Wiley
Dermatologic Therapy
Volume 2025, Article ID 8215967, 15 pages
https://doi.org/10.1155/dth/8215967

WILEY

Review Article

Management of Bullous Pemphigoid in Special Populations: A Narrative Review of the Literature

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Received 13 March 2025; Revised 2 September 2025; Accepted 6 November 2025

Academic Editor: Suraiya Saleem

Bullous pemphigoid (BP) mostly affects elderly patients who have age-related comorbidities, and BP itself is associated with neurologic comorbidities independently of the patients' age. Identifying comorbidities in patients with newly diagnosed BP is important to define the prognosis, to choose the best therapeutic strategy, and to plan follow-ups. Comorbidities are associated with polypharmacy, and drug-induced BP should be always ruled out. Topical or systemic corticosteroids (CSs) represent the mainstay of treatment for BP. CS-sparing agents might be useful in frail patients and include dapsone, tetracyclines, methotrexate (MTX), mycophenolate mofetil (MMF), azathioprine (AZA), rituximab, omalizumab, dupilumab, intravenous immunoglobulins (IVIGs), and immunoadsorption. In this complex therapeutic scenario, clinicians should tailor the therapeutic approach accordingly to the patient's characteristics. Preexisting and newly arising therapy-related comorbidities should be monitored during the patient's follow-up.

1. Introduction

Bullous pemphigoid (BP) is the most common autoimmune bullous disease (AIBD), and its prevalence increases with age [1, 2]. On average, in Europe, patients develop BP around the age of 80 years [3, 4]. Therefore, BP mostly affects a subset of patients who are frail and have age-related comorbidities, including neurological, cardiovascular, metabolic, thromboembolic, neoplastic, respiratory, ocular, or osteoporotic conditions [1, 2]. On the other hand, other comorbidities, such as neurologic diseases, are directly associated with BP independently of the patient's age.

Some comorbidities in BP patients have been associated with a poor prognosis; a meta-analysis highlighted the association between dementia, stroke, heart disease, and diabetes mellitus and a greater risk of mortality [5–7].

Identifying comorbidities in patients with newly diagnosed BP is important to define the prognosis, to choose the best therapeutic strategy, and to plan follow-ups.

This paper encloses a narrative review of the literature and the clinical experience of the Italian Group for Cutaneous Immunopathology of the Italian Society of Dermatology and Venereology (SIDeMaST) in the management of special populations of patients with BP.

2. General Considerations

2.1. Baseline Assessments. A thorough anamnesis, an in-depth physical examination, and specific work-up are recommended to identify possible comorbidities prior to starting treatment (Table 1) [3]. Neurological conditions, diabetes, osteoporosis, cardiovascular diseases, malignancies, chronic kidney diseases (CKDs), chronic liver diseases, latent infections, and ocular diseases should be investigated [1, 2, 9].

Comorbidities are associated with polypharmacy, and drug-induced BP should be always ruled out. Offending drugs may include commonly used medications. The strongest evidence for drug-induced BP was seen with gliptins (especially vildagliptin), PD-1/PD-L1 inhibitors, loop diuretics, penicillin, and derivatives [10], as well as aldosterone antagonists, anticholinergics, and dopaminergics [7, 11]. New drug intake in the preceding 6 months should be considered, but even though longer delay is possible for gliptins and immune checkpoint inhibitors [7, 11, 12]. Once culprit drugs are discontinued, patients still might require immunosuppressive therapy, as the autoimmune phenomenon rapidly becomes independent of the initial trigger.

The overall well-being of BP patients should also be assessed. Risk factors for mortality in BP include a poor general condition and a low Karnofsky score [7]. Moreover, clinicians should evaluate the patient's level of dependency in terms of activities of daily living and the availability of support given by caregivers. These aspects may determine the choice of treatment. For instance, topical treatments are difficult to apply for a person with impaired mobility [13].

Immunization status should be checked before starting long-term immunosuppressive treatment. Immunosuppressive drugs are associated with higher risks of developing severe forms of infectious diseases, and elderly patients tend to have age-related immune system impairment. Patients receiving for 2 weeks or more prednisone ≥ 20 mg daily, methotrexate (MTX) ≥ 0.4 mg/kg/weekly, azathioprine (AZA) ≥ 3 mg/kg/daily, rituximab, mycophenolate mofetil (MMF), or combination therapies are significantly immunocompromised and should be immunized accordingly [14, 15]. Patients should be vaccinated against seasonal influenza, pneumococcal disease, and SARS-CoV-2 [3].

2.2. Therapeutic Considerations. Comorbidities should be considered when deciding on the best therapeutic strategy. Senior patients benefit from a conservative and tailored therapeutic approach.

High-potency corticosteroid (CS), such as clobetasol propionate 0.05% cream, is the best option, especially in mild localized forms, but they can also be used for non-localized mild–moderate forms or in severe forms of BP [3, 16, 17]. However, if high-potency CSs are applied to an extensive body surface area, they may have systemic side effects [18] and should be slowly tapered over 4 months or longer [7, 19]. Moreover, applying topical CS over extensive areas might require the elderly the assistance of a caregiver.

Systemic CS, namely, prednisone at the starting dose of 0.5 mg/kg/day, is the first choice [3, 18, 20, 21]. This dose is rather well tolerated in patients with a Karnofsky score of ≥ 70; however, elderly patients might have poorer global conditions [22] and long-term administration requires strict monitoring [23].

Traditional CS-sparing agents in BP include dapsone, tetracyclines, MTX, MMF, and AZA. Newer options include rituximab, omalizumab, dupilumab, and intravenous immunoglobulins (IVIGs) [3].

Dapsone warrants caution in patients with cardiovascular diseases, and its efficacy in BP remains overall doubtful [24, 25]. Low-dose MTX showed the best risk-benefit profile in the elderly with atopic dermatitis among immunosuppressive drugs [26], but patients should be carefully monitored as severe adverse events, including deaths, are linked to incorrect daily, not weekly, administration [27]. AZA in monotherapy has a high frequency of adverse events in the elderly [28], and it has been linked to the highest risk of malignancy among the immunosuppressive agents [29]. MMF at reduced dosage is recommended, and caution is needed for patients with impaired heart or liver function and for increased risk of infection [26]. IVIGs are a generally safe option in recalcitrant BP [7], but side effects include acute renal failure and thromboembolic events. A recent meta-analysis on IVIG did not demonstrate an elevated risk attributable to IVIG [30]; however, an increased risk of venous thromboembolism in patients with BP has been described [31]. Notably, omalizumab and dupilumab are very interesting options as they are immunomodulant rather than immunosuppressant drugs. Omalizumab is currently off-label for BP treatment, but its efficacy was reported in case reports and confirmed by a retrospective multicenter study [32–34]. Dupilumab is the most promising immunomodulant drug and has been recently approved by the FDA. The

Table 1: Baseline assessment of comorbidities in newly diagnosed patients with BP.

Patient History
Medications. Paying special attention to BP-inducing drugs: aldosterone antagonists, dipeptidyl peptidase 4 inhibitors, PD-1/PDL-1 inhibitors, anticholinergics, and dopaminergic medications.
Short-term memory loss, family history of degenerative neurological disorders (e.g., Alzheimer's disease)
Clinical fracture risk factor assessment: previous fractures, family history of fracture, smoking history, alcohol use, fall history, height loss
Clinical Examination
Detailed clinical neurological examination
Mini-Mental State Examination or Montreal Cognitive Assessment
Karnofsky Performance Status Scale
Body mass index
Blood pressure measurement and signs of congestive heart failure (e.g., swelling of legs, ankles, and feet)
Laboratory analyses
CBC—complete blood count
Transaminases, gamma-GT, alkaline phosphatase, and bilirubin
Creatinine, blood electrolytes, urine analysis
Fasting glucose glycated hemoglobin* (in known diabetics to better evaluate disease control)
Serology* for hepatitis B, hepatitis C, and HIV, QuantiFERON if immunosuppressive therapy is planned
25-hydroxy vitamin D, calcemia*
Imaging
Osteodensitometry if CS therapy is planned ≥ 3 months
Chest X-ray* if immunosuppressive therapy is planned
Echocardiogram*
Referrals
Vaccination center, to assess baseline immunization status before starting systemic immunosuppressive treatments
Neurologist*, if undiagnosed neurological conditions are found at clinical examination
Endocrinologist (diabetes specialist)*, if uncontrolled diabetic disease and/or systemic CS is planned or if gliptin-induced BP is suspected, in order to make appropriate therapeutic adjustments
Rheumatologist or endocrinologist (osteoporosis specialist)* or, if long-term systemic CS therapy is planned and a more accurate fracture risk assessment is needed for selecting osteoporosis therapy
Cardiologist*, if preexisting cardiovascular comorbidities are present and/or systemic CS, dapsone or IVIGs are planned
Nephrologist* if preexisting renal disease
Ophthalmologist*, preexisting ocular disorders, including glaucoma, cataract, and systemic CS therapy, are planned
Geriatrician* if poor general condition and multiple comorbidities

*In selected cases.

recommended dosage for adult patients is an initial dose of 600 mg (two 300 mg injections), followed by 300 mg given every other week (Q2W) [Available at: https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=697319 on 20 August 2025]. The LIBERTY-BP ADEPT, a multicenter, randomized, double-blind, placebo-controlled clinical trial to evaluate the efficacy and safety of dupilumab in adults with BP, was recently completed with promising results [35, 36].

In this complex therapeutic scenario, clinicians should tailor the therapeutic approach accordingly to the patient's characteristics (Table 2).

2.3. Monitoring and Follow-Up. Preexisting and newly arising therapy-related comorbidities should be monitored during the patient's follow-up (Table 2). Monitoring should be performed biweekly until the disease is controlled and subsequently monthly for the following 3 months or 3 times per year until the treatment is stopped [3]. Management and follow-up of subjects with BP and comorbidity may involve multiple health professionals, including dermatologists, general practitioners, cardiologists, endocrinologists, neurologists, nephrologists, infectious disease specialists, ophthalmologists, and nurses. In addition, caregivers or nurses are relevant for the patients' hygiene and dressings for skin lesions.

3. Specific Considerations

3.1. Neurological Disorders. The association of BP with neurological disorders is the strongest and well documented [37, 38], especially for Alzheimer's disease [39], Parkinson's disease [39–41], dementia [40–42], stroke [41, 43], and multiple sclerosis [44]. Clinical neurological examination and brief cognitive assessment of mental status [e.g., Mini-Mental State Examination (MMSE) or Montreal Cognitive Assessment (MoCA)] should be considered as a baseline assessment in patients with BP [45, 46]. Repeated assessments should be encouraged at each follow-up visit. Notably, attention should be paid to levels of circulating eosinophils. Higher serum levels of eosinophil-derived neurotoxin have been found in patients with amyotrophic lateral sclerosis as compared to healthy controls [47], while hypereosinophilia was described in patients with dementia [48] and Alzheimer's disease [49]. Medications used to treat such neurological diseases, including anticholinergics and

Table 2: Therapeutic considerations, baseline assessment, and follow-up based on the comorbidities associated with BP.

Comorbidity	Therapeutic considerations	Baseline assessments	Follow-up
Neurological comorbidities	• Caregiver involvement for medications and topical CS • Oral CS might worsen dementia and psychiatric symptoms • Consider with caution in patients with cognitive impairment: • AZA • MMF • MTX	• Anticholinergic and dopaminergic medications may be linked to drug-induced BP, MMSE, or MoCA • Karnofsky score • Eosinophilic blood count • Referral to neurologist*	Consider repeating*: • Neurological examination • MMSE or MoCA • Karnofsky score
Diabetes mellitus	• High-potency topical CS may lead to significant systemic absorption • Oral CS at the lowest dose and for the shortest duration possible • Consider steroid-sparing agents	• Gliptins are linked to drug-induced BP • Fasting glucose • Referral to diabetologist*	If systemic CS ≥ 3 months, repeat every 3–6 months: • Fasting glucose • HbA1C test
Osteopenia or Osteoporosis	• High-potency topical CS may lead to significant systemic absorption • Oral CS at the lowest dose and for the shortest duration possible • Consider steroid-sparing agents • Consider prophylaxis for osteoporosis in patients requiring oral CS treatment ≥ 3 months: • Bisphosphonates • calcium supplements (1000–1200 mg/day) • Vitamin D (600–800 IU/day) intake	• Clinical fracture risk factor assessment • 25-hydroxy vitamin D, calcemia • Osteodensitometry • Referral to endocrinologist or rheumatologist*	• If long-term oral CS therapy, consider annually: • Osteodensitometry • 25-hydroxy vitamin D, calcemia • After completing CS treatment, bisphosphonates are needed until bone mineral density normalization
Cardiovascular comorbidities	• Systemic CS (use with caution or avoid in patients with severe congestive heart failure) • Consider steroid-sparing agents: • MMF (safe in heart transplant patients) • MTX (possible cardioprotective role) • Consider with caution or avoid using as steroid-sparing agents: • dapsone (if coronary artery disease or congestive heart failure) • high osmolarity IVIGs (if congestive heart failure) • rituximab (risk of angina, ACS, arrhythmia)	• Aldosterone and loop diuretics are linked to drug-induced BP • Clinical assessment (heart rate, blood pressure measurement, signs of congestive heart failure) • Echocardiogram* • Referral to cardiologist*	• Home blood pressure diary at the beginning of CS therapy

Table 2: Continued.

Comorbidity	Therapeutic considerations	Baseline assessments	Follow-up
Solid or hematological tumors	Systemic CS (caution in using high doses) Consider steroid-sparing agents: • Doxycycline • Dapsone • IVIGs (anticancer activity) • Omalizumab • Dupilumab (used in melanoma patient with ICI-induced BP) Caution using high-dose steroid-sparing agents (increased risk of infections and impact on fighting cancer): • AZA • MMF • MTX	• Consider age-appropriate cancer screening as for general population • Referral to oncologist*	• If long-term use of AZA or MMF, consider annual screening for skin tumors
Chronic Kidney Disease	Consider steroid-sparing agents: • dapsone • doxycycline • MMF (safe CKD; eGFR< 25 mL/min/1.73 m^2) • omalizumab • dupilumab • rituximab Consider with caution as steroid-sparing agents: • MTX (use low dose: 5–10 mg/weekly) • AZA (lowest dose possible) • IVIGs (risk of AKI in CKD)	• CBC—complete blood count, creatinine, blood electrolytes, albumin • Urinalysis • Referral to nephrologist*	• Close monitoring of baseline blood test
Chronic Liver Diseases	Consider steroid-sparing agents: • doxycycline • AZA • MMF • omalizumab • dupilumab Consider with caution or avoid as steroid-sparing agents: • dapsone (higher risk of cholestatic injury) • MTX (contraindicated in patients with severe hepatic insufficiency or bilirubin levels > 5 mg/dL; use with caution if ARLD or SLD)	• Transaminases, GGT, ALP, and bilirubin levels • markers for HBV and HCV infections • Referral to hepatologist*	• During treatment with MTX, liver function is monitored every 2 weeks, then monthly for the first 2 months, and every 3 months thereafter • During treatment with dapsone, liver function tests, monthly in the first 3–6 months and then every 2–4 months • mycophenolate, azathioprine, doxycycline, routine monitoring of liver function every 3 months

Table 2: Continued.

Comorbidity	Therapeutic considerations	Baseline assessments	Follow-up
HIV infection	• Consider steroid-sparing agents: • dapsone (useful in prophylaxis of PJP) • doxycycline, omalizumab • dupilumab • IVIGs • Consider with caution as steroid-sparing agents: • AZA • MMF • MTX	HIV antigen/antibody	
Tuberculosis	• Consider steroid-sparing agents: • dapsone • doxycycline, omalizumab • dupilumab • IVIGs • Consider with caution as steroid-sparing agents: • AZA (moderate risk of reactivation) • MTX (high risk of reactivation) • MMF	IGRA	
Pregnancy and Lactation	• Clobetasol propionate 0.05% (avoid nipple area in breastfeeding women) • Prednisone ≤ 20 mg/day • Consider as steroid-sparing agents: • Dapsone • AZA • rituximab • IVIG • plasmapheresis • Contraindicated: • tetracyclines • MTX • MMF		
Childhood	• Consider with caution as steroid-sparing agents: • rituximab • Contraindicated: • tetracyclines age < 12 years		

Note: ALP = alkaline phosphatase; ASLD = steatotic liver disease; AZA = azathioprine; CS = corticosteroids; HbA1C = glycated hemoglobin; IVIGs = intravenous immunoglobulins; MMF = mycophenolate mofetil; MoCA =Montreal Cognitive Assessment; MTX = methotrexate.

Abbreviations: ACS = acute coronary syndrome; ARLD = alcohol-related liver disease; GGT = gamma-glutamyl transferase; IGRA = interferon gamma release assay; MMSE = Mini-Mental State Examination; PJP = Pneumocystis jiroveci pneumonia.

*In selected cases.

dopaminergic drugs, may increase the risk of BP [37], and drug-induced BP should be considered in these cases [12]. Neurological patients may have impaired or altered cognitive functions, making it difficult to evaluate the intensity of pruritus and drug tolerance. Additionally, adequate compliance with treatment can be challenging. Therefore, it is important to adequately inform, support, and engage relatives or caretakers in managing the disease, as well as schedule more frequent follow-up visits [13]. Systemic steroids should be used with caution as they can worsen dementia and psychiatric symptoms [50]. For this reason, systemic CS should be preferably associated with steroid-sparing agents. On the other hand, systemic immunosuppressive agents should be administered by nurses or caregivers in patients with dementia or altered cognitive function, as incorrect administration may lead to severe adverse events [28].

3.2. Diabetes Mellitus. DM is one of the three most common comorbidities associated with BP [51], and it represents a potential risk factor for BP onset [52, 53]. DM prevalence among BP patients has increased from 13.2% to 25.2% over recent decades [54], probably due to the introduction of dipeptidyl peptidase-IV inhibitors (gliptins), as they are possible BP-inducing drugs. BP should be considered drug-induced if the patient is taking dipeptidyl peptidase-IV inhibitors [55], and hypoglycemic treatment should be modified [56]. Moreover, due to CS therapy, new-onset DM can manifest during BP treatment [52, 53]. Careful attention should be paid to identify clinical signs of diabetes, and it is advisable to analyze impaired fasting glucose or impaired glucose tolerance prior to the initiation of chronic CS (Table 1) and in subsequent follow-up visits. A referral to a diabetologist is suggested in case of i) uncontrolled diabetic disease and ii) gliptin-induced BP to make appropriate therapeutic adjustments. Also, a nutrition specialist can be useful.

Individuals with BP and diabetes tend to have more severe symptoms and to be more resistant to treatment, particularly if the DM is poorly controlled [57]. For this reason, BP patients with DM represent a management challenge to the clinician.

Many experts suggest reducing the initial doses of oral CS or, if possible, not using any oral CS [24] (Table 2). Immunomodulating therapy such as MTX, AZA, and MMF is valuable steroid-sparing agent in these patients [3]. In a good general condition of the patient, when self-application is feasible or external help is available, it could be preferable to introduce topical CS therapy [3]. Clinicians should be cautious of possible systemic absorption of high-potency topical steroids (Table 2). Omalizumab or dupilumab could help in these therapeutic challenges (Table 2).

3.3. Osteopenia or Osteoporosis. The incidence of osteoporosis in BP patients ranges from 5.5% to 12.1% [58, 59]. BP is associated with an increased risk of osteoporosis and pathological fractures [60], primarily due to the long-term use of systemic CS, but also because of older age at onset, chronic inflammation, and low vitamin D levels found in these patients [60, 61]. The highest rate of bone loss occurs within the first 3–6 months of systemic CS therapy [62]. Daily doses of prednisolone ≥ 2.5 mg, or its equivalent, significantly increased the risk of spine and hip fractures [63]. Systemic CS therapy should be at the lowest dose and for the shortest duration possible, if necessary, with the aid of steroid-sparing agents. Additionally, it is important to note that prolonged use of potent topical steroids can also be harmful to bone health [62, 64]. It is essential to identify any preexisting risk factors or osteoporosis diagnosis, as severe osteoporosis contraindicates oral CS [62]. Clinical fracture risk factor assessment involves dose/duration/pattern of CS use, advanced age, low body mass index, previous fracture, family history of fracture, smoking history, alcohol use, fall history, and height loss. Osteodensitometry should be performed if long-term systemic CS therapy is planned for at least 3 months [3, 63]. Based on this, the patient's fracture risk should be assessed, and calcium and vitamin D levels should be checked to ensure adequate intake and identify any deficiency that could increase bone loss risk [62].

Osteoporosis prophylaxis is advisable if the expected duration of systemic CS is more than 3 months. BP patients should be advised on general measures for osteoporosis prevention, including weight-bearing and cardiovascular exercise, avoiding excessive alcohol use and smoking, and reducing risk for falls [62]. Vitamin D and calcium supplementation are recommended at the initiation of CS treatment [65]. An adequate calcium (1000–1200 mg/day) and vitamin D (600–800 IU/day) intake should be ensured to keep serum vitamin D levels > 30 ng/mL [66]. Treatment with bisphosphonates is recommended in patients at risk (postmenopausal women, men > 50 years on glucocorticoid treatment > 3 months) to prevent osteoporosis [67, 68]. An endocrinology or rheumatology referral can assist in patient's risk assessment and in selecting the best therapy for osteoporosis [63]. After completing CS treatment, patients should continue bisphosphonate therapy until their bone mineral density normalizes [62].

Serum 25-hydroxy vitamin D levels should also be measured each year [69].

3.4. Cardiovascular Comorbidities. Cardiovascular issues are a significant comorbidity for elderly patients and become even more critical in those with BP. Cardiovascular diseases might be underlying or could be potentially accentuated by therapy. Also, BP patients have been reported to be at higher risk of venous thromboembolism [31], especially during the acute phase; therefore, they should be carefully checked for signs of deep venous thrombosis during their baseline and follow-up visits. Clinical assessment including blood pressure, heart rate, and signs of congestive heart failure can help identify cardiovascular comorbidities. In such cases, an echocardiography might be advisable before initiation of therapy with either systemic CS, dapsone, or IVIGs [3, 70]. CS is the primary therapeutic approach for BP patients, and the literature indicates an increased risk of major adverse cardiovascular events (MACE) with oral CS even at low

doses [71]. Patients should be advised to monitor blood pressure at home and keep a blood pressure diary when starting CS.

Diuretics, especially aldosterone antagonists, have been identified as potential triggers of drug-induced BP [12]. Patients with hypertension or cardiac insufficiency taking such medications should be referred to cardiologic evaluation to modify therapy accordingly.

In patients with congestive heart failure, CS with mineralocorticoid activity should be avoided or used at a minimal dose [24].

Dapsone has a low risk of methemoglobinemia in the general population, but overdose can lead to major cardiovascular events [72]. MTX appears to have a cardioprotective role in rheumatoid arthritis, and MMF has a high cardiologic safety profile in heart transplant patients. While these data cannot be directly applied to BP patients, they may support pharmacological choices [73, 74]. Rituximab, on the other hand, can cause angina, acute coronary syndrome, and arrhythmias in patients with a history of cardiovascular disease, though its detailed cardiotoxicity profile remains unclear in the medical literature [75]. Concentrated IVIG preparations that require a high volume of infusions can lead to volume overload in patients with cardiac conditions. Also, high sodium-containing products should be used cautiously. [76].

3.5. Solid or Hematological Tumors. Since the frequency of BP and cancer increases with age, clinicians frequently face with BP patients with underlying malignancies [77]. Some studies found an increased incidence of malignancy in BP patients [78–81] or associations with hematological malignancies [9, 81]. On the other hand, several studies including a comparative statistical evaluation did not confirm an association between malignancy and BP [83]. The debate is further augmented by the fact that, unlike paraneoplastic pemphigus and its unique antigenic profile [84], there is yet no evidence of an immunologically distinct subset of BP, which is specifically linked with cancer [77].

Although the potential association between BP and malignancies remains inconsistent, checking for an underlying neoplasm in line with the patient's age may be recommended [83].

The management of a BP patient with a coexisting cancer is challenging. High doses of systemic CS and conventional immunosuppressive drugs (e.g., MTX, AZA, and MMF) should be used with caution and be evaluated together with the oncologist, as they increase the risk of infections and impact the fighting of the immune system against cancer [85]. Topical CS and antibiotics such as doxycycline and dapsone may thus be preferred as first-line therapy for patients with mild–moderate disease. Among targeted therapies, IVIGs are a valuable choice due to their anticancer activity [86]; their efficacy in BP has been demonstrated in clinical trials [87]. Despite being currently off-label, drugs targeting Type 2 immunity, including omalizumab and dupilumab, are generally safe in this medically complex situation [88, 89]. Interestingly, dupilumab showed efficacy in melanoma patients with immune checkpoint inhibitor–induced BP [90], an increasingly recognized subset of malignancy-associated BP [91]. However, Type 2 immunity and eosinophils appear to have a protective role in certain cancers, including melanoma [92], and thus, further investigation is needed to evaluate the safety of these drugs in cancer patients.

3.6. CKD. BP often affects older individuals, who frequently suffer from CKD. A 1.3-fold higher risk of BP has been reported in patients with CKD than in general population, which is even higher (1.8-fold) in patients undergoing dialysis: the uremia-related dysfunction of regulatory T cells could be responsible for loss of self-tolerance and of consequent autoimmune response [58, 93]. The severity of BP has been found to correlate with the severity of renal disease [94]. Alteration of bone metabolism (i.e., osteoporosis, uremic osteodystrophy) in patients with CKD has to be considered when considering long-term treatment with systemic CS [95]. In patients with decreased renal function, MTX must be used very cautiously; a low dosage (5–10 mg/wk) has been reported as an effective treatment option without being associated with a higher risk of death. When prescribing low-dose MTX to patients with low eGFR, it is mandatory to monitor serum creatinine and glomerular filtration rate periodically and to adjust posology whenever necessary [96, 97]. MMF can be used safely even in patients with severe chronic renal impairment (glomerular filtration $< 25\,\text{mL/min/1.73}\,\text{m}^2$) [98]. AZA should be started at the minimum dose in patients with impaired renal function and under nephrological supervision [99]. Patients under MMF or AZA should be monitored for dose-related adverse events, particularly for erythrocyte count since they are at risk for anemia because of erythropoietin deficiency. CKD is not a contraindication for the administration of dapsone. Doxycycline can be used in patients with renal failure since it is mainly excreted with the feces. Rituximab, omalizumab, and dupilumab can be used without dose adjustment [100]. IVIGs are at risk for acute renal failure in patients with preexisting renal disease when using sucrose-containing preparations due to their osmotic effect [101].

3.7. Chronic Liver Diseases. To investigate potential chronic liver diseases, baseline laboratory tests should include aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), and serum albumin. Some experts also recommend measuring serum bilirubin and prothrombin time [102]. Baseline screening for HBV and HCV is recommended for patients starting immunosuppressive therapies.

Although there is no definitive link between BP, HBV, or C infections, a small case–control study revealed a higher prevalence of antibodies against these viruses in patients with AIBDs [103]. Thus, it has been hypothesized that these viruses could be factors precipitating BP. Conversely, there are no data on the association between BP and noninfectious liver diseases [103].

Patients with chronic HBV and HCV infections are at risk of worsening liver disease due to drug-related injury and potential rare reactivation of infections [104].

Immunosuppressive therapies predispose to the reactivation of occult HBV and HCV infections. Among the therapies for BP, rituximab and moderate to high CS doses (for more than 4 weeks) are associated with the highest risk [105]. However, according to a recent study, rituximab seems to be a safe choice for BP patients with HBV infection [106]. Patients positive for hepatitis B core antibody should be referred to a hepatologist for regular HBV-DNA monitoring and possible antiviral therapy to manage HBV reactivation, based on individual reactivation risk and planned immunosuppression. All patients with HCV infection should receive antiviral treatment [107].

Dapsone must be used cautiously in patients with severe chronic liver diseases due to the risk of cholestatic injury, which can lead to hemolysis responsible for hepatic iron overload, and toxic or cholestatic hepatitis in case of hypersensitivity syndrome [108, 109].

MTX is contraindicated in patients with severe hepatic insufficiency or bilirubin levels above 5 mg/dL. For patients with preexisting liver disease, particularly those related to alcohol, MTX should be used carefully with potential dose reductions [110]. Although prospective trials on MTX in patients with metabolic dysfunction-associated steatotic liver disease are lacking, MTX may probably hasten progression to metabolic dysfunction-associated steatohepatitis [111]. In patients with liver disease associated with BP, during treatment with MTX, blood exams should be monitored at Week 2, then monthly for the first 2 months, and every 3 months thereafter [104, 112]. MTX should be discontinued if ALT/AST levels rise to more than three times the upper limit of normal but can be reintroduced at a lower dose after normalization. MTX must be permanently stopped if no other cause for liver dysfunction is found and enzyme levels remain elevated [113]. In patients treated with dapsone, liver function tests, in addition to complete blood cell count and methemoglobin level, should be performed monthly in the first 3–6 months and then every 2–4 months. If any abnormality is detected, the dosage of dapsone should be decreased or the drug discontinued until the source is established [109]. For other treatments used in BP (e.g., MMF, AZA, doxycycline), routine monitoring of liver function every 3 months is sufficient, as only a small proportion of patients develop transaminase abnormalities, which are generally mild. The number of clinically apparent and/or severe cases of impaired liver function is rare, and since they usually occur in the first week of treatment, it may be advisable to monitor transaminase levels after the initial administrations [114–116].

3.8. Chronic Infections. Identifying chronic latent infections in BP patients is relevant when systemic prolonged immunosuppression is needed. Mycobacterium tuberculosis, hepatitis B, hepatitis C, and HIV infections should be investigated.

3.8.1. HIV. Topical CSs are the gold standard in localized disease; however, many BP patients with HIV require systemic therapy, demanding careful monitoring for possible opportunistic infections. Systemic CSs are the most commonly utilized treatment for patients with BP and HIV. Sometimes, additional drugs need to be added to achieve disease control. In HIV-infected patients, collaboration with an infectious disease specialist is recommended. Generally, nonimmunosuppressive drugs should be preferred [117]. For example, dapsone is a nonimmunosuppressive treatment choice; also, it is useful in the prophylaxis of Pneumocystis jiroveci pneumonia [118]. Patients with AIDS and BP in treatment with dapsone should be monitored for methemoglobinemia, hemolysis, agranulocytosis, liver function alterations, and distal motor neuropathy.

IVIGs are a nonimmunosuppressive treatment option, but the literature lacks studies in the setting of BP patients with HIV infection. Overall, it seems to be a safe therapeutic alternative [117]. Interestingly, the literature lacks reports on the use of tetracyclines and niacinamide in HIV-infected patients with BP, although such medications could represent a therapeutic alternative without immunosuppression. New biological, nonimmunosuppressive agents such as omalizumab or dupilumab could be helpful.

3.8.2. Tuberculosis. Risk of tuberculosis reactivation during immunosuppressive therapy has been investigated in patients with other immune-mediated inflammatory diseases. In southern European countries, such as Italy, the prevalence of tuberculosis increases with age [119]. MTX and AZA are both associated with a risk of TB reactivation, and this should be considered in TB-endemic areas [120]. MTX showed the highest risk, and AZA showed a moderate risk [119] of tuberculosis reactivation. Patients with latent tuberculosis should not be administered such systemic treatments until the latent TB has been treated as per local regulations.

3.9. Pregnancy and Lactation. Very rarely, pregnant women develop a variant of BP, namely, pemphigoid gestationis (PG) [121]. It is preferable to use high-potency topical CS in mild cases; for moderate and severe cases, the first choice is low dosage (< 20 mg/day prednisone) oral CS, which showed an acceptable safety profile during pregnancy and lactation. Dapsone represents a safe option in pregnant women. It may be used either as monotherapy or together with oral steroids. IVIGs have been more extensively studied in pemphigus vulgaris of pregnancy, where they also prevent the transplacental transfer of autoantibodies with a good safety profile, even in the early phases of pregnancy; however, they are considered a useful option, either as monotherapy or in combination with systemic CS. Plasmapheresis/plasma exchange showed good results in the treatment of PG, with or without systemic CS [122]. MTX and tetracyclines are contraindicated in pregnancy [123].

During lactation, the use of topical CS to treat BP is acceptable, as long as it is not applied on the nipple area before breastfeeding. Amounts of prednisone in breastmilk are very low, and no adverse effects have been reported in breastfed infants with maternal use of any CS during breastfeeding. Although it is often recommended to avoid breastfeeding for 4 h after a dose, this is not strictly necessary

as prednisone milk levels are very low [124]. Dapsone is safe even during lactation, provided that the newborn is monitored for glucose-6-phosphate dehydrogenase deficiency and hemolysis. AZA is considered compatible with lactation, as breastfed children showed no adverse effects and no active metabolites of mercaptopurine. IVIG, plasmapheresis, and immunoadsorption appeared well-tolerated and safe in lactation. Rituximab might be used if other options are not available, as it is a large molecule, thus excreted in human milk in minimal amounts. In contrast, tetracyclines, cyclophosphamide, MMF, and MTX may be transferred across the mammary tissue; therefore, they are contraindicated in lactation. Dupilumab and omalizumab also appear to be two safe options. A recent systematic review and meta-analysis that evaluated the effects of exposure to dupilumab during pregnancy in women with atopic dermatitis found no significant increase in the risk of miscarriage or congenital malformations compared to the general population [125]. A prospective, observational study on pregnant women exposed to omalizumab found no apparent increased birth prevalence of major anomalies or patterns of major anomalies have been observed [126].

3.10. Childhood. BP in children is rare, and it is similar to adult BP, but acral and genital (vulvar) are more common [127–129]. Moreover, prognosis is better in children with an average disease duration of 14 months and an optimal response to treatment [129]. The treatment of choice is generally steroids with or without dapsone. Additional successful treatments reported in the literature include cyclosporine [130], erythromycin, doxycycline plus niacinamide and AZA [131], MMF [132], IVIGs [133], plasma exchange and extracorporeal photochemotherapy [134], and rituximab [135]. Severe side effects and two deaths have been reported in association with rituximab for the treatment of severe cases of BP in children [135, 136]. Tetracyclines are contraindicated in children under the age of eight, as they are associated with permanent discoloration of teeth [123].

4. Conclusions

In conclusion, baseline assessment of comorbidities and overall well-being of the patient is crucial for managing the patient appropriately and making the correct therapeutic choices. Topical or oral CSs are the pillar of treatment of BP, but whenever possible, steroid-sparing agents should be used. The most promising drugs for the treatment of BP are target therapies, such as omalizumab and dupilumab, which are not broad-spectrum immunosuppressive but rather immunomodulant drugs [8, 82].

Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Conflicts of Interest

The authors declare no conflicts of interest.

Funding

The authors have nothing to report.

Acknowledgments

This article was written as a joint effort of the members of the Italian Group for Cutaneous Immunopathology of the Italian Society of Dermatology and Venereology (SIDeMaST).

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