineffective, the dose was increased weekly to 1.5 mg/kg/day oral prednisolone, 2 mg/kg/day intramuscular methylprednisolone, and 2 mg/kg/day intramuscular methylprednisolone with (maximum permissible) 3 mg/kg/day oral cyclophosphamide.
Outcomes	1. Control of blister formation, erythema, and pruritus: number of participants controlled at certain doses of prednisolone (0.3 mg/day, 1.0 mg/day, $\geq$ 1.5 mg/day); daily and cumulative dose of prednisolone needed to control disease (cumulative dose was calculated at the time point when no new blisters appeared, no more pruritus, erythema, urticae) was measured 2. Assessment of therapeutic response (page 487: The number of new bullae reported in the last 48 hours of a 7-day therapeutic period). Treatment was considered effective 3. Side-effects 4. Mortality
Notes	-

**Risk of bias**

Bias	Authors' judgement	Support for judgement
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**Roujeau 1984** (Continued)

Random sequence generation (selection bias)	Low risk	Randomised. Quote: "Assigned to groups according to lists drawn by micro-computer for each participating centre and equilibrated after every 4 patients." (Page 487)
Allocation concealment (selection bias)	Unclear risk	Probably done as randomisation was computerised.
Blinding (performance bias and detection bias) All outcomes	High risk	Not blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	<p>41 randomised, 2 from each group were excluded from analysis, reasons accounted for in Results (page 487).</p> <p>2 participants from each group withdrawn from study, before treatment was initiated (1 had no BP, 2 accidentally received higher initial doses of prednisolone, 1 no plasma exchange). Dropouts not included in the analysis (they were randomised, but did not really start proper trial treatment and were excluded).</p> <p>Outcomes (disease control) are reported for the remaining 37 participants the groups they were randomised to. (Table 2, page 488). Side-effects and mortality are reported in the text. (Table II and III).</p>
Selective reporting (reporting bias)	Low risk	Yes. Control of blister formation, erythema, and pruritus, although this is only reported as a composite when bullae, pruritus, and erythema has resolved; this was reported as disease control.
Other bias	Low risk	No other bias.

**Characteristics of ongoing studies** [ordered by study ID]

**ACTRN12607000104459**

Trial name or title	Rituximab in the adjuvant treatment of bullous pemphigoid: A prospective open-label pilot study in three patients to study remission of disease with rituximab
Methods	A prospective open-label pilot study in three participants to study remission of disease with rituximab
Participants	Bullous pemphigoid
Interventions	Rituximab 375 mg m <sup>-2</sup> weekly for 4 weeks
Outcomes	<p>Primary:</p> <ol style="list-style-type: none"> <li>Participants response rate. Measured at 1 and 3 months after rituximab administration and 3-monthly thereafter until completion of study. Completion of study was at 17 months post-rituximab but in 1 participant, follow-up was ceased at 13 months post-rituximab when they demonstrated clinical remission</li> </ol> <p>Secondary:</p> <ol style="list-style-type: none"> <li>Complete or partial response</li> <li>Response duration</li> <li>Per cent of participants able to discontinue steroids</li> <li>Toxicity</li> </ol>



**ACTRN12607000104459** (Continued)

## 5. Reduction in skin antibody levels

These secondary outcomes were measured at 1 and 3 months post-rituximab and 3-monthly thereafter until study completion. Completion of study was at 17 months post-rituximab but in 1 participant, follow-up was ceased at 13 months post-rituximab when they demonstrated clinical remission

Starting date	February 2007
Contact information	Professor H. Miles Prince (miles.prince@petermac.org) Chair, Haematology Services Peter MacCallum Cancer Centre Locked Bag 1, A'Beckett St, East Melbourne Victoria 8006 Australia
Notes	-

**ISRCTN13704604**

Trial name or title	A randomised controlled trial to compare the safety and effectiveness of doxycycline (200 mg/day) with prednisolone (0.5 mg/kg/day) for initial treatment of bullous pemphigoid
Methods	Prospective, 2-arm, single-blind, parallel group, multicentre randomised controlled trial
Participants	256 participants with bullous pemphigoid, confirmed by immunofluorescence tests
Interventions	Doxycycline (200 mg/day) versus prednisolone (0.5 mg/kg/day)
Outcomes	<p>Primary:</p> <ol style="list-style-type: none"> <li>1. Proportion of participants classed as treatment success (3 or less significant blisters present on examination) at 6 weeks</li> <li>2. Number of reported grade 3, 4, and 5 (mortality) adverse events for 1 year</li> </ol> <p>Secondary:</p> <p>Differences in the 2 treatment arms in the:</p> <ol style="list-style-type: none"> <li>1. Proportion of participants classed as treatment success (3 or less significant blisters present on examination) at 6 weeks and are alive at 1 year</li> <li>2. Proportion of participants classed as treatment success (3 or less significant blisters present on examination) after 3 and 12 months of treatment</li> <li>3. Proportion of participants who have a further episode of bullous pemphigoid during their participation in the study after previously being classed as a treatment success</li> <li>4. Number of reported grade 1 and 2 adverse events for 1 year following the start of study treatment</li> <li>5. Quality of life</li> <li>6. Cost-effectiveness</li> </ol> <p>Tertiary:</p> <p>Differences in the 2 treatment arms in the:</p> <ol style="list-style-type: none"> <li>1. Proportion of participants who, on examination at 6 weeks, are completely blister-free</li> <li>2. Proportion of participants who are alive 1 year after the start of study treatment</li> <li>3. Proportion of participants in each treatment arm who, on examination at 3 weeks, are classed as treatment success (3 or less significant blisters present)</li> </ol>

**ISRCTN13704604** (Continued)

## 4. Difference in the amount of potent and super-potent topical corticosteroids used

Starting date	March 2009
Contact information	Mrs Caroline Onions ( <a href="mailto:blister@nottingham.ac.uk">blister@nottingham.ac.uk</a> ) Clinical Trials Unit Office, B39 Medical School Queens Medical Centre Nottingham NG7 2UH England
Notes	-

**NCT00286325**

Trial name or title	Rituximab in the treatment of participants with bullous pemphigoid
Methods	Non-randomised, open label, active control, single group assignment, safety/efficacy study
Participants	Bullous pemphigoid
Interventions	Infusion of 1000 mg of rituximab on day 0 and day 14
Outcomes	1. To determine the safety of rituximab for treatment of participants with bullous pemphigoid (time frame: 1 year) (designated as safety issue: yes)
Starting date	March 2005
Contact information	Russell Hall, III, MD Duke University Medical Center Durham, North Carolina 27710 United States
Notes	-

**NCT00472030**

Trial name or title	An open label case series on the effects of Xolair (Omalizumab) in bullous pemphigoid
Methods	An open label case series on the effects of Xolair (Omalizumab) in bullous pemphigoid
Participants	Bullous pemphigoid
Interventions	Subcutaneous administration of omalizumab, dose dependent on weight and circulating levels of IgE. Omalizumab will be administered every 4 weeks for 12 weeks. Additional injections will be given on weeks 2, 6, 10, and 14 if required based on weight and IgE levels  Versus prednisone
Outcomes	1. Assessment of total and new blister numbers over the 16-week period. Time to the cessation of new blister formation. The total dose of prednisone (mg/kg/day) during the 16-week treatment period. Parameters will be compared to the controls (time frame: 24 total week) (designated as safety issue: no)

**NCT00472030** (Continued)

Starting date	August 2007
Contact information	Janet A Fairley (janet-fairley@uiowa.edu) & Debra S Brandt (debra-brandt@uiowa.edu) Department of Dermatology University of Iowa USA
Notes	<a href="mailto:janet-fairley@uiowa.edu">janet-fairley@uiowa.edu</a>

**NCT00525616**

Trial name or title	Assessment of rituximab efficiency and tolerance in treatment of bullous pemphigoid
Methods	Non-randomised, open label, uncontrolled, single group assignment, safety/efficacy study
Participants	20 participants with bullous pemphigoid
Interventions	2 IV perfusions of 1000 mg at 15 day intervals
Outcomes	<p>Primary outcomes:</p> <ol style="list-style-type: none"> <li>Clinical and biological controls of bullous pemphigoid were estimated every 7 days during a period of 1 month and every month during a period of 2 years (time frame: 2 years) (designated as safety issue: yes)</li> </ol> <p>Secondary outcomes:</p> <ol style="list-style-type: none"> <li>Adverse reactions will be estimated during all the period of this clinical trial (time frame: 3 years) (designated as safety issue: yes)</li> </ol>
Starting date	December 2008
Contact information	Pascal Joly, MD, PhD (pascal.joly@chu-rouen.fr) Rouen University Hospital Direction de la Recherche et de l'Innovation Rouen 76031 France
Notes	<a href="mailto:pascal.joly@chu-rouen.fr">pascal.joly@chu-rouen.fr</a>

**NCT00802243**

Trial name or title	Leflunomide associated with topical corticosteroids for bullous pemphigoid. An open prospective study
Methods	Open label, uncontrolled, single group assignment, efficacy study
Participants	54 participants with bullous pemphigoid
Interventions	40 g topical clobetasol propionate cream per day plus 20 mg leflunomide per day
Outcomes	Primary outcomes:

**Interventions for bullous pemphigoid (Review)**

**NCT00802243** (Continued)

1. Stage 1: complete clinical remission after 6 months treatment for 9 participants at least among 15 appraisable participants
2. Stage 2: complete clinical remission after 6 months treatment for 27 participants at least among 43 appraisable participants

Secondary outcomes:

1. To determine the rate of clinical complete remission at M9 and M12
2. To estimate the number of participants with immunological remission at M6, M9, and M12
3. To evaluate monthly the tolerance of leflunomide

Starting date	September 2007
Contact information	Christophe Bedane (christophe.bedane@chu-limoges.fr) Limoges University Hospital Limoges 87042 France
Notes	Christophe

**NCT00809822**

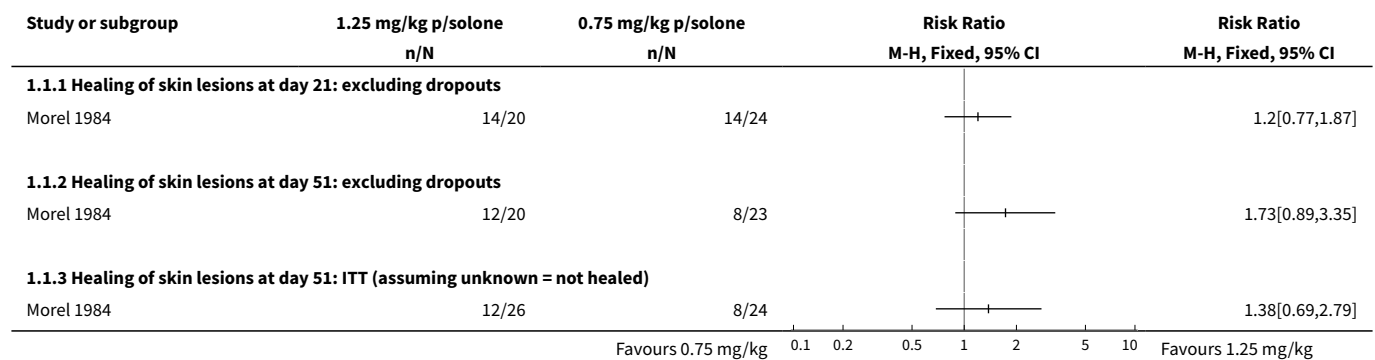
Trial name or title	NPB-01 (intravenous immunoglobulin) therapy for patients with bullous pemphigoid unresponsive to corticosteroids: Randomized, double-blind, placebo control, parallel assignment study (phase II)
Methods	Randomised, double-blind (subject, investigator), placebo-control, parallel assignment, safety/efficacy study
Participants	20 participants with bullous pemphigoid
Interventions	NPB-01 Intravenous immunoglobulin versus placebo physiological saline
Outcomes	1. Skin lesion area (%), number of new blisters/day, pemphigoid activity score, pemphigus disease area Index(PDAI), anti-BP180 and -BP230 antibody titers, steroid dose, time to escape from the protocol and its ratio (time frame: 57 days) (designated as safety issue: no)
Starting date	December 2008
Contact information	Yasumasa Ogawa (kaihatsu@nihon-pharm.co.jp) Nihon Pharmaceutical Co. Ltd Japan
Notes	-

**DATA AND ANALYSES**

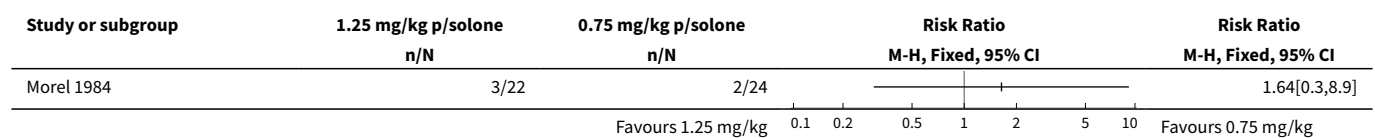
**Comparison 1. Higher dose prednisolone (1.25 mg/kg p/solone) versus lower dose prednisolone (0.75 mg/kg p/solone)**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Disease control	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Healing of skin lesions at day 21: excluding dropouts	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Healing of skin lesions at day 51: excluding dropouts	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Healing of skin lesions at day 51: ITT (assuming unknown = not healed)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Mortality at day 51	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

**Analysis 1.1. Comparison 1 Higher dose prednisolone (1.25 mg/kg p/solone) versus lower dose prednisolone (0.75 mg/kg p/solone), Outcome 1 Disease control.**



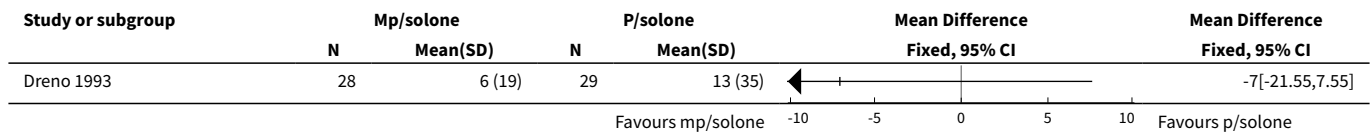
**Analysis 1.2. Comparison 1 Higher dose prednisolone (1.25 mg/kg p/solone) versus lower dose prednisolone (0.75 mg/kg p/solone), Outcome 2 Mortality at day 51.**



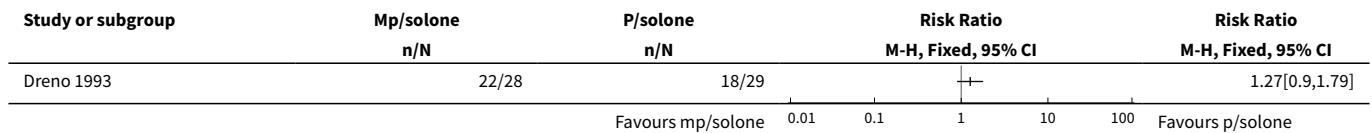
**Comparison 2. Methylprednisolone (mp/solone) versus prednisolone (p/solone)**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Disease control - number of blisters at day 10	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2 Overall improvement	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Disease control - extent of erythema at day 10 (score out of 3)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4 Quality of life - extent of itching (score out of 3)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

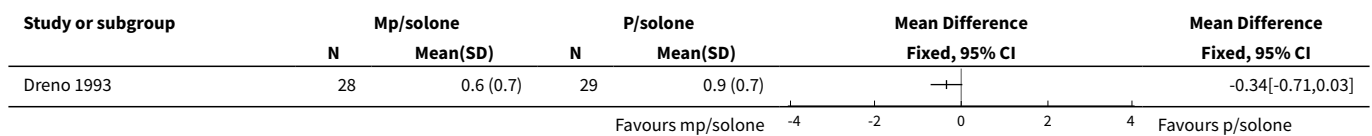
**Analysis 2.1. Comparison 2 Methylprednisolone (mp/solone) versus prednisolone (p/solone), Outcome 1 Disease control - number of blisters at day 10.**



**Analysis 2.2. Comparison 2 Methylprednisolone (mp/solone) versus prednisolone (p/solone), Outcome 2 Overall improvement.**



**Analysis 2.3. Comparison 2 Methylprednisolone (mp/solone) versus prednisolone (p/solone), Outcome 3 Disease control - extent of erythema at day 10 (score out of 3).**



**Analysis 2.4. Comparison 2 Methylprednisolone (mp/solone) versus prednisolone (p/solone), Outcome 4 Quality of life - extent of itching (score out of 3).**

Study or subgroup	Mp/solone		P/solone		Mean Difference		Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Dreno 1993	28	0.6 (0.8)	29	0.9 (0.8)			-0.27[-0.69,0.15]

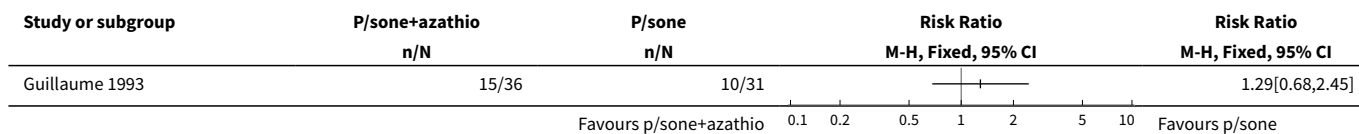
**Comparison 3. Prednisone + azathioprine (p/sone+azathio) versus prednisone (p/sone)**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Disease control	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Disease control at 6 months	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Disease control: well at 3 years, either needing or not needing further treatment	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Mortality and severe adverse events at 6 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Mortality	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 Mortality at 6 months	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Mortality at 3 years	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

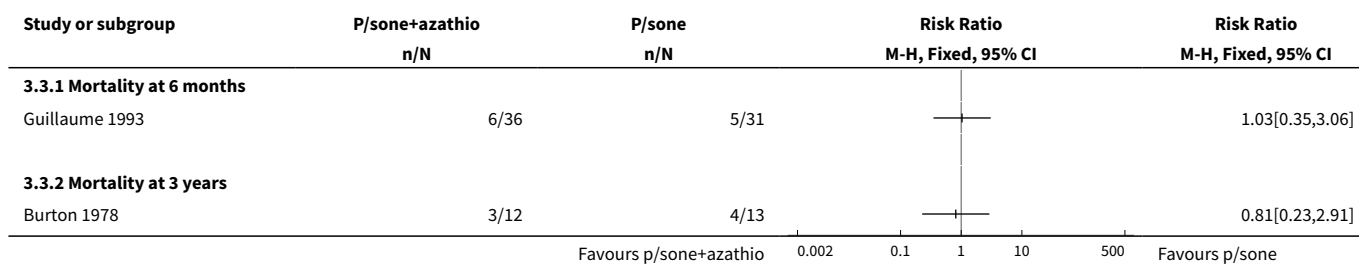
**Analysis 3.1. Comparison 3 Prednisone + azathioprine (p/sone +azathio) versus prednisone (p/sone), Outcome 1 Disease control.**

Study or subgroup	P/sone+azathio	P/sone	Risk Ratio	
	n/N	n/N	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
<b>3.1.1 Disease control at 6 months</b>				
Guillaume 1993	14/36	13/31		
<b>3.1.2 Disease control: well at 3 years, either needing or not needing further treatment</b>				
Burton 1978	9/12	9/13		

**Analysis 3.2. Comparison 3 Prednisone + azathioprine (p/sone+azathio) versus prednisone (p/sone), Outcome 2 Mortality and severe adverse events at 6 months.**



**Analysis 3.3. Comparison 3 Prednisone + azathioprine (p/sone +azathio) versus prednisone (p/sone), Outcome 3 Mortality.**

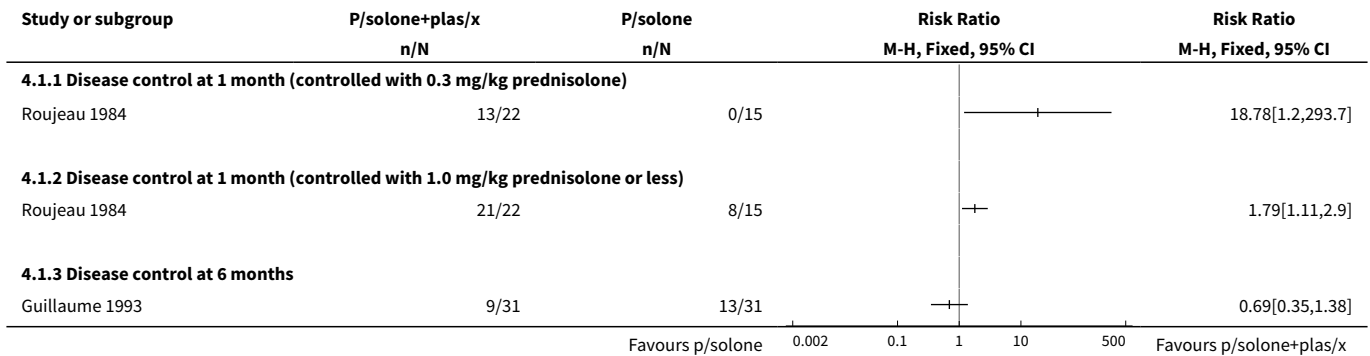


**Comparison 4. Prednisolone plus plasma exchange (p/solone+plas/x) versus prednisolone**

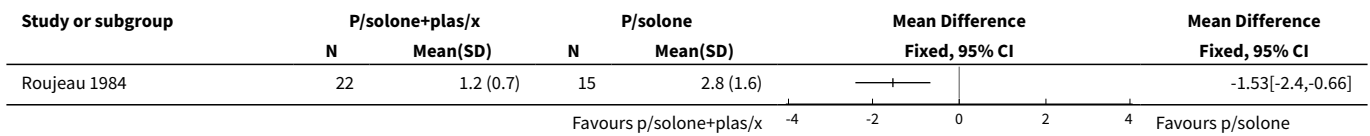
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
<a href="#">1 Disease control</a>	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Disease control at 1 month (controlled with 0.3 mg/kg prednisolone)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Disease control at 1 month (controlled with 1.0 mg/kg prednisolone or less)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Disease control at 6 months	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
<a href="#">2 Disease control at 1 month - cumulative steroid dose (g)</a>	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
<a href="#">3 Mortality and severe adverse events at 6 months</a>	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
<a href="#">4 Mortality</a>	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1 Mortality at 1 month: excluding dropouts	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Mortality at 1 month: ITT worst case	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.3 Mortality at 6 months	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]



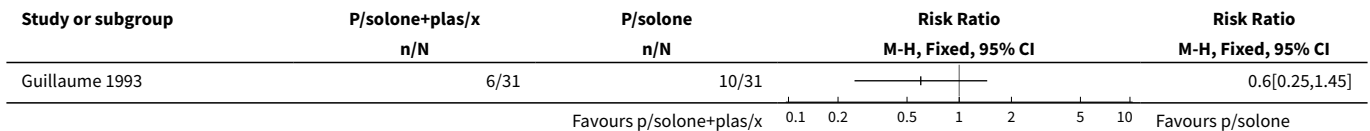
**Analysis 4.1. Comparison 4 Prednisolone plus plasma exchange (p/solone+plas/x) versus prednisolone, Outcome 1 Disease control.**



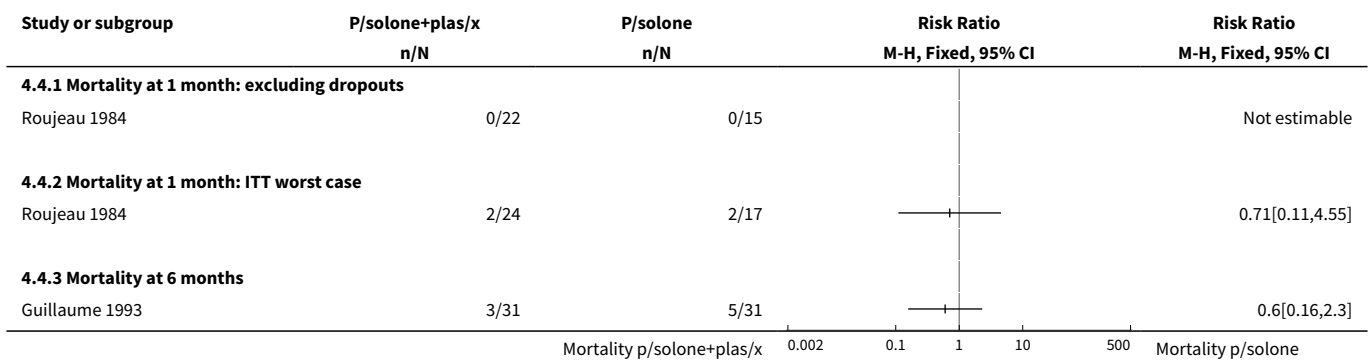
**Analysis 4.2. Comparison 4 Prednisolone plus plasma exchange (p/solone+plas/x) versus prednisolone, Outcome 2 Disease control at 1 month - cumulative steroid dose (g).**



**Analysis 4.3. Comparison 4 Prednisolone plus plasma exchange (p/solone+plas/x) versus prednisolone, Outcome 3 Mortality and severe adverse events at 6 months.**



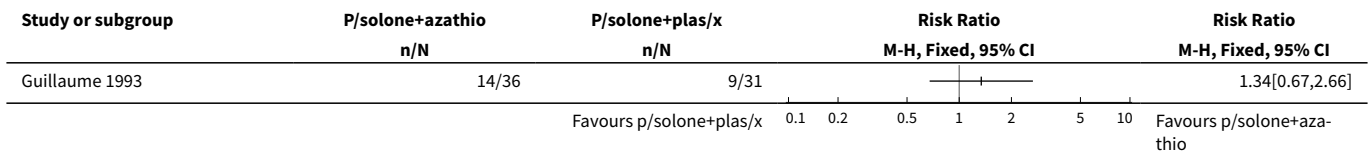
**Analysis 4.4. Comparison 4 Prednisolone plus plasma exchange (p/solone+plas/x) versus prednisolone, Outcome 4 Mortality.**



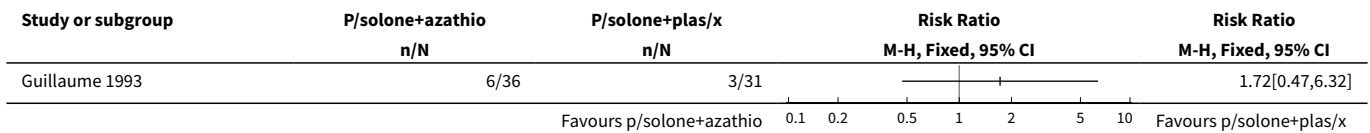
**Comparison 5. Prednisolone plus azathioprine (p/solone+azathio) versus prednisolone plus plasma exchange (p/solone+plas/x)**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Disease control at 6 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Mortality at 6 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Mortality and adverse events at 6 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

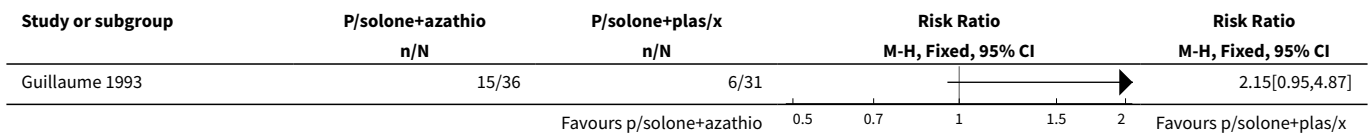
**Analysis 5.1. Comparison 5 Prednisolone plus azathioprine (p/solone+azathio) versus prednisolone plus plasma exchange (p/solone+plas/x), Outcome 1 Disease control at 6 months.**



**Analysis 5.2. Comparison 5 Prednisolone plus azathioprine (p/solone+azathio) versus prednisolone plus plasma exchange (p/solone+plas/x), Outcome 2 Mortality at 6 months.**



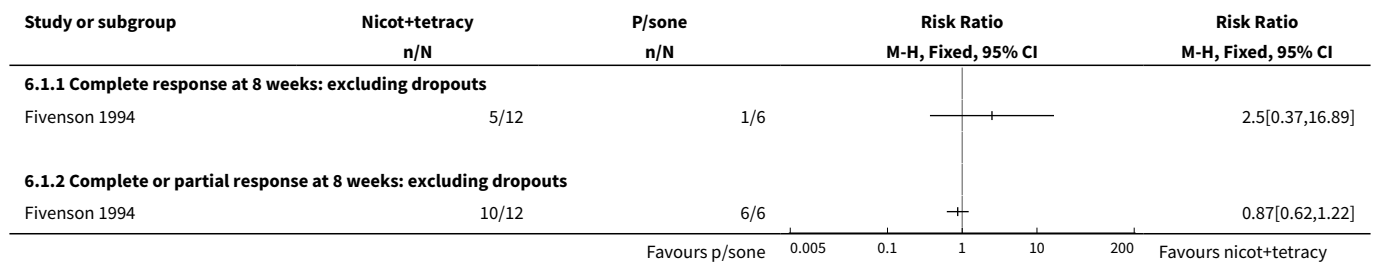
**Analysis 5.3. Comparison 5 Prednisolone plus azathioprine (p/solone+azathio) versus prednisolone plus plasma exchange (p/solone+plas/x), Outcome 3 Mortality and adverse events at 6 months.**



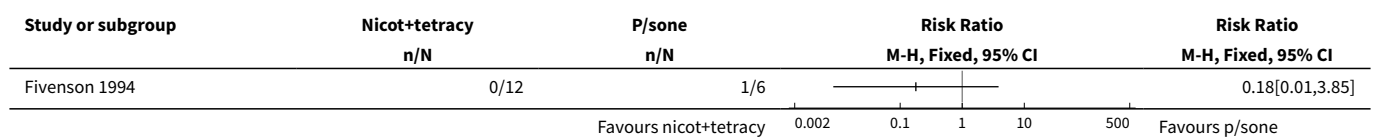
**Comparison 6. Nicotinamide plus tetracycline (nicot+tetracy) versus prednisone (p/sonne)**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Disease control	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Complete response at 8 weeks: excluding dropouts	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Complete or partial response at 8 weeks: excluding dropouts	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Mortality at 6 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

**Analysis 6.1. Comparison 6 Nicotinamide plus tetracycline (nicot+tetracy) versus prednisone (p/sonne), Outcome 1 Disease control.**



**Analysis 6.2. Comparison 6 Nicotinamide plus tetracycline (nicot+tetracy) versus prednisone (p/sonne), Outcome 2 Mortality at 6 months.**

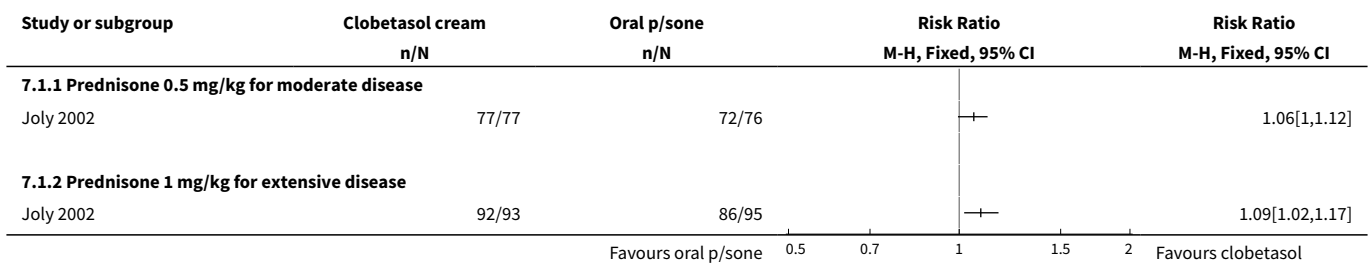


**Comparison 7. Clobetasol propionate cream (clobetasol) versus oral prednisone (oral p/sonne)**

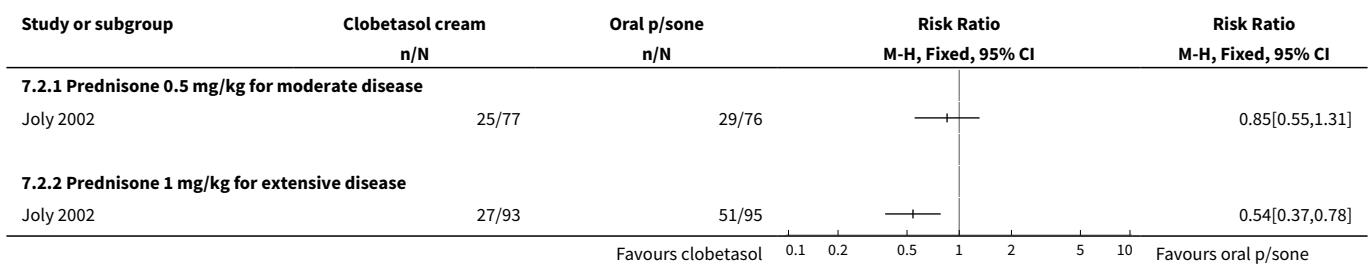
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Disease control at day 21	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Prednisone 0.5 mg/kg for moderate disease	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Prednisone 1 mg/kg for extensive disease	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
<b>2 Severe complications</b>	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 Prednisone 0.5 mg/kg for moderate disease	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Prednisone 1 mg/kg for extensive disease	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
<b>3 Mortality at 1 year</b>	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 Prednisone 0.5 mg/kg for moderate disease	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Prednisone 1 mg/kg for extensive disease	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

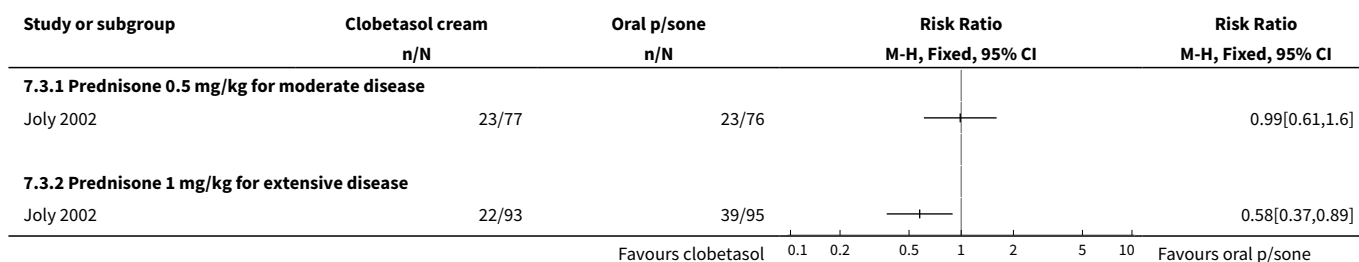
**Analysis 7.1. Comparison 7 Clobetasol propionate cream (clobetasol) versus oral prednisone (oral p/sone), Outcome 1 Disease control at day 21.**



**Analysis 7.2. Comparison 7 Clobetasol propionate cream (clobetasol) versus oral prednisone (oral p/sone), Outcome 2 Severe complications.**



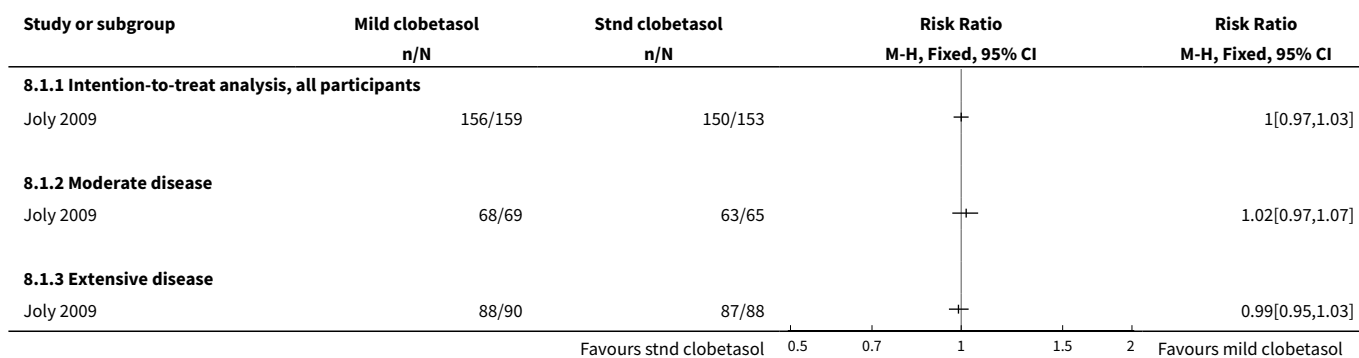
**Analysis 7.3. Comparison 7 Clobetasol propionate cream (clobetasol) versus oral prednisone (oral p/sone), Outcome 3 Mortality at 1 year.**



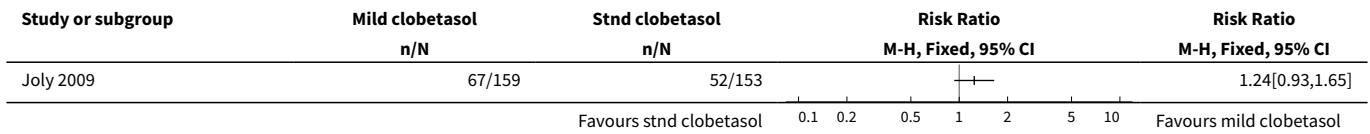
**Comparison 8. Mild regimen clobetasol propionate cream (mild clobetasol) regimen versus standard clobetasol propionate cream (stnd clobetasol) regimen**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
<a href="#">1 Healing of skin lesions: complete (at day 21)</a>	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Intention-to-treat analysis, all participants	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Moderate disease	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Extensive disease	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
<a href="#">2 Number of relapses</a>	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
<a href="#">3 Mortality</a>	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 Moderate disease	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Extensive disease	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

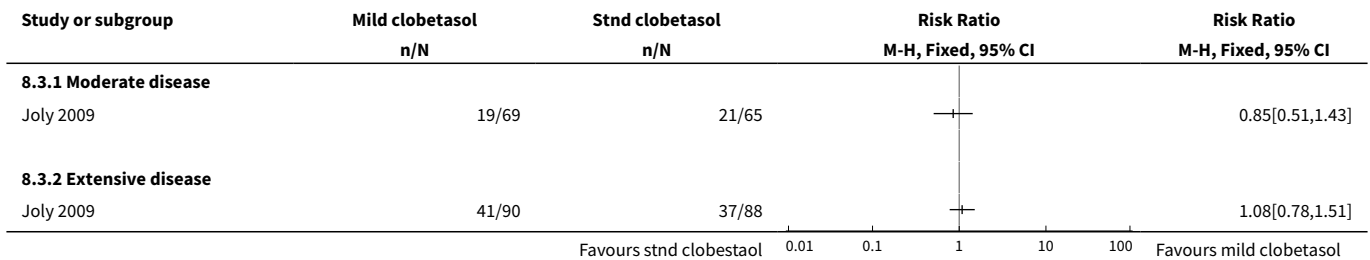
**Analysis 8.1. Comparison 8 Mild regimen clobetasol propionate cream (mild clobetasol) regimen versus standard clobetasol propionate cream (stnd clobetasol) regimen, Outcome 1 Healing of skin lesions: complete (at day 21).**



**Analysis 8.2. Comparison 8 Mild regimen clobetasol propionate cream (mild clobetasol) regimen versus standard clobetasol propionate cream (stdn clobetasol) regimen, Outcome 2 Number of relapses.**



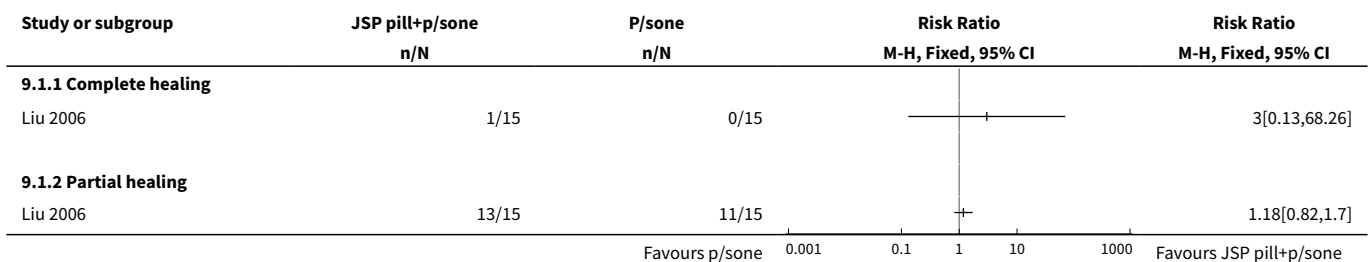
**Analysis 8.3. Comparison 8 Mild regimen clobetasol propionate cream (mild clobetasol) regimen versus standard clobetasol propionate cream (stdn clobetasol) regimen, Outcome 3 Mortality.**

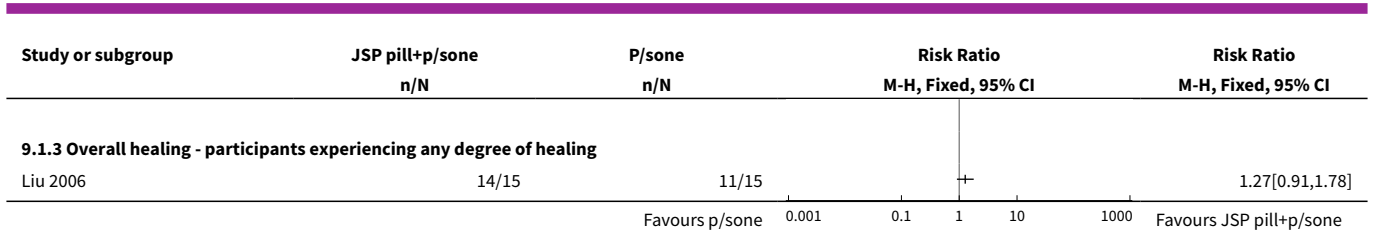


**Comparison 9. Jingui Shenqi Pill (JSP) 1# bid plus prednisone (JSP pill+p/sone) versus prednisone (p/sone) alone**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
<b>1 Healing at 4 weeks</b>	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Complete healing	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Partial healing	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Overall healing - participants experiencing any degree of healing	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

**Analysis 9.1. Comparison 9 Jingui Shenqi Pill (JSP) 1# bid plus prednisone (JSP pill+p/sone) versus prednisone (p/sone) alone, Outcome 1 Healing at 4 weeks.**

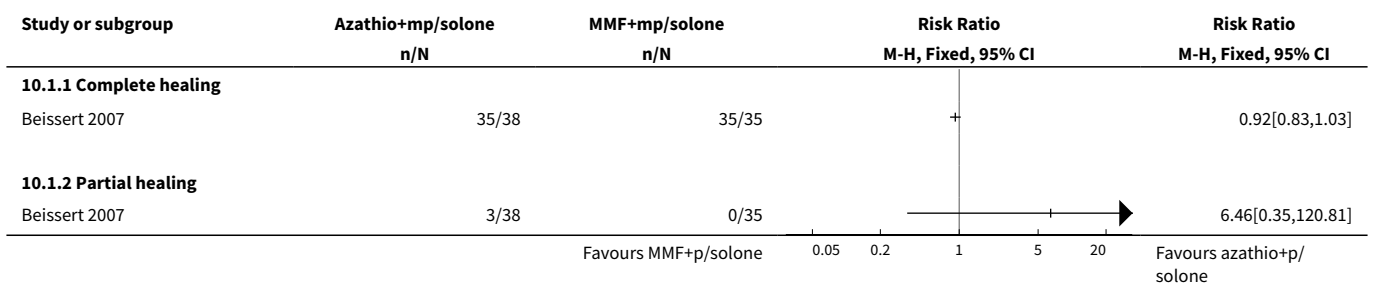




**Comparison 10. Azathioprine plus methylprednisolone (azathio+mp/solone) versus mycophenolate mofetil plus methylprednisolone (MMF+mp/solone)**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Healing of lesions	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Complete healing	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Partial healing	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

**Analysis 10.1. Comparison 10 Azathioprine plus methylprednisolone (azathio+mp/solone) versus mycophenolate mofetil plus methylprednisolone (MMF+mp/solone), Outcome 1 Healing of lesions.**



**ADDITIONAL TABLES**

**Table 1. Adverse events in the included studies**

Study ID	Drug and dose	Infection / Low WCC	Organ im- pairment	Cardiovas- cular	Other	Total ad- verse events	Death
Beissert 2007	Oral methylprednisolone 0.5 mg/kg/day plus azathioprine 2 mg/kg/day (n = 38)	1	7 (1 hypergly- caemia 6 liv- er)	0	3	11 (grade 3/4)	2
	Oral methylprednisolone 0.5 mg/kg/day plus mycophenolate mofetil 2000 mg twice/day (n = 35)	4	6 (5 hypergly- caemia 1 liv- er)	0	3	13 (grade 3/4)	0
Burton 1978	Prednisone 30 to 80 mg/kg/day (n = 13)	1	1	3		5	4
	Azathioprine 2.5 mg/kg + prednisone 30 to 80 mg/kg/day (n = 12)	2		3		5	3
Dreno 1993	Prednisolone (average) 1.16 mg/kg/day (n = 29)		1	1	1	3	0
	Methylprednisolone (average) 1.17 mg/kg/day (n = 28)	1	1	2	1	5	0
Fivenson 1994	Prednisone 40 to 80 mg/kg/day (n = 6)	2	3	2	1	8	1
	Tetracycline 500mg 4x/day + nicotinamide (n = 14)	1	1		2	4	0
Guillaume 1993	Prednisolone 1 mg/kg/day (n = 31)					10	5
	Prednisolone 1 mg/kg/day + azathioprine 100 to 150 mg/day (n = 36)					15	6
	Prednisolone 1 mg/kg/day + plasma exchange (n = 31)					6	3
July 2002	Moderate disease: topical steroids (n = 77)	11	5	15		31	23



**Table 1. Adverse events in the included studies** (Continued)

	Prednisone 0.5 mg/kg/day (n = 76)	16	14	16		46	23
	Extensive disease: topical steroids (n = 93)	8	6	16		30	22
	Prednisone 1 mg/kg (n=95)	22	23	20		65	39 P = 0.02
<b>Joly 2009</b>	Mild regimen topical steroids (n = 159)	27	18 (DM)	21	41% (skin)	194 (grade 3/4)	60
	Standard regimen topical steroids (n = 150)	32	34 (DM)	35	52% (skin)	227 (grade 3/4)	58
<b>Liu 2006</b>	Jingui Shenqi Pill (JSP) 1# bid plus prednisone 0.5 to 1.0 mg/kg/day (n = 15)					not men- tioned	not men- tioned
	Prednisone alone 0.5 to 1.0 mg/kg/day (n = 15)					not men- tioned	not men- tioned
<b>Morel 1984</b>	Prednisolone 0.75 mg/kg/day (n = 26)	1	2			3	2
	Prednisolone 1.25 mg/kg/day (n = 26)	1	1	1	2	5	3
<b>Roujeau 1984</b>	Prednisolone 0.3 mg/kg/day (n = 17)		7			7	0
	Plasma exchange + prednisolone 0.3 mg/kg/day (n = 24)	10	7	7		7	0

## APPENDICES

### Appendix 1. CSG Specialised Register search strategy

((bullous and pemphigoid) OR (pemphigoid AND NOT gestationis)) AND ((drug AND therapy) OR treatment\* OR medication\* OR predniso\* OR corticosteroid\* OR steroid\* OR azathioprine OR immunosuppres\* OR dapsone OR erythromycin\* OR tetracyclin\* OR nicotinamide OR cyclophosphamide OR cyclosporin\* OR sulph\* OR methotrexate OR plasmaph\* OR (mycophenolate and mofetil))

### Appendix 2. Cochrane Library search strategy

#1(bullous pemphigoid) OR (pemphigoid NOT gestationis)  
 #2MeSH descriptor Pemphigoid, Bullous explode all trees in MeSH products  
 #3(#1 OR #2)  
 #4SR-SKIN in All Fields in all products  
 #5(#3 AND NOT #4)

### Appendix 3. MEDLINE search strategy

1. randomised controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. clinical trials as topic.sh.
6. randomly.ab.
7. trial.ti.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. (animals not (human and animals)).sh.
10. 8 not 9
11. bullous pemphigoid.mp. or exp Pemphigoid, Bullous/
12. pemphigoid gestationis.mp. or exp Pemphigoid Gestationis/
13. 11 not 12
14. 13 and 10

### Appendix 4. EMBASE search strategy

1. random\$.mp.
2. factorial\$.mp.
3. (crossover\$ or cross-over\$).mp.
4. placebo\$.mp. or PLACEBO/
5. (doubl\$ adj blind\$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
6. (singl\$ adj blind\$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
7. (assign\$ or allocat\$).mp.
8. volunteer\$.mp. or VOLUNTEER/
9. Crossover Procedure/
10. Double Blind Procedure/
11. Randomized Controlled Trial/
12. Single Blind Procedure/
13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14. bullous pemphigoid.mp. or exp Bullous Pemphigoid/
15. pemphigoid gestationis.mp. or exp Pemphigoid Gestationis/
16. 14 not 15
17. 16 and 13

## WHAT'S NEW

Date	Event	Description
7 October 2015	Amended	Author information (affiliation) updated.

## HISTORY

Protocol first published: Issue 3, 2000

Review first published: Issue 3, 2003

Date	Event	Description
11 September 2013	Amended	Contact author's out-of-date email address removed and current email address and second affiliation added. Another author's affiliation also updated
7 November 2011	Amended	Correction made to the data relating to the Beissert 2007 study ('1000' mg MMF amended to '2000' mg MMF)
6 September 2010	New citation required but conclusions have not changed	Change in authorship
6 September 2010	New search has been performed	Review updated with 3 new studies
5 February 2010	New citation required but conclusions have not changed	New studies found and included or excluded, authors changed
5 February 2010	New search has been performed	Updated
8 August 2008	Amended	Converted to new review format
5 June 2008	New citation required but conclusions have not changed	New studies found and included or excluded
16 May 2005	New citation required and conclusions have changed	Substantive amendment
5 June 2003	New search has been performed	Minor update

## CONTRIBUTIONS OF AUTHORS

GK contributed to the writing of the protocol, extraction of data, analysis of the results, the writing of the systematic review, and updating the review.

PM contributed to the extraction of the data, analysis of the results (statistics), writing of the systematic review, and provided comments on the updated review.

CB contributed to the 'Risk of bias' tables for the updated review, corresponded with trial investigators, contributed to writing and editing the text, revised some of the analyses, and (with GK) responded to the peer referees' comments.

DFM contributed to the writing of the protocol, extraction of data, and analysis of the results of the first version of the systematic review and editing the text of the current version.

FW contributed to the writing of protocol and analysis of the results of the first version of the systematic review.

NPK was the first author of the first version of the systematic review and was the main contributor to that version of the review.

## DECLARATIONS OF INTEREST

None known.

## SOURCES OF SUPPORT

### Internal sources

- No sources of support supplied

### External sources

- Nuffield Trust Fellowship scheme, UK.

## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We changed the wording of the primary outcome "regression or healing of skin lesions" which referred to the "rate of" and "when/how soon?" as these are time-to-event measures which are complicated to measure and analyse (and not often reported in trials). We added "at time periods specified by individual trials".

We made minor changes to the secondary outcomes of systemic infection and mortality. We had originally intended to look at systemic infection and mortality as a result of the primary disease and as a result of treatment. At the time of the first published version of the review, we decided that these data were unlikely to be available and we no longer include them.

The original protocol of this review stated that the Jadad quality assessment scale would be used, which also similarly assesses randomisation, blinding, withdrawals, and dropouts ([Jadad 1996](#)). We assessed all these aspects but reported them individually (see 'Risk of bias' tables in the [Characteristics of included studies](#)) rather than as a summary score, as the use of scales for assessing quality or risk of bias is explicitly discouraged in Cochrane reviews ([Higgins 2008](#); section 8.3.3).

We have reclassified the outcomes as primary and secondary outcomes.

We have changed the measures of treatment effect to risk ratio (RR) from odds ratio (OR) in accordance with Cochrane Skin Group policy.

## INDEX TERMS

### Medical Subject Headings (MeSH)

\*Plasma Exchange; Azathioprine [therapeutic use]; Clobetasol [therapeutic use]; Combined Modality Therapy [methods]; Drug Therapy, Combination [methods]; Drugs, Chinese Herbal [therapeutic use]; Glucocorticoids [\*therapeutic use]; Immunosuppressive Agents [\*therapeutic use]; Niacinamide [therapeutic use]; Pemphigoid, Bullous [drug therapy] [\*therapy]; Prednisolone [therapeutic use]; Prednisone [therapeutic use]; Randomized Controlled Trials as Topic; Tetracycline [therapeutic use]

### MeSH check words

Humans