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A Literature Review and Clinical Consensus Guidelines on the Management of Bullous Pemphigoid

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Abstract

Bullous pemphigoid (BP) is the most common autoimmune blistering disease primarily characterized by tense blisters and occasionally with urticarial plaques, affecting the skin and mucous membranes. These are caused by autoantibodies against BP180 and BP230 which target antigens on the basement membrane zone. The diagnosis relies on the integration of clinical, histopathological, immunopathological, and serological findings. The management depends on the clinical extent and severity. We present in this article a literature review and the clinical consensus guidelines of the Immunodermatology Subspecialty Core Group of the Philippine Dermatological Society in the management of BP.

Keywords: Bullous pemphigoid, clinical consensus guidelines, literature review

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Introduction

Bullous pemphigoid (BP) is the most common autoimmune blistering disease. There are a total of 1063 new cases of BP with a female: male ratio of 1.4 listed in the Philippine Dermatological Society Health Information System (PDS HIS) from 2011 to 2022. The incidence of BP in 2020 is 0.38/10 million. Elderly patients are more commonly affected.

It is caused by immunoglobulin (Ig) G autoantibodies acting against the basement membrane zone. It has two targets: BP180, which is a transmembrane protein; and BP230, which is an intracellular constituent of the hemidesmosomal plaque.[1] Antibodies against the epitopes in the NC16a domain of BP180, which is located at the extracellular region closest to the cell membrane of the basal cells, are pathogenic. The pathogenicity of the C-terminal of the BP230 antigen in blister formation is still unknown.[2]

After the autoantibodies bind with the target antigen, inflammatory cell infiltration is locally induced through complement activation and blister formation due to proteolytic enzymes.[3] Another proposed mechanism

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is that the antigen is internalized into the basal cell as the auto-antibody binds to the target antigen, thereby creating fragility in the basement membrane zone.[2] IgE autoantibodies to the basement membrane zone may be detected by immunofluorescence studies. Serum IgE autoantibody titer correlates with the extent of the wheals or erythema.[4]

The management of BP is founded on the principles of disease classification and definition of its clinical phases. We present the results of an extensive literature review and consensus exercises to come up with the guidelines that are relevant to the Filipino dermatology practice.

Methodology

A group of 13 board-certified dermatologists from the Philippine Dermatological Society with a subspecialization in Immunodermatology convened to discuss consensus guidelines in the management of BP in the country. This effort started with literature search using Pubmed. Keywords used were as follows: bullous pemphigoid, guidelines, recommendations, clinical trials, case reports, and case series. These articles were grouped as to either recommendations or guidelines from an international pool of experts, systemic reviews, randomized controlled trials, case reports, retrospective studies, comparative effectiveness, and general review articles [Figure 1].

After an extensive literature search, the panel of experts gathered 6 recommendations or guidelines from an international pool of experts, 2 systematic reviews, 6 randomized controlled trials, and 28 other articles that were a combination of case reports, retrospective studies, comparative effectiveness studies, and general review articles. Articles were assessed using the Modified Jadad Scale.[5,6] To come up with the consensus guidelines in treating BP, a Delphi survey was conducted over three separate virtual meetings. There was a 100% response rate in all meetings. Each dermatologist provided Likert Scoring per statement (1 strongly disagree, 2 disagree, 3 neutral, 4 agree, and 5 strongly agree). Statements that have a mean score of >4.0 achieved consensus. Statements that have a mean score of >3.5 but <4.0 achieved near consensus. Statements that have a mean score of <3.5 have no consensus.

Review of Literature

Clinical features

The classical form of BP would appear as pruritic erythematous urticarial plaques that would eventually develop tense blisters usually located on the flexural areas of the arms, medial thighs and abdomen. Rarely do they develop mucosal involvement.[7] The Bullous Pemphigoid Disease Area Index (BPDAI) is a validated scoring system for determining the severity of bullous pemphigoid [Appendix 1]. To calculate BPDAI, the patient's skin is thoroughly examined to check for the extent of erythema, vesicles, bullae, and erosions. The skin is examined per area, namely head, neck, chest, left arm, right arm, hands, abdomen, genitals, back/buttocks, left leg, right leg, and feet. All the mucosal surfaces are examined as well. These include the eyes, nose, mouth (palate, gingivae, tongue, labial, pharynx, and floor or the mouth), and anogenital areas. The erosions, blisters, erythema, and urticaria on the skin are counted per body area and an activity score (0, 1, 2, 3, 5, or 10) is assigned depending on the severity. The erosions and blisters on the mucosal surfaces are also counted and activity score (1, 2, 5, and 10) is assigned. The activity scores are added with a total of 0–360.[8] There are no guidelines as to how often BPDAI has to be performed, but the group recommends recording BPDAI on each visit. BP is classified based on the extent of disease activity, if they are corticosteroid-dependent, or recalcitrant based on the S2k[9] and French Guidelines[10] [Table 1].

Observation points in the disease course of BP have been defined by an international panel of experts.[8] This is assessed starting at baseline, on every visit, and until when the patient is in complete remission off therapy [Table 2].

Diagnostic steps

Clinicians must get a detailed history and document the character and extent of the lesions on physical examination. Additional laboratory work-up should be done to strengthen the diagnosis of BP [Tables 3 and 4].[7]

The diagnosis of BP is an integration of both clinical examination and laboratory investigations. The diagnosis

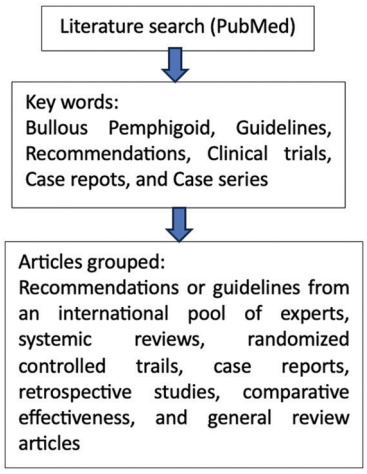

Figure 1: Process of literature review

of BP is likely or probable if there is positive clinical and histopathological evidence of the disease. The diagnosis of BP is very likely or highly probable if there is positive clinical, histopathological, and direct immunofluorescence (DIF) evidence of the disease. The diagnosis of BP is almost certain or guaranteed if there is positive clinical, histopathological, DIF, and enzyme-linked immunosorbent assay (ELISA) evidence of the disease.

Table 1: Definition of terms used when classifying bullous pemphigoid based on the S2k[9] and French guidelines[10]

	Definitions
Localized BP	Vesicles/bullae/inflammatory lesions (urticarial papules or plaques, erythematous patches) on one area of the body
Limited BP	<10 new vesicles/bullae/inflammatory lesions per day, BPDAI <20
Extensive BP	Overlap between moderate and severe BP≥10 vesicles/bullae/inflammatory lesions per day in different areas of the body, BPDAI >20
Corticosteroid-dependent BP	Appearance of ≥3 new lesions/month or ≥1 large (>10 cm diameter) lesion that do not heal ≤7 days, or extension of established lesions or pruritus 1 ×/day when topical or systemic steroids are tapered down
Recalcitrant/refractory/ resistant BP	Generalized lesions that are unresponsive despite weeks of topical and systemic steroid therapy and other steroid-sparing agents

BP: Bullous pemphigoid, BPDAI: BP disease area index

There are other immunopathological tests that may be requested, but these are not yet available in the Philippines [Table 5].

Drug-induced bullous pemphigoid

In contrast to idiopathic BP, the clinical presentations in drug-induced BP are heterogeneous and usually affect younger patients. The drugs commonly associated with BP may be classified based on its chemical structure. The main drug classes that may induce BP are thiol-drugs, phenol-drugs, and nonthiol nonphenol drugs. Included in the thiol group is penicillamine and enalapril whereas cephalosporins and aspirin belong to the phenol group. Among the nonthiol nonphenol drugs are dipeptidyl peptidase-4 inhibitors (DPP-4i) and losartan.[11] There are no known differences in clinical presentations among these drug classes. In the majority of reported cases, histopathology of drug-induced BP showed the following features: prominent eosinophilic infiltrate, necrotic keratinocytes may be present, intraepidermal vesicles, and thrombi formation may be apparent. However, for DPP-4i induced BP, histopathology revealed few eosinophils.[12] The DIF and indirect immunofluorescence (IIF) revealed no difference with conventional BP. In patients with DPP-4i-induced BP, ELISA revealed the absence of BP180-NC16A antibodies; this corresponds to a noninflammatory clinical form of BP.[12-14] The laboratory test usually shows marked serum

Table 2: Observation points during the disease course in bullous pemphigoid[8]

Observation points	Outcome measure definitions
Baseline	Start of BP therapy
CDA	Day when lesions stopped forming and established lesions start healing or pruritus starts to improve
Beginning of consolidation phase	Time to CDA; disease control Interval between baseline and CDA
End of consolidation phase	Day when there are no more new lesions appearing for ≥2 weeks and about 80% of current lesions have healed and pruritus is minimal
Transient lesions	Healing of new lesions ≤1 week or improvement of pruritus ≤1 week without therapy
Nontransient lesions	Nonhealing of new lesions within a week or worsening of pruritus ≤1 week without therapy
Complete remission during therapy	No lesions or pruritus while receiving more than minimal therapy
Minimal therapy	Prednisone ≤0.1 mg/kg/day; or Clobetasol propionate ≤20 g/week
Partial remission on minimal therapy	Appearance of transient lesions while on minimal therapy for ≥2 months
Complete remission on minimal therapy	No new or established lesions or pruritus while on minimal therapy for ≥2 months
Partial remission off therapy	Appearance of transient lesions while patient is not receiving any BP treatment for ≥2 months
Complete remission off therapy	No new or established lesions or pruritus while patient is not receiving any BP treatment for ≥2 months
Mild new activity	<3 lesions/month that do not heal ≤1 week, or extension of established lesions, or pruritus once a week but <1 ×/day in a patient who was already in CDA; lesions must heal ≤2 weeks
Relapse/flare	≥3 new lesions/month or≥1 large (>10 cm diameter) lesion that do not heal ≤1 week, or extension of established lesions or pruritus 1 ×/day in a patient who was already in CDA
Failure of therapy for initial control	Presence of new nontransient lesions or extension of old lesions; inability of established lesions to heal, or persistent pruritus despite treatment with Clobetasol propionate 40 g/day×4 weeks; or Prednisone 0.75 mg/kg/day for at least 3 weeks; or Full dose of tetracycline×4 weeks; or Dapsone 1.5 mg/kg/day; or Methotrexate 15 mg/week×4 weeks; or Azathioprine 2.5 mg/kg/day×4 weeks Mycophenolate mofetil 40 mg/kg/day×4 weeks

CDA: Control of disease activity, BP: Bullous pemphigoid

eosinophilia in drug-induced BP. Serum eosinophilia is less common in patients with DPP-4i-related BP. In conventional BP eosinophilia is present in 50%.[15-17] Drug-induced BP appears to have a better prognosis, noted as prompt response with steroid treatment and possible improvement with cessation of the triggering agent.[18] Further studies are needed to ascertain features and differences of drug-induced BP due to some conflicting published studies.

Pretreatment screening

The following are suggested work up and pretherapy screening for newly diagnosed BP patients.

- Complete blood count, erythrocyte sedimentation rate, C-reactive protein
- Creatinine, blood electrolytes
- Fasting blood sugar
- Transaminases, gamma-GT, alkaline phosphatase, bilirubin
- Albumin
- Pregnancy test (if of child-bearing age)
- TPMT level test, if available (if azathioprine treatment is considered)
- G6PDH test (if dapsone treatment is considered)
- Serum IgE (if intravenous Ig [IVIg] is considered)
- Check for an underlying neoplasm in line with the patient's age, clinical history and examination (if immunosuppressant is to be initiated)
- Check for an infection (rule out tuberculosis: chest radiograph, PPD testing, sputum examination and quantiferon testing; rule out parasitic infection: fecalysis; rule out viral infection: serology for hepatitis B, C and HIV especially if immunosuppressive therapy is planned)
- Bone densitometry (if systemic corticosteroid therapy is planned)
- Ocular examination (if systemic corticosteroid therapy is planned);
- Local bacteriological sampling (if there is any clinical evidence for lesion infection)
- Echocardiography (before initiation of systemic corticosteroids, dapsone, or IVIg).

Table 3: Clinical examination for a possible bullous pemphigoid patient[7]

History	Physical examination	Assessment
Elderly patient Onset of skin lesions Evolution of signs and symptoms Recent drug intake (over the past 1–6 months) to rule out possible drug-induced BP Elderly patient with refractory itch of unknown origin	Classical bullous form of BP: Symmetric distribution of vesicles and blisters over an erythematous or nonerythematous skin, located on flexural surfaces of the limbs, medial surface of thighs, trunk; oral mucosal involvement may be rare Nonbullous or atypical forms of BP: Excoriations, prurigo, prurigo nodularis-like lesions, localized blister, erosions, eczematous and urticarial lesions, dyshidrosiform	Determine the extent of BP (using BPDAI scoring) Check on the general condition and comorbidities of the patient Request for laboratory work-ups according to patient's condition and treatment choice

BP: Bullous pemphigoid, BPDAI: BP disease area index

Therapeutics

The following are the treatment goals in managing BP:[19]

a. To assess clinical condition, comorbidities, and risk factors
b. To specify the extent of the disease
c. To consider therapeutic options based on the clinical condition, comorbidities, risk factors, and the extent of the disease
d. Treat the skin condition, reduce itch, and prevent the risk of recurrence
e. Improve the quality of life of patients
f. Limit the side effects of the medication.

Table 4: Laboratory investigations for bullous pemphigoid[7]

Histopathology (lesional skin)	Direct immunofluorescence (perilesional skin)	Immune serological tests
Subepidermal blister with eosinophils and/or neutrophils Dermal infiltrate of eosinophils and/or neutrophils Marginalization of eosinophils along the dermal-epidermal junction Nonspecific findings in atypical forms	Linear (n-serrated) deposits of IgG and/or C3 along the epidermal-dermal junction Sometimes IgA and IgE with similar pattern	Indirect immunofluorescence microscopy on normal human salt-split-skin (or suction-split): IgG anti-basement membrane antibodies binding to the epidermal side (sometimes epidermal and dermal) of the split ELISA for IgG antibodies to BP180/BPAG2 and, if negative, for BP230/BPAG1

IgG: Immunoglobulin G, IgA: Immunoglobulin A, IgE: Immunoglobulin, ELISA: Enzyme-Linked Immunosorbent Assay

Table 5: Other immunopathological tests[7]

Immunoblotting	Biochip	FOAM	Immunohistochemistry
Search for reactivity with BP180 (BPAG2) and/or BP230 (BPAG1). Rarely, additional targeted autoantigens	Indirect immunofluorescence with purified BP180 recombinant protein spotted on slide and transfected cells expressing BP230	Assessment of relative location of detected IgG deposits compared to other proteins within the basement membrane zone	In a significant proportion of patient's linear deposits of C3d and C4d along the basement membrane zone can be demonstrated using the same tissue sample obtained for light microscopy studies

FOAM: Fluorescence overlay antigen mapping, IgG: Immunoglobulin G

Table 6: Immunosuppressives that may be used in the treatment of bullous pemphigoid

Immunosuppressive	Mechanism of action	Dose	Monitoring	Complications to watch for
Corticosteroids[20,21]	Inhibition of the nuclear factor kappa B transcription factor that results in decreased chemokine and cytokine production, particularly the cyclooxygenases, ILs 1 thru 6, TNF-a and macrophage stimulating factors	Prednisone 0.5–0.75 mg/kg/day	Weight and blood pressure checked at baseline and every 1–3 months thereafter Blood glucose, electrolytes, lipids checked every 6 months Ophthalmologic examination every 12 months Stool exam for occult blood and chest radiograph as needed Pain, whether abdominal pain or bone pain, must be evaluated as soon as possible. If aseptic bone necrosis is suspected, MRI may be necessary Consultation with an endocrinologist may also be necessary for those on chronic glucocorticoid use at risk for HPA axis suppression Note Prevent exposure to infections Slow tapering of systemic corticosteroids to minimize the risk of HPA axis suppression Proton pump inhibitors must be given to those with gastrointestinal symptoms Calcium and Vitamin D supplementation for all adults taking prednisone >2.5 mg/day for >3 months Lifestyle modifications for all adults taking prednisone >2.5 mg/day for >3 months Balanced diet Maintaining the weight in recommended range Smoking cessation Regular weight-bearing or resistance training exercise Limiting alcohol intake to 1–2 alcoholic beverages/day Use of bisphosphonates for selected patients based on risk stratification based on the 2017 ACR guideline for the prevention and treatment of glucocorticoid-induced osteoporosis	Short term effects Mood changes, nervousness, insomnia Gastrointestinal intolerance Weakness, muscle effects Fluid, sodium retention Increased appetite, weight gain Amenorrhea Increased infections Acneiform eruption Blood sugar effects Wound healing effects Long-term effects Musculoskeletal Osteoporosis, aseptic bone necrosis, growth retardation, muscle atrophy Ophthalmologic Cataracts, glaucoma, infection, hemorrhage, exophthalmos Gastrointestinal Nausea, vomiting, peptic ulcer disease, intestinal perforation, pancreatitis, esophagitis Metabolic Hyperglycemia, hyperlipidemia, obesity, hypocalcemia, hypokalemic alkalosis Cardiovascular Hypertension, edema, atherosclerosis Gynecologic Amenorrhea, fetal effects Hematologic Leukocytosis, lymphopenia, eosinopenia, immunosuppression, impaired fibroplasia, decreased mitotic rate Nervous Mood, personality changes, psychiatric problems, seizures, pseudotumor cerebri, peripheral neuropathy Cutaneous Atrophy, striae, vascular effects, purpura, hair changes, pigmentary changes, acne, acneiform eruptions, infections HPA axis suppression
Azathioprine[22]	Purine analog that is incorporated in to the DNA during the S phase that stops normal development of and division of B-cells and T-helper cells	1–3 mg/kg/day	Before initiation of therapy Hepatic function tests CBC with differential count Urinalysis TB screening Hepatitis B and C screening Pregnancy test if indicated During therapy CBC with differential count every 2 weeks for the 1st 2 months, monthly for the next 2 months, and then every 2 months thereafter Liver function tests monthly for the first 3 months and then every 2 months thereafter Semiannual physical examination focusing on evidence of lymphadenopathy and nonmelanoma skin cancers	Short-term toxicity: Nausea, hypersensitivity Medium-term toxicity: Myelotoxicity Long-term toxicity: Carcinogenesis

Contd...

Table 6: Contd...

Immunosuppressive	Mechanism of action	Dose	Monitoring	Complications to watch for
Mycophenolate mofetil[23,24]	Inhibits inosine monophosphate dehydrogenase which inhibits biosynthesis of guanine nucleotides needed in T-cell and B-cell proliferation; depletes monocytes and macrophages resulting in reduction of cytokine proliferation	1–3 g/day	Before initiation of therapy CBC and platelet count TB screening Hepatic function tests Pregnancy test if indicated During therapy CBC and platelet count 1× weekly for 1 month, then every 2 weeks for the next 2 months, and then monthly thereafter Monthly hepatic function tests Monthly comprehensive metabolic panel Semiannual physical examination focusing on evidence of lymphadenopathy and nonmelanoma skin cancers Pregnancy test if indicated	Gastrointestinal: Diarrhea, nausea, vomiting, abdominal pains Hematologic: Leukopenia, anemia, thrombocytopenia Genitourinary: Urgency, frequency, dysuria, sterile pyuria Metabolic: Hypercholesterolemia, hypophosphatemia, hyperkalemia, hypokalemia Others: Progressive multifocal leukoencephalopathy, fever, myalgias, headache, insomnia, peripheral edema, hypertension
Methotrexate[25]	Folate analog that competitively and irreversibly inhibits dihydrofolate reductase resulting in decreased RNA and DNA synthesis of B-cells and T-cells	5–25 mg/week	Before initiation of therapy TB screening Hepatitis B and C screening CBC with differential count Hepatic function test Renal function test Pregnancy test if indicated During therapy CBC, hepatic function tests, renal function tests, electrolytes every 1–2 weeks for the 1st month until a steady dosing regimen is achieved Once dose is stable, labs may be done every 2–3 months If with impaired renal function, monitor BUN and creatinine closely and check CBC 5–7 days after a test-dose Pregnancy test if indicated Note Folic acid supplementation while on methotrexate to reduce risk of methotrexate toxicity	Nausea Hepatotoxicity Myelosuppression Increased susceptibility to infections Teratogenicity Interstitial lung disease

CBC: Complete blood count, MRI: Magnetic resonance imaging, TB: Tuberculosis, ACR: Albumin and creatinine ratio, HPA: Hypothalamic-pituitary-adrenal, TNFa: Tumour necrosis factor alpha, ILs: Interleukins, BUN: Blood urea nitrogen

There are various immunosuppressants and anti-inflammatories that may be used in the treatment of BP. They are grouped as to the following: immunosuppressive anti-inflammatory agents (steroidal and nonsteroidal), nonimmunosuppressive anti-inflammatory agents, immunomodulating, and biological therapies [Tables 6-9].

Consensus Guidelines for the Management of Bullous Pemphigoid: Result of the Delphi Survey Exercise

The following are the results of the Delphi survey among 13 immunodermatologists in the Philippines based on the disease classification of BP.

Localized bullous pemphigoid

Localized BP, being defined as eruption of inflammatory lesions or blisters on one area of the body, can primarily be controlled with super-potent topical corticosteroids starting at 10 g/day. This may either be tapered over 4–12 months or increased to 20–30 g/day depending on the disease response. If Control of Disease Activity (CDA) is still not achieved in 15 days, you may treat it as a limited form of BP. There is no need to monitor ELISA titers for localized BP. After 3 months of successful tapering and there is still CDA, treatment may be discontinued. The statements for localized BP have all reached consensus [Table 10].

Limited bullous pemphigoid

Limited form of BP is defined as having <10 new inflammatory lesions or blisters or having a BPDAI score of <20. The first option is to start with super-potent topical corticosteroids at 20–30 g/day to be applied on the entire body to achieve better CDA. This is then either tapered for over 4–12 months or increased further to 30–40 g/day,

Table 7: Nonimmunosuppressives that may be used in the treatment of bullous pemphigoid

Nonimmunosuppressive	Mechanism of action	Dose	Monitoring	Complications to watch for
Doxycycline±nicotinamide[26,27]	Down regulation of cytokines (particularly TNF-a); Inhibition of nitric oxide synthesis	Doxycyline 200 mg/day±nicotinamine up to 2 g/day	No routine laboratory monitoring recommended	Photosensitivity
Dapsone[28,29]	Suppresses neutrophil migration and production of toxic secretory products	Up to 1.5 mg kg day, maximum 150 mg/day	Before initiation of therapy Glucose-6-phosphate dehydrogenase CBC Reticulocyte count Hepatic function tests Renal function tests During therapy CBC with differential count and reticulocyte count, 1× weekly for the 1st month, and 2× monthly for the next 2 months, and then periodically thereafter	Hematology: Hemolysis, methemoglobinemia Liver: Toxic hepatitis, cholestatic jaundice, transaminitis, hypoalbuminemia Skin: Exfoliative dermatitis, erythema multiforme, urticaria, erythema nodosum, morbilliform exanthem, scarlatiniform exanthem, photosensitivity Others: Nausea, headache, fatigue, insomnia, psychosis, peripheral neuropathy, motor neuropathy

CBC: Complete blood count, TNF-a: Tumour necrosis factor alpha

Table 8: Immunomodulating agent that may be used in the treatment of bullous pemphigoid

Immunomodulating	Mechanism of action	Dose	Monitoring
Intravenous immunoglobulin[30]	Lowers pathogenic antibodies by increasing catabolism of immunoglobulin molecules	2 g/kg/cycle	Watch out for leg swelling

depending on the disease response. The addition of a systemic agent (either corticosteroid or a steroid sparing agent) may be necessary if CDA is still not achieved within 30 days of purely topical steroids. The second option is to start right away with oral prednisone at 0.5 mg/kg/day, which may be increased in 2 weeks to 0.75 mk day or add your super-potent topical corticosteroids in case there is no CDA. The addition of a steroid sparer will help in the successful tapering of steroids. The onset of action of steroid sparers are longer, hence, we wait for 6–8 weeks before we see its therapeutic effects. The third option is to start with super-potent topical corticosteroids combined with steroid sparers for 2 weeks before starting with oral prednisone if still needed. For limited BP, monitoring of ELISA levels is necessary to assess for response to treatment. The first two options have all reached consensus. The first statement of the third option; however, only achieved near consensus. We have to keep in mind that the onset of action of steroid sparers is longer compared to oral prednisone [Table 11].

Extensive bullous pemphigoid

Extensive BP is defined as ≥10 inflammatory lesions or blisters per day in different areas of the body with a BPDAI >20. First option is to start with a super-potent topical corticosteroid at 30 g/day. This may be either decreased to 10–20 g/day or increased to 40 g/day depending on the response to treatment. If there is still no CDA after 10 days, the addition of oral Prednisone at 0.5–0.75 mg/kg/day or any steroid sparers is needed. The 3rd statement in this option did not achieve consensus. Topical corticosteroids may have its side effects with prolonged use (i.e. striae, acne, etc.) Hence, the continuous application of steroids on clinically normal skin may be difficult to comply with. The second option is to start with super-potent topical corticosteroids combined with oral prednisone at 0.5–0.75 mg/kg/day and steroid sparers. Once CDA is achieved, taper the prednisone while maintaining the steroid sparer. ELISA titers must be monitored regularly to check for treatment response. All statements under this option achieved consensus [Table 12].

Steroid-dependent bullous pemphigoid

Steroid-dependent BP is defined as those who develop ≥3 new lesions/month or ≥1 large (>10 cm diameter) lesion that do not heal ≤7 days, or extension of established lesions or pruritus 1x/day when topical or systemic steroids are being tapered down.[37,38] For those who have not started any steroid sparer, they are to start one at the recommended dose. For those who have already started a steroid sparer at ceiling doses, they may shift to a different steroid sparer or combine with another steroid sparer. All statements for this type achieved consensus [Table 13].

Recalcitrant/refractory/resistant bullous pemphigoid

Recalcitrant BP is defined as having generalized lesions that are unresponsive despite weeks of topical and systemic steroid therapy and steroid-sparing agents at ceiling doses for 6–8 weeks.[39] You may add any of the biological agents,

Table 9: Biological therapies that may be used in the treatment of bullous pemphigoid

Biological therapy	Mechanism of action	Dose	Monitoring	Complications to watch for
Rituximab[31,32]	Binds with CD20 surface antigen resulting in lysis of pre-B and B-lymphocytes, decreasing production of autoantibodies	RA protocol 2, 1 g IV, 2 weeks apart Lymphoma protocol 375 mg/m^2 IV, 1 ×/week×4 weeks	Before initiation of therapy CBC with differential count Hepatic function tests Renal function tests Fasting blood sugar Urinalysis Stool exam Chest radiograph TB and hepatitis screening During therapy CBC with differential count every 2 weeks during the 1st month, and then monthly for the next 6 months	Neutropenia Increased risk for infections (bacterial pneumonia, pneumocystis carinii pneumonia, hepatitis B and TB reactivation)
Omalizumab[33,34]	Humanized monoclonal antibody that blocks the binding of IgE to its receptors in BP patients with IgE anti-BP180 autoantibodies	300 mg every 4 weeks SC	No routine laboratory monitoring recommended based on safety profile	Rarely, anaphylaxis
Dupilumab[35,36]	Recombinant fully human IgG4 monoclonal antibody with binding specificity to human IL-4 receptor IL-4Ra	600 mg initially followed by 300 mg every other week up to weekly SC	No routine laboratory monitoring recommended	Eye inflammation, eosinophilia

IgE: Immunoglobulin E, IgG: Immunoglobulin G, BP: Bullous pemphigoid, CBC: Complete blood count, TB: Tuberculosis, IL: Interleukin, SC: Subcutaneous

IVIg or perform immunoadsporption. This statement achieved consensus [Table 14].

The use of steroids and steroid-sparing agents, although effective in the majority of cases, carry with it a myriad of side effects that limit the quality of life of patients. In these cases, we recommend tapering the dose as soon as efficacy is attained and/or shifting to another class of steroid-sparing agent.

Toxicity of oral corticosteroids necessitates limiting the cumulative dosage and rapidly tapering high doses, reducing by one-third steps every 2 weeks until reaching minimal effective control of disease.[40] The recommended doses of oral corticosteroids are anticipated to regulate disease activity within 2 weeks after initiation.[41,42] Therefore, taper oral corticosteroids after 2 weeks of sustained disease control.[8]

Patients on prednisone (or prednisolone) 0.5 mg/kg/day:
- 0.3 mg/kg/day for 2 weeks,
- 0.2 mg/kg/day for 2 weeks,
- 0.1 mg/kg/day for 2 weeks,
- 0.05 mg/kg/day for 2 weeks, then discontinuation.

Patients on prednisone (or prednisolone) 0.75 mg/kg/day:
- 0.5 mg/kg/day for 2 weeks,
- 0.3 mg/kg/day for 2 weeks,
- 0.2 mg/kg/day for 2 weeks,
- 0.1 mg/kg/day for 2 weeks,
- 0.05 mg/kg/day for 2 weeks, then discontinuation.

Table 10: Clinical Consensus Guidelines for Localized BP

	CONSENSUS LEVEL
1. Super-potent topical corticosteroid at 10 g/day should be applied once a day only on involved areas, until CDA is achieved.	5
2. Continue super-potent topical corticosteroid at 10 g/day once a day until 15 days after CDA.	4.92
3. Beginning 15 days after CDA is achieved, the use of the super-potent topical corticosteroid should be tapered over 4-12 months, depending on the disease severity and response: • First month of taper: Three times a week • Second month of taper: Two times a week • Third month of taper: Once a week	4.75
4. Once tapering is completed and new lesions and/or pruritus are absent for at least two months, super-potent topical corticosteroids can be discontinued.	4.83
5. If CDA is not achieved in 15 days, increase the dose and frequency of super-potent topical corticosteroids to 20-30 g divided into twice daily application.	4.17
6. If there is still no CDA after 15 days of increased dose and frequency of super-potent topical corticosteroids, treat as limited form of bullous pemphigoid.	4.75

It is important to note that tapering of steroids should be done under the close supervision of a healthcare professional. Serum cortisol levels should be monitored to ensure that tapering is not too rapid and does not result in adrenal insufficiency.

Steroid-sparers may be started at the minimum recommended dose, then slowly increased based on patient response, comorbidities, tolerance, and laboratory

Table 11: Clinical Consensus Guidelines for Limited BP

OPTION # 1	CONSENSUS LEVEL
1. Super-potent topical corticosteroids at 20-30g total dose per day divided in once to twice a day application on the entire body until CDA is achieved.	4.75
2. Once CDA is achieved, continue for 10-15 more days, then taper over 4-12 months. • First month of taper: Three times a week • Second month of taper: Two times a week • Third month of taper: Once a week	4.92
3. If there is still no CDA in 15 days, increase super-potent topical corticosteroid dose to 30-40g/day divided in once or twice daily application.	4.75
4. If there is still no CDA after 30 days of maximal topical steroid use (30-40 g/day of super-potent topical corticosteroid), may combine with oral prednisone 0.3-0.5 mg/kg/day (or its equivalent). Topical corticosteroid use may be decreased (in terms of dose or potency) accordingly.	4.33
5. If there are any contraindications to oral corticosteroid use, may combine with any of the following: Methotrexate 5-25 mg/week Mycophenolate Mofetil 1-3 g/day (or mycophenolic acid 1440 mg/day) Azathioprine 1-3 mg/kg/day Doxycycline 200 mg/day Dapsone up to 150 mg/day	5
6. If there is still no CDA after 6-8 weeks, treat as extensive form of Bullous Pemphigoid.	5
OPTION # 2	**CONSENSUS LEVEL**
1. Oral prednisone is given at a dose of 0.5mg/kg/day (or its equivalent), with gradual tapering over 4-9 months.	4.75
2. If there is no CDA in 15 days, either: • Increase prednisone dose to 0.75mg/kg/day, or • Add super-potent topical corticosteroid at 20-30 g/day	4.08
3. If there is no CDA in 8-10 days, may combine with any of the following: • Methotrexate 5-25 mg/week • Mycophenolate Mofetil 1-3 g/day (or mycophenolic acid 1440 mg/day) • Azathioprine 1-3 mg/kg/day • Doxycycline 200 mg/day • Dapsone up to 150 mg/day	5
4. If there is still no CDA after 6-8 weeks, treat as extensive form of Bullous Pemphigoid.	5
OPTION # 3	**CONSENSUS LEVEL**
1. Super-potent topical corticosteroid at 20-30 g/day to be combined with either • Methotrexate 5-25 mg/week • Mycophenolate mofetil 1-3 g/day or Mycophenolic acid 1440 mg/day • Azathioprine 1-3 mg/kg/day • Doxycycline 200 mg/day • Dapsone up to 150 mg/day	3.83
2. If there is still no CDA in 15 days, increase the potency of topical corticosteroid (30-40 g/day), or add prednisone at 0.5 mg/kg/day (or its equivalent)	4.42
3. If there is still no CDA after 6-8 weeks, treat as extensive form of Bullous Pemphigoid.	5

work up. Tapering of steroid-sparers is based on disease improvement or to mitigate possible side effects.

Monitoring of Enzyme-linked Immunosorbent Assay Testing and when to Discontinue Treatment

Immune serological testing using ELISA for anti-BP180 and/or BP230 IgG is performed by sending serum samples to a reference lab. IIF testing is not available in the Philippines. For ELISA testing, the choice of the approach depends on availability, cost and local expertise.[7] Serologic testing using ELISA may also be used to determine therapeutic effects and may be used for follow-up to determine disease activity, especially at the time of considered treatment discontinuation.[44] It is recommended to perform first an ELISA for anti-BP180 IgG, and, if negative, for anti-BP230 IgG.[9]

Serum levels of both anti-BP180 IgG and anti-BP230 IgG were significantly correlated with disease severity at diagnosis. However, only anti-BP180 IgG showed significant fluctuation in parallel to the BP activity and reflected the disease severity over time. High baseline levels of anti-BP180 IgG (>53.09 U/mL using MBL kits) is a predictive marker for relapse at later stages of BP.[43]

For patients with active BP, ELISA testing for anti-BP180 IgG may be done at days 0, 60 and 150 (baseline, 2 months, 5 months) to help predict outcome. A small decrease of <20% in ELISA serum levels of anti-BP180 IgG between days 0 and 60 is associated with disease relapse within the 1st year of therapy. Furthermore, a low or negative anti-BP180 IgG level by ELISA (<23 U/mL or <2 times the upper limit of one of the commercially available kits) at day 150 (5 months) has a good negative predictive value, as in this case the probability of durable remission is approximately 90%.[43]

Prior to cessation of treatment, DIF studies or ELISA testing for anti-BP180 IgG should be performed. In case of a positive

Table 12: Clinical Consensus Guidelines for Extensive BP

OPTION # 1	CONSENSUS LEVEL
1. Super-potent topical corticosteroid at 30 g/day to be applied once or twice daily on the entire body until CDA is achieved.	4.42
2. Once CDA is achieved with super-potent topical corticosteroid 30 g/day, continue for 10-15 more days, then taper over 4 months. • First month of taper: Three times a week • Second month of taper: Two times a week • Third month of taper: Once a week	4.33
3. Despite achieving CDA, if ELISA anti-BP180 IgG is not yet negative, decrease super-potent topical corticosteroid to 10-20 g/day over 6-12 months.	3.33
4. If there is no CDA with super-potent topical corticosteroid at 30 g/day in 15 days, increase to 40 g/day.	4.25
5. If there is no CDA on super-potent topical corticosteroid at 40 g/day in 8-10 days: • Add Prednisone 0.5 mg/kg/day; if not responding within 2 weeks, increase Prednisone to 0.75 mg/kg/day (or its equivalent), OR • Add any of the following: • Methotrexate 5-25 mg/week • Mycophenolate mofetil 1-3 g/day or Mycophenolic acid 1440 mg/day • Azathioprine 1-3 mg/kg/day • Doxycycline 200 mg/day • Dapsone up to 150 mg/day	5
6. If there is still no CDA after 6-8 weeks of ceiling dose of systemic treatment, treat it as refractory BP.	5
OPTION # 2	**CONSENSUS LEVEL**
1. Super-potent topical corticosteroid at 20-30 g/day should be applied once or twice daily on the entire body, given with oral Prednisone 0.5 mg/kg/day over 2 weeks, and combined with any of the following: • Methotrexate 5-25 mg/week • Mycophenolate mofetil 1-3 g/day or Mycophenolic acid 1440 mg/day • Azathioprine 1-3 mg/kg/day • Doxycycline 200 mg/day • Dapsone up to 150 mg/day	4.25
2. If there is no CDA after 2 weeks, increase Prednisone to 0.75 mg/kg/day, maintain topical corticosteroids and steroid-sparer for another 2 weeks then reassess.	4.92
3. If CDA is achieved, taper super-potent topical corticosteroid and Prednisone over 2-4 months while maintaining the dose of the steroid-sparer for 3 months. Taper steroid-sparer over 6-12 months based on ELISA anti-BP180 IgG.	4.58
4. If CDA is not achieved with increased prednisone dose and steroid-sparer at the recommended ceiling dose in 6-8 weeks, consider shifting to another steroid-sparer while maintaining topical and oral corticosteroids.	5
5. If there is still no CDA after 6-8 weeks of ceiling dose of systemic treatment, treat it as refractory BP.	5

Table 13: Clinical Consensus Guidelines for Steroid-dependent BP

OPTION #	CONSENSUS LEVEL
1. For patients initially treated with topical and systemic corticosteroids, add any of the following: • Methotrexate 5-25 mg/week • Mycophenolate mofetil 1-3 g/day or Mycophenolic acid 1440 mg/day • Azathioprine 1-3 mg/kg/day • Doxycycline 200 mg/day • Dapsone up to 150 mg/day	5

2. For those initially treated with topical and systemic corticosteroids and immunosuppressive drugs at ceiling doses
• Consider shifting to another steroid-sparer
  • Methotrexate 5-25 mg/week
  • Mycophenolate mofetil 1-3 g/day or Mycophenolic acid 1440 mg/day
  • Azathioprine 1-3 mg/kg/day
  • Doxycycline 200 mg/day
  • Dapsone up to 150 mg/day
	5
	
	4.25

• Consider combining with another steroid-sparer
  • Methotrexate 5-25 mg/week
  • Mycophenolate mofetil 1-3 g/day or Mycophenolic acid 1440 mg/day
  • Azathioprine 1-3 mg/kg/day
  • Doxycycline 200 mg/day
  • Dapsone up to 150 mg/day	

DIF study, or a positive ELISA anti-BP180 IgG test (if value >27 U/mL) there is an increased risk of relapse, and therefore treatment discontinuation should be reconsidered.[43]

Monitoring of ELISA levels is ideal if access is not an issue. Short of this, we can solely rely on clinical improvement and regular monitoring for any appearance of skin lesions. If there is absence of new lesions in 3 months, treatment may be tapered and maintained on that dose for another 3 months, until we are able to successfully discontinue

treatment without appearance of new lesions.

There are 2 available ELISA test kits: Euroimmun (U/mL) and MBL (RU/mL). Based on an extrapolated analysis of 28 serum samples done at RITM, the formula that can be used to convert Euroimmun values to MBL value would be: (Euroimmun value-0.27)/0.019 = MBL value. These test kits are available locally at the Research Institute for Tropical Medicine, Rizal Medical Center, and Philippine General Hospital.

Supportive Measures

There are various supportive measures that may be done in patients diagnosed with BP.

- Antiseptic or wheat starch-containing baths are recommended for patients
- Bandages using nonadherent dressing may be used in patients with extensive lesions to reduce bacterial superinfection and pain, and to promote wound healing
- Small-and medium-sized blisters may be left intact. For large blisters, use a sterile needle to puncture and drain blister fluid from the dependent side. Leave the blister roof intact
- Effort must be made to ensure that patients have updated vaccination status, such as for COVID-19, seasonal influenza, and pneumonia. Live attenuated vaccines cannot be given to patients receiving immunosuppressive therapy
- Malnourished patients may be given dietary supplementation as indicated
- Educate patients about possible signs of infection, and advise them to seek consultation early if these signs occur
- Screening and prophylaxis for osteoporosis, along with vitamin D and calcium supplementation, must be recommended for all patients. Bisphosphonate treatment may be considered for those deemed at risk for osteoporosis
- *Mycobacterium tuberculosis* and *Pneumocystis jirovecii* prophylaxis or treatment may be considered if necessary.

Table 14: Clinical Consensus Guidelines for Recalcitrant BP

	Consensus level
Add any of the following:	4.58
• Rituximab:	
• RA protocol 2 1g IV, 2 weeks apart	
• Lymphoma protocol 375 mg/m2 IV, 1x/wk x 4 weeks	
Omalizumab 300 mg SC every 4 weeks	
Dupilumab 600 mg SC initially followed by 300 mg every other week up to weekly	
• IVIg 2g/kg/cycle every 4 weeks	
• Immunoadsorption	

Novel Treatment Options

Current research has been revolving on the development of targeted therapy for BP [Table 15].[45]

Limitation of the study

This clinical consensus guideline is applicable only to adult BP patients 18 years old and above. BP in children may be seen. However, due to its rarity, there are no recent guidelines in the treatment of such special populations. A significant proportion of these immunosuppressive agents may not be appropriate for patients who are pregnant or lactating. The authors would like to encourage the reader to refer to the pregnancy category risk stratification for this special population of patients.[46]

Summary

The management of BP requires a long-term follow up with patients, taking into consideration their response to treatment clinically and serologically. This clinical consensus guideline provides a detailed approach on the various treatment options depending on the disease severity based on the current guidelines available.

Table 15: Novel treatment options for BP

	MECHANISM OF ACTION
B-CELL TARGETED	
Blinatumomab	Blockade of CD19-expressing B cells including plasma cells
Inebilizumab	
Erpatuzumab	Enhancement of the normal inhibitory role of CD22 on B-cell function
AUTOANTIBODY TARGETED	
Efgartigimod	Blockade of the interaction of neonatal Fc receptor with IgGs & subsequent inhibition of IgGs rescue & recycling
CYTOKINE & CHEMOKINE TARGETED	
Etanercept	Blockade of human TNFa
Infliximab	
Ustekinumab	Blockade of IL-12 induced Th1 cell activation & IL-23 induced Th17 cell effector function
Atacicept	Inhibition of activation & proliferation of B cells
Belimumab	
Bertilimumab	Blockade of eosinophil homing & migration into tissues

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There are no conflicts of interest.

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Appendix 1: Bullous Pemphigoid Disease Area Index (BPDAI)

	BPDAI				
SKIN	**ACTIVITY**		**ACTIVITY**		**DAMAGE**
Anatomical location	Erosion/Blisters	Number of lesions if <3	Urticaria/Erythema/Other	Number of lesions if <3	Pigmentation/ Other
	0 absent 1 1-3 lesions, none >1cm diameter 2 1-3 lesions, at least one >1cm diameter 3 >3 lesions, none >2cm diameter 5 >3 lesions, and at least one >2cm 10 >3 lesions, and at least one lesion >5cm diameter or entire area		0 absent 1 1-3 lesions, none >6cm diameter 2 1-3 lesions, at least one lesion >6 cm diameter 3 >3 lesions, or at least one lesion >10 cm 5 >3 lesions and at least one lesion >25 cm 10 >3 lesions and at least one lesion >50 cm diameter or entire area		Absent 0 Present 1
Head					
Neck					
Chest					
Left arm					
Right arm					
Hands					
Abdomen					
Genitals					
Back/Buttocks					
Left Leg					
Right Leg					
Feet					
Total skin	/120		/120		
MUCOSA	Erosions/Blisters 1 1 lesion 2 2-3 lesions 5 >3 lesions, or 2 lesions >2cm 10 entire area				
Eyes					
Nose					
Buccal Mucosa					
Hard palate					
Soft palate					
Upper gingiva					
Lower gingiva					
Tongue					
Floor of Mouth					
Labial Mucosa					
Posterior Pharynx					
Anogenital					
Total Mucosa	/120				

Note. Reprinted from "Definitions and outcome measures for bullous pemphigoid: Recommendations by an international panel of experts" Murrell, Dedee F., Benjamin S. Daniel, Pascal Joly, Luca Borradori, Masayuki Amagai, Takashi Hashimoto, Frédéric Caux et al. Journal of the American Academy of Dermatology 66, no. 3 (2012): 479-485. Retrieved from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3883429/

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