International Journal of Basic & Clinical Pharmacology
Subhan A et al. Int J Basic Clin Pharmacol. 2025 Jul;14(4):597-602
http://www.ijbcp.com
pISSN 2319-2003 | eISSN 2279-0780

DOI: https://dx.doi.org/10.18203/2319-2003.ijbcp20251846

Review Article

Breaking the blisters: a comprehensive guide to treating bullous pemphigoid

Amber Subhan*, Lolla Siddhartha, Mudimala Rekha Goud, Safura Khanam

Department of Pharmacy, Pulla Reddy Institute of Pharmacy, Hyderabad, India

Received: 09 April 2025
Accepted: 15 May 2025

***Correspondence:**
Dr. Amber Subhan,
Email: ambersubhan21@gmail.com

ABSTRACT

In adapting the treatment plan, the severity of the disease in correlation with the patient should be put onto consideration. Recent RCTs demonstrated adjuvant treatment with doxycycline, dapsone, and immunosuppressants for the treatment of bullous pemphigoid is of advantage and safe in terms of diminished total steroid dose and mortality. The British association of dermatologists has produced dermatologists' guidelines. These provide evidence-based treatment recommendations with respect to candidness, and offer a summary on, among others, epidemiological features, diagnosis, and research. The evidence on which the guidelines rest was retrieved from Medline, Embase, the Cochrane Library, literature searches, and the authors' 10 years of experience treating patients with bullous pemphigoid in general and special clinics. However, it should be noted that findings from the literature should be interpreted with great care as only six randomized controlled trials with small patient groups are available.

Keywords: Antibiotics, Bullous pemphigoid, Corticosteroids, Nicotinamides

INTRODUCTION

The objective of therapy is to reduce the formation of blisters, urticarial lesions, and pruritus-the clinical manifestations of BP-to a point that can be tolerated by each patient. The disease commonly resolves within five years and is inherently self-limiting. Older patients with BP commonly take numerous medications and are at a greater risk of having adverse reactions and side effects to these drugs.[1,2] These patients are likely to suffer from a potentially fatal condition due to too high dosages of immunosuppressants that are far worse than high BP. The various treatments work through different mechanisms. While some, for example, corticosteroids, antibiotics like tetracyclines and sulphones, among others, seek to suppress the inflammatory process itself. Other immunosuppressive drugs, including high doses of corticosteroids, azathioprine, methotrexate, cyclophosphamide, and cyclosporin, are given to suppress the creation of the pathogenic antibodies. Plasmapheresis removes inflammatory mediators and harmful antibodies from the system. Intravenous immunoglobulins are one of the drug categories under immunomodulation drugs. There are two approaches to initial management, and neither has sufficient evidence available today. Some clinicians recommend the use of low dosages of systemic medicine and personalized treatment plans and acknowledge that sometimes more aggressive therapy may be needed for certain patients. A few medical practitioners believe that the initial therapy for controlling all patients should be high dosages. The treatment is then tapered down after the disease has been controlled. An occasional blister during long-term maintenance treatment does not mean that the dosage should be changed or increased. When the illness has been under control for a month or more, the amount of treatment should be decreased. This makes it feasible to make sure the patient isn't receiving excessive care. Using Medline, Embase, and the Cochrane Library, a systematic review of BP therapies identified only six RCTs enrolling 293 participants.[3] Taking all this into account, comprehensive analysis of treatment for BP allows us to make three deductions.

First, any systemic corticosteroid dose above 0.75 mg kg 1 or prednisolone doses greater than 30 mg per day were associated with high mortality; prednisolone doses of more than 0.75 mg kg) 1 per day (52.5 mg per day for a 70 kg patient) did not seem to confer any additional advantage. Second, it is not easy to judge the effectiveness of plasma exchange and azathioprine. More studies must be conducted on tetracyclines and nicotinamide in order to know if they are helpful.[4-8]

TREATMENT

Systemic corticosteroids

The systemic corticosteroid treatment for BP is proven to be effective based on uncontrolled clinical trials and is established in clinical practice.[9-11] However, optimal dosing schedules are still debated due to the various treatment regimens and the differences between patients regarding the illness severity such that very few of the researches are comparable. Unless otherwise indicated, doses are based on prednisolone and prednisone, which are the most commonly used corticosteroids. Extensive disease requires an initial daily dose of approximately 1 mg kg. The dose should be continued until fresh blister formation stops, after which it should be tapered according to the clinical course.[7,12,13] However, most studies use a uniform induction dose, typically between 40 and 80 mg/day, with 60 mg/day most commonly used, and increase the corticosteroid dose proportionally with body weight rather strictly.[10] More recently, initiation doses as low as 20 to 40 mg/day have been advocated.[14] The experience in clinical practice is that the amount of systemic corticosteroid required to control the disease is approximately proportional to the severity of the disease.[11,15,16] A retrospective examination of 23 patients receiving daily doses of prednisone at 1 mg kg revealed that the number of blisters at baseline and the duration of therapy required for control were significantly correlated. Aggressive treatment with intravenous methylprednisolone 750-1800 mg daily in eight older subjects decreased blistering within 24 hours but still left significant morbidity after that.[17]

Topical corticosteroids

Complete improvement of all the 10 cases of significant and widespread BP occurred within a period of as short as 17 days, with the intervention of 0.05% clobetasol propionate cream. Till reporting, seven patients were still on remission phase for 1-10 months in the same course.[18] In a second study, twenty patients with BP (involvement of less than 60% body surface) were treated with very potent topical corticosteroids; seven of these patients had complete abolition of their BP, and the same number entered remission over an 11-month follow-up.[19] Skin atrophy and cutaneous infection were minimal side effects. Multiple case reports and smaller series of less than five patients have also reported the use of topical corticosteroids.[19-22] Thus, topical corticosteroids alone are likely to be effective for mild to moderate and localized disease (Strength of recommendation A, quality of evidence III). They could be effective as an adjunct to systemic therapy.[23] Besides drawing attention to the mortality associated with high-dose oral corticosteroids, a recent study by Joly et al further supports the use and benefits of topical corticosteroids as the sole treatment for moderate to severe disease.[24]

Antibiotics and nicotinamide

Antibiotics and nicotinamide should be considered as the first line of treatment for localized and mild to moderate disease, one small RCT12, very small uncontrolled trials, and case reports; strength of recommendation B, Quality of evidence II-ii ⁄iii. Tetracycline or erythromycin have been used in the treatment of BP in 38 cases (183 patients), commonly in combination with nicotinamide and sometimes in combination with topical or even oral corticosteroids. Such blister formation occurs in the majority of studies, which accept it as occasional. There are numerous case reports and merely two case series of 11 and 15 patients that establish the beneficial effects of erythromycin for adults and children.[25-27] Children would be especially advised to receive erythromycin at an adult dosage: 1000-3000 mg per day, possibly in combination with topical corticosteroids. A positive result is likely to occur within one to three weeks after initiating therapy.[8,28-32] Strength of recommendation B, quality of evidence II-iii. Many case reports and series describe the beneficial effects of tetracyclines, usually in combination with nicotinamide. Most responded within 1-3 weeks, but some also received topical or even systemic corticosteroids. In comparison to systemic corticosteroids, this treatment has fewer side effects, a small RCT suggested. Adults should be treated with tetracyclines and nicotinamide, possibly in combination with topical corticosteroids (Strength of recommendation B, quality of evidence II-ii). The optimal dosages are unknown. Dosages of 500-2000 mg of tetracycline, 200-300 mg of doxycycline, and 100-200 mg of minocycline have all been used. Patients with hepatic impairment should avoid doxycycline and minocycline, and those with renal impairment should avoid tetracycline. Hyperpigmentation should prompt discontinuation of minocycline. Minocycline must be withdrawn as adverse because of a few reported cases of eosinophilia and pneumonia associated with the drug. The starting dose for nicotinamide is 500-2500 mg/day, which should be titrated up to 1500-2500 mg/day. Once blister formation has been adequately inhibited, the antibiotics and nicotinamide must be tapered, one at a time, over months to prevent recurrence.[8]

Azathioprine

The most commonly used drug for BP, after systemic corticosteroids, is azathioprine in doses of up to 2 mg kg per day. Due to its perceived steroid-sparing effect, it is primarily employed as an adjuvant to systemic corticosteroids. Yet, only two RCTs have compared the

efficacy of azathioprine as a steroid-sparing agent in BP, with conflicting results. Within a period of three years, one RCT reported that cumulative prednisolone dose had reduced by 45%.[5] Alternatively, a larger RCT demonstrated no difference between remission at 6 months in patients receiving corticosteroid monotherapy and those on prednisolone as well as azathioprine combination therapy.[7]

In very small, uncontrolled series, azathioprine has been used as a single drug for treatment in inducing remission and maintaining a remission induced by corticosteroids. Though this is not always possible, thiopurine methyltransferase (TMPT) activity should be assessed beforehand to adjust the dose of azathioprine both in terms of efficacy as well as risk of myelosuppression. Azathioprine can only be reserved for a second-line agent after prednisolone in situations when the response was poor and disease suppression has failed or intolerable and bothersome side effects, considering its side-effect profile.[7]

Dapsone and sulphonamides

RCTs have not been performed on the treatment with sulphonamides or dapsone as adjuncts or alone for BP. Dapsone 50-200 mg per day or, less commonly, sulfapyridine or sulfmethoxypyridazine 1-1.5 g per day were reported in four retrospective datasets in 110 patients. They were both applied as treatments alone and in combination with topical corticosteroids.[33-35] In three series, the response rate was about 45%, but in the fourth, only 15%.[36] In comparison with systemic corticosteroids, the response was slower to appear (2-3 weeks). In a small uncontrolled series, patients who were treated with dapsone as well as prednisolone and azathioprine had a possible steroid-sparing effect.[37] Glucose-6-phosphate dehydrogenase deficiency should be excluded in predisposed races as it predisposes to haematological side effects. In elderly patients, sulphonamides and dapsone's side-effect profile could be hazardous. Only in instances when alternative treatments prove ineffective or inappropriate should they be considered.[37]

OTHER IMMUNOMODULATORY TREATMENTS

The following treatments may be useful in individual resistant cases.

Cyclophosphamide

Cyclophosphamide has little published experience. The co-administration with oral and intravenous cyclophosphamide and intravenous pulsed dexamethasone was helpful in three individual cases of otherwise extremely resistant BP. Oral cyclophosphamide 100 mg per day in a small group of 10 patients resulted in an unacceptable rate of drug-related death and morbidity and no steroid-sparing effect. Cyclophosphamide should only be considered in instances where other treatments have failed or are contraindicated.[38]

Methotrexate

No controlled trials are done. Low doses of methotrexate (5-10 mg weekly) permitted the concurrent oral prednisolone to be tapered in one small study. In an open prospective study, methotrexate (range of dose: 5-12.5 mg weekly) was the sole systemic agent that controlled the disease for three months to two years in 11 patients with BP not responsive to topical corticosteroids alone. For people who have both psoriasis and high BP, methotrexate should be taken into consideration.[39]

Cyclosporin

Experience with cyclosporin is limited to only five different case reports and a small series of seven patients. Even at fairly high dosages (> 6 mg kg) 1 day, there is unconvincing evidence of effectiveness, and responses were primarily noted in patients receiving concomitant oral corticosteroid therapy.[40]

Mycophenolate mofetil

Since 1997, mycophenolate mofetil, an immunosuppressive drug well tolerated in general, has been employed to avoid kidney graft rejection by suppressing purine synthesis in activated T and B cells. It has been employed twice daily in doses of 0.5-1 g safely to control BP in six individual cases; in three of them, it was an adjuvant to oral prednisolone. Its role in BP needs more evidence.

Intravenous immunoglobulin

There are only five small series of published experience with intravenous immunoglobulin in BP, and this implies that its utility is restricted. It was given mainly at a dose of 0.4 mg kg polyvalent immunoglobulin daily for five days, either alone or combined with oral prednisolone, and it sometimes showed dramatic but unfortunately short-lived effects that were too short-lived to be of any use.[41,42]

Chlorambucil

In an open study, 26 BP patients received 40-60 mg/day of prednisolone and 0.1-0.15 mg kg/day of chlorambucil. The chlorambucil maintenance dose was usually 2 mg/day; after 2 weeks, doses of both drugs were gradually reduced.

In comparison with other-studies employing corticosteroids and azathioprine, the mean duration of treatment and the mean total corticosteroid requirement were both reduced. If other more recognized immunosuppressants have failed, are not tolerated, or are not suitable, chlorambucil must be considered as an alternative. Careful monitoring is required for possible hematological toxicity.[43]

Plasmapheresis (Plasma exchange)

Just two RCTs, small series of cases, and many case reports (100-150 patients) have been done on plasmapheresis, or plasma exchange, use in the treatment of high BP. The adjunct therapy, regimens, and results have all differed significantly. While a steroid-sparing effect was noted with low dosages of corticosteroids, there is no evidence for the routine use of plasmapheresis in BP. Plasmapheresis has a possible role in resistant BP cases in which side effects are a major issue or in cases where the disease is uncontrolled.[44,46]

Table 1: Evidence-based treatment for bullous pemphigoid according to disease severity.

Medication	Dose	BP severity	Level of evidence
First-line treatment			
High-potency topical steroid (0.05% clobetasol cream)	10-30 g/day topical	Mild to moderate	1A
Systemic steroid (prednisone)	0.5-1.0mg/kg/day PO	Moderate to severe	1A
Second-line treatment			
Doxycycline (>12 years)	100 mg BID PO	Mild to moderate	1B
Dapsone	Adult:100 mg/day PO Children-0.5-2.0 mg/kg/day PO	Mild to moderate	1B
Methotrexate	15 mg/week PO	Moderate to severe	3B
Azathioprine	0.5-2.0 mg/kg/day PO	Moderate to severe	1B
Mycophenolate mofetil	35-45 mg/kg/day PO (up to 3g/day)	Moderate to severe	1B
Intravenous immunoglobulin	400 mg/kg/day for 5 consecutive days IV	Severe	1B
Rituximab	1g on day 1 and day 14 or 375 mg/m^2/ week for 4 weeks IV	Severe	4
Omalizumab	300 mg every 2-4 weeks SC	Severe	4

Levels of evidence: adapted from the centre for evidence-based medicine, Oxford; 1A: systematic review (with homogeneity) of randomized controlled trials; 1B: individual randomized controlled trials (with narrow confidence interval); 3B: individual case-control study; 4: case series (poor-quality cohort or case-control studies).[45]

CONCLUSION

A holistic approach is employed to manage bullous pemphigoid aiming to minimize therapeutic risks and control clinical symptoms. BP is self-limiting and often resolves with time but requires symptom treatment of blisters, itching, and urticarial lesions by balancing the patient's age, severity of disease, and risk of adverse drug reactions. Although other immunosuppressive and immunomodulatory drugs such as azathioprine, methotrexate, and intravenous immunoglobulins are also often used alone or for more advanced cases, systemic and topical corticosteroids remain the mainstay of treatment. Individualization of therapy is still important, and data on the optimal regimens of therapy are still unfolding despite the myriads of present drugs. The aim is to strike a balance between efficacy and side effect risk so that patients obtain symptom control with minimal harm. Further research will be required to optimize these strategies and enhance patient outcomes. Plasmapheresis [plasma exchange] only two RCTs cases are taken steroid sparing effect was noted in low doses of corticosteroids. this plasma exchange can also cause major effect where the BP might not be in control. This article was written by undertaking six RCTs enrolling 293 subjects suffering from mild, moderate and severe bullous pemphigoid.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Lever WF. Pemphigus. Medicine. 1953;32(1):1-123.
2. Cruz PD Jr. Annual Trainee Awards for 1996 and 1997. Arch Dermatol. 1998;134(3):343.
3. Khumalo NP, Murrell DF, Wojnarowska F, Kirtschig G. A Systematic review of treatments for bullous pemphigoid. Arch Dermatol. 2002;138(3):385-9.
4. Morel P, Guillaume JC. Treatment of bullous pemphigoid with prednisolone only: 0.75 mg/kg/day versus 1.25 mg/kg/day. A multicenter randomized study. Ann Dermatol Venereol. 1984;111(10):925-8.
5. Burton JL, Harman RR, Peachey RD, Warin RP. Azathioprine plus prednisone in treatment of pemphigoid. BMJ. 1978;2(6146):1190-1.
6. Roujeau J, Morel P, Dalle E, Guillot B, Gorin I, Lorette G, et al. Plasma exchange in bullous pemphigoid. The Lancet. 1984;324(8401):486-9.
7. Anstey A. Controlled trial of azathioprine and plasma exchange in addition to prednisolone in the treatment of bullous pemphigoid. Arch Dermatol. 1993;129(9):1203.
8. Fivenson DP. Nicotinamide and tetracycline therapy of bullous pemphigoid. Arch Dermatol. 1994;130(6):753.
9. Stevenson CJ. Treatment In Bullous Diseases with Corticosteroid Drugs and Corticotrophin. Brit J Dermatol. 1960;72(1):11-21.
10. Church R. Pemphigoid treated with corticosteroids. Brit J Dermatol. 1960;72(12):434-8.

11. Downham TF. Bullous pemphigoid. Arch Dermatol. 1978;114(11):1639.
12. Chosidow O, Saada V, Diquet B, Revuz J, Revuz J. Correlation between the pretreatment number of blisters and the time to control buUous pemphigoid with prednisone 1 mg/kg/day. Brit J Dermatol. 1992;127(2):185-6.
13. Fine JD. Management of acquired bullous skin diseases. N Eng J Med. 1995;333(22):1475-84.
14. Champion RH, Burton JL, Ebling FJG. Clinical Dermatology. Oxford; Blackwell Scientific. 5 ed. 1992.
15. Venning V, Wojnarowska F. Lack of predictive factors for the clinical course of bullous pemphigoid. J Am Academy Dermatol. 1992;26(4):585-9.
16. Person JR, Rogers RS, Perry HO. Localized pemphigoid. British J Dermatol. 1976;95(5):531-4.
17. Siegel J. High-Dose methylprednisolone in the treatment of bullous pemphigoid. Arch Dermatol. 1984;120(9):1157.
18. Westerhof W. Treatment of bullous pemphigoid with topical clobetasol propionate. J Am Academy Dermatol. 1989;20(3):458-61.
19. Zimmermann R. Prospective study of treatment of bullous pemphigoid with class I topical corticosteroid. J Eur Academy Dermatol Venereol. 1998;11:S138.
20. Muramatsu T, Iida T, Shirai T. Pemphigoid and Pemphigus Foliaceus Successfully Treated with Topical Corticosteroids. J Dermatol. 1996;23(10):683-8.
21. Spuls PI, Brakman M, Westerhof W, Bos JD. Treatment of generalized bullous pemphigoid with topical corticosteroids. Acta Dermato Venereologica. 1995;75(1):89.
22. Paquet P, Richelle M, Lapiere CM. Bullous pemphigoid treated by topical corticosteroids. Acta Dermato Venereologica. 1991;71(6):534-5.
23. Loche F, Bazex J, Giard A, Grolleau P, Marguery M. Efficacy and tolerability of topical corticosteroid treatment in the initial phase of bullous pemphigoid: An open study of 13 cases. J Dermatological Treat. 1995;6(2):69-72.
24. Joly P, Roujeau J, Benichou J, Picard C, Dreno B, Delaporte E, et al. A Comparison of Oral and Topical Corticosteroids in Patients with Bullous Pemphigoid. N Eng J Med. 2002;346(5):321-7.
25. Fox BJ, Odom RB, Findlay RF. Erythromycin therapy in bullous pemphigoid: Possible anti-inflammatory effects. J Am Academy Dermatol. 1982;7(4):504-10.
26. Alzolibani AA, Zedan K. Macrolides in chronic inflammatory skin disorders. Mediators Inflammation. 2012;1-7.
27. Krausse S. Erythromycin in der Behandlung des bullösen Pemphigoids: vergleichende Untersuchung zur konventionellen Therapie. 1988.
28. Thomas I, Khorenian S, Arbesfeld DM. Treatment of generalized bullous pemphigoid with oral tetracycline. J Am Academy Dermatol. 1993;28(1):74-7.
29. Kimura K, Kawai K. Doxycycline as an initial treatment of bullous pemphigoid in Japanese patients. J Cutaneous Immunol Allergy. 2020;3(4):80-5.
30. Kolbach DN, Remme JJ, Bos WH, Jonkman MF, Jong MC, Pas HH, Meer JB. Bullous pemphigoid successfully controlled by tetracycline and nicotinamide. Brit J Dermatol. 2006;133(1):88-90.
31. Hornschuh B, Hamm H, Wever S, Hashimoto T, Schröder U, Bröcker E, et al. Treatment of 16 patients with bullous pemphigoid with oral tetracycline and niacinamide and topical clobetasol. J Am Academy Dermatol. 1997;36(1):101-3.
32. Venning V, Taghipour K, Mustapa MM, Highet A, Kirtschig G, Hughes J, et al. British Association of Dermatologists' guidelines for the management of bullous pemphigoid 2012. Brit J Dermatol. 2012;167(6):1200-14.
33. Wojnarowska F, Kirtschig G, Highet A, Venning V, Khumalo N. Guidelines for the management of bullous pemphigoid. Brit J Dermatol. 2002;147(2):214-21.
34. Venning V, Millard P, Wojnarowska F. Dapsone as first line therapy for bullous pemphigoid. Brit J Dermatol. 1989;120(1):83-92.
35. Bouscarat F, Chosidow O, Picard-Dahan C, Sakiz V, Crickx B, Prost C, et al. Treatment of bullous pemphigoid with dapsone: Retrospective study of thirty-six cases. J Am Academy Dermatol. 1996;34(4):683-4.
36. Person JR. Bullous pemphigoid responding to sulfapyridine and the sulfones. Arch Dermatol. 1977;113(5):610.
37. Jeffes E, Ahmed A. Adjuvant therapy of bullous pemphigoid with dapsone. Clin Exp Dermatol. 1989;14(2):132-6.
38. Itoh T, Hosokawa H, Shirai Y, Horio T. Successful treatment of bullous pemphigoid with pulsed intravenous cyclophosphamide. Brit J Dermatol. 1996;134(5):931-3.
39. Heilborn JD, Ståhle-Bäckdahl M, Albertioni F, Vassilaki I, Peterson C, Stephansson E. Low-dose oral pulse methotrexate as monotherapy in elderly patients with bullous pemphigoid. J Am Academy Dermatol. 1999;40(5):741-9.
40. Thivolet J, Barthelemy H, Rigot-Muller G, Bendelac A. Effects of cyclosporin on bullous pemphigoid and pemphigus. The Lancet. 1985;325(8424):334-5.
41. Tappeiner G, Steiner A. High-dosage intravenous gamma globulin: Therapeutic failure in pemphigus and pemphigoid. J Am Academy Dermatol. 1989;20(4):684-5.
42. Harman KE, Black MM. High-dose intravenous immune globulin for the treatment of autoimmune blistering diseases: an evaluation of its use in 14 cases. Brit J Dermatol. 1999;140(5):865-74.
43. Milligan A, Hutchinson PE. The use of chlorambucil in the treatment of bullous pemphigoid. J Am Academy Dermatol. 1990;22(5):796-801.

44. Egan CA, Meadows KP, Zone JJ. Plasmapheresis as a steroid saving procedure in bullous pemphigoid. Int J Dermatol. 2000;39(3):230-5.
45. Miyamoto D, Santi CG, Aoki V, Maruta CW. Bullous pemphigoid. Anais Brasileiros De Dermatologia. 2019;94(2):133-46.
46. Wojnarowska F, Kirtschig G, Highet A, Venning V, Khumalo N. Guidelines for the management of bullous pemphigoid. Brit J Dermatol. 2002;147(2):214-21.

Cite this article as: Subhan A, Siddhartha L, Goud MR, Khanam S. Breaking the blisters: a comprehensive guide to treating bullous pemphigoid. Int J Basic Clin Pharmacol 2025;14:597-602.