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Alternative Therapies to Immunoglobulin for Autoimmune Blistering Diseases

Rapid Review

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Table of Contents

List of Tables

List of Figures

Abbreviations

BP	bullous pemphigoid
EADV	European Academy of Dermatology and Venereology
IVIg	IV immunoglobulin
PF	pemphigus foliaceus
PV	pemphigus vulgaris
RCT	randomized controlled trial

Key Messages

- We did not find any evidence regarding the clinical effectiveness and safety of alternative treatments to IV immunoglobulin (IVIg) compared to IVIg or placebo for bullous pemphigoid (BP) or pemphigus vulgaris (PV) and pemphigus foliaceus (PF) that met our inclusion criteria for this review.
- We identified 6 consensus guidelines presenting treatment algorithms for BP (3 guidelines) or PV and PF (3 guidelines). All guidelines recommend that IVIg may be used as a third-line treatment for severe or refractory cases.
- For severe or refractory BP, other therapeutic options than IVIg include monoclonal antibodies, immunosuppressive drugs, immunoadsorption, and plasma exchange (3 guidelines).
- For severe or refractory PV and PF, other therapeutic options than IVIg include immunosuppressive drugs, dapsone, immunoadsorption, plasma exchange, and IV corticosteroid pulse therapy (3 guidelines).
- The evidence base supporting these guidelines was unclear; recommendations should be interpreted with caution.

Context and Policy Issues

Autoimmune blistering diseases are rare autoimmune diseases of the skin and/or mucous membrane, such as pemphigus and pemphigoid.[1] Pemphigus is a group of rare, potentially life-threatening diseases that affect the outer layer of the skin (epidermis) and that are mediated by immunoglobulin G against structural proteins of the desmosomes at the cell-cell junctions, leading to the formation of fragile blisters that rupture easily and leave open sores that may become infected.[2] Pemphigus encompasses 2 distinct forms that are caused by humoral autoimmune response: pemphigus vulgaris (PV) and pemphigus foliaceus (PF).[2] PV is the most common form in which blisters develop deep in the epidermis in the area of the mouth, then spread to the skin and even the genitals.[3] PF is a less severe type in which blisters occur in the superficial layers of the epidermis, form on the scalp and face first, and then spread to the chest and back.[3] The annual incidence of pemphigus varies among countries and ethnicities, ranging from 0.6 cases per million in Switzerland (from 2001 to 2002) to 32.0 cases per million in Israel (from 1972 to 1977).[4]

Pemphigoid refers to a group of subepidermal autoimmune bullous diseases that are characterized by firm blisters and erosions of the skin or mucus membranes that usually will not rupture upon contact, due to autoantibodies against proteins of the hemidesmosomes at the epidermal-dermal junctions.[2] Bullous pemphigoid (BP) is a common subtype of pemphigoid diseases that develop predominantly in the abdomen, back, arms, and legs.[3] The annual incidence of BP in Europe varied from 2.5 cases per million to 42.8 cases per million.[2] Incidence and prevalence data of both pemphigus and pemphigoid in Canada were not available. However, the 2003 record from Statistics Canada reported 15 deaths related to pemphigus and 15 deaths related to BP.[5] Among pemphigus-related deaths, 1 was due to PV, 0 to PF, 10 to unspecified pemphigus, and 4 to other types.[5] Death occurred mostly in people aged 80 and older.[5]

There is currently no cure for either pemphigus or pemphigoid; however, the cornerstone of treatment for the diseases is corticosteroids, which are administered topically or orally.[3] Immunosuppressive drugs such as mycophenolate mofetil, azathioprine, or methotrexate may be used in combination with corticosteroids to reduce the overall dose of steroids.[3] In severe or treatment-resistant cases, other therapies such as IV immunoglobulin (IVIg), rituximab, immunoadsorption, plasma exchange, cyclophosphamide, or pulse steroid therapy may be used.[2] IVIg appears to be effective for refractory cases by reducing the levels of circulating autoantibodies associated with pemphigus and pemphigoid through catabolism.[6,7]

The demand for IVIg has been steadily increasing every year for the treatment of various autoimmune and inflammatory diseases. Due to the COVID-19 pandemic, which has had a strong impact on global blood and plasma collection, countries around the world are experiencing a decline in Ig products.[8,9] The shortage of the Ig products, their high cost, and their increasing demand has made it necessary to reevaluate alternative treatment options.

The objective of this report is to summarize the evidence regarding the clinical effectiveness and safety of alternative treatments to IVIg, specifically rituximab, azathioprine, mycophenolate mofetil, cyclophosphamide, and leflunomide, compared to IVIg or placebo for PV, PF, and BP. This report also aims to summarize the recommendations from evidence-based guidelines regarding alternative treatments to IVIg for these populations.

Research Questions

1. What is the clinical effectiveness of alternative treatments to IVIg compared to IVIg or placebo for autoimmune blistering diseases?
2. What is the safety of alternative treatments to IVIg compared to IVIg or placebo for autoimmune blistering diseases?
3. What are the evidence-based guidelines regarding the use of alternative treatments to IVIg for autoimmune blistering diseases?

Methods

Literature Search Methods

An information specialist conducted a literature search on key resources, including MEDLINE, the Cochrane Database of Systematic Reviews, the International HTA Database, and the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search approach was customized to retrieve a limited set of results, balancing comprehensiveness with relevancy. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. Search concepts were developed based on the elements of the research questions and selection criteria. The main search concepts were rituximab, azathioprine, mycophenolate mofetil, cyclophosphamide, or leflunomide; and pemphigus or pemphigoid. An additional focused search

for guidelines was conducted using the concepts pemphigus or pemphigoid, and CADTH-developed search filters were applied to this search to limit retrieval to guidelines. Retrieval was limited to the human population. The search was completed on April 12, 2023, and limited to English-language documents published since January 1, 2018.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Criteria	Description
Population	Patients with autoimmune blistering diseases (i.e., pemphigus vulgaris, pemphigus foliaceus, and bullous pemphigoid)
Intervention	Rituximab, azathioprine, mycophenolate mofetil, cyclophosphamide, leflunomide
Comparator	Q1 to Q2: IV Immunoglobulin, placebo Q3: NA
Outcomes	Q1: Clinical effectiveness (e.g., remission, rate of relapse, HRQoL) Q2: Safety (e.g., adverse events, severe adverse events) Q3: Recommendations regarding best practices (e.g., which alternative to use, dose and timing of treatment, indications)
Study designs	Health technology assessments, systematic reviews, evidence-based guidelines

HRQoL = health-related quality of life; NA = not applicable.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, or were published before 2018. Guidelines with unclear methodologies were excluded.

Critical Appraisal of Individual Studies

The included publications were critically appraised by 1 reviewer using the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument[10] for guidelines. Summary scores were not calculated for the included studies; rather, the strengths and limitations of each included publication were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 531 citations were identified in the literature search. Following screening of titles and abstracts, 494 citations were excluded and 37 potentially relevant reports from the electronic search were retrieved for full-text review. No potentially relevant publications were retrieved from the grey literature search for full-text review. Of these potentially relevant articles, 31 publications were excluded for various reasons, and 6

publications (i.e., guidelines) met the inclusion criteria and were included in this report. Appendix 1 presents the PRISMA[11] flow chart of the study selection.

Summary of Study Characteristics

Additional details regarding the characteristics of included publications are provided in Appendix 2.

Study Design

This report identified and included 6 guidelines, all of which were consensus guidelines for the management of BP[12-14] or PV and PF[15-17] that were based on information from existing guidelines. Guidelines for the management of BP were the European Academy of Dermatology and Venereology (EADV) guideline by Borradori et al. (2022),[12] the Japanese guideline by Ujiie et al. (2019),[13] and the Italian guideline by Cozzani et al. (2018).[14] The 3 guidelines for the management of PV and PF were the Taiwanese Dermatology Association guideline by Chu et al. (2022),[15] the EADV guideline by Joly et al. (2020),[16] and the Italian guideline by Feliciani et al. (2018).[17]

The methods for evidence collection, selection, and synthesis were not reported; instead, expert panels reviewed and discussed evidence from previous guidelines. Specific methods for evaluating the quality of evidence that supports the recommendations were not reported in 5 guidelines.[12,13,15-17] The quality of evidence in 1 guideline[14] was assessed and given a grade ranging from 1 (i.e., randomized controlled trial [RCT]) to 5 (i.e., expert opinion).

The recommendations were made mostly through experts' opinions. In each guideline, the working groups consisted of experts who reviewed the previous guideline recommendations, input their expert opinions, and prepared different versions of the statements until consensus was reached through voting. The methods for grading the strength of recommendations were not reported in 3 guidelines.[14,15,17] Three guidelines[12,13,16] provided the strength of each recommendation, which was voted by consensus. Two guidelines[12,16] used syntax to grade the strength of recommendations ranging from highest ("is recommended" for strong recommendations) to lowest ("is not recommended" for negative recommendations). One guideline[13] labelled its recommendations from A (strongly recommended) to D (recommended not to implement).

Country of Origin

The guidelines were conducted by authors from Europe,[12,16] Taiwan,[15] Japan,[13] and Italy.[14,17]

Patient Population

The target population in the included guidelines was patients with BP[12-14] or patients with PV or PF.[15-17]

The intended users in all included guidelines were health professionals who are involved in the patients' management.

Interventions

The included guidelines[12-17] considered diagnostic steps and treatment algorithms for the management of BP or PV and PF.

Outcomes

The included guidelines[12-17] considered all clinical outcomes related to diagnosis, treatment, and monitoring of the diseases.

Summary of Critical Appraisal

All included guidelines[12-17] were explicit in terms of scope and purpose (i.e., objectives, health questions, and populations), and clearly presented recommendations (i.e., they were specific, unambiguous, and it was easy to find key recommendations, with options for managing the different conditions or health issues). Recommendations were in the forms of treatment algorithms for specific conditions that were easy to follow.[12-17] In terms of stakeholder involvement, all included guidelines[12-17] clearly defined their target users and their development groups. However, it was unclear if the views and preferences of the patients were sought in all guidelines.[12-17] In all included guidelines,[12-17] recommendations were formulated through consensus based on information from previous guidelines, current evidence, and experts' opinions. However, methods for evidence collection, criteria for selection, and methods for evidence synthesis were not provided. Therefore, it is unclear if the search and selection of relevant evidence was comprehensive, and the evidence base supporting the recommendations is uncertain. The procedures for updating the guidelines were not reported in all guidelines.[12-17] None of the guidelines clearly described facilitators and barriers to application, advice and/or tools on how the recommendations can be put into practice, resource implications, or monitoring or auditing criteria.[12-17] For editorial independence, all guidelines[12-17] reported on the competing interests of guideline development group members, but did not report if the views of the funding body had any influence on the content of the guidelines. Overall, all the included guidelines were limited in terms of rigour of development, reporting, and applicability, which reduced certainty in the findings.

Additional details regarding the strengths and limitations of the included guidelines[12-17] are provided in Appendix 3.

Summary of Findings

Clinical Effectiveness of Alternative Treatments to IVIg Compared to IVIg or Placebo for Autoimmune Blistering Diseases

No relevant health technology assessments or systematic reviews were identified regarding the clinical effectiveness of alternative treatments to IVIg for BP or PV and PF.

Safety of Alternative Treatments to IVIg Compared to IVIg or Placebo for Autoimmune Blistering Diseases

No relevant health technology assessments or systematic reviews were identified regarding the clinical safety of alternative treatments to IVIg for BP or PV and PF.

Guidelines Regarding the Use of Alternative Treatments to IVIg for Autoimmune Blistering Diseases

Appendix 4 presents the summary of recommendations from the included guidelines. All the identified guidelines (3 for BP[12-14] and 3 for PV and PF)[15-17] provided treatment algorithms that included options for first-

line treatment, second-line treatment, and third-line treatment for treatment-resistant or hard-to-treat cases. Topical and oral corticosteroids were the first choice of treatments for BP, while systemic corticosteroids and rituximab were the first-line therapies for PV and PF. As IVIg was 1 of the options for third-line treatment or treatment-resistant cases, other third-line treatment options in each guideline were considered alternative treatments to IVIg and are discussed here.

Details of stepladder treatments, including first-line and second-line treatments in each guideline, are presented in Appendix 4 for BP or PV and PF, respectively.

Treatment Management of BP

The guideline from the EADV by Borradori et al. (2022)[12] recommends that immunosuppressants such as methotrexate, azathioprine, or mycophenolate may be used as add-on therapy to corticosteroids in treatment-recalcitrant BP (i.e., resistant to 0.75 mg/kg per day of prednisone). In this guideline, IVIg is considered as a therapeutic option for recalcitrant BP, but not for severe BP, corticosteroid-dependent, or relapsing BP. Other therapeutic options in the same group with IVIg were rituximab, omalizumab, dupilumab, and immunoadsorption. The strength of both recommendations was labelled as "may be recommended," which is the rating assigned if the evidence was derived from small RCTs, nonrandomized prospective multicentre studies, or large retrospective multicentre studies.

The Japanese guideline by Ujiie et al. (2019)[13] describes options for the management of moderate, severe, and treatment-resistant BP, including IVIg and other therapies. It recommends oral steroids as first-line treatment, and that additional treatments may be considered if sufficient efficacy could not be achieved with oral steroids. These treatments include immunosuppressants (e.g., azathioprine, mizoribine, oral cyclophosphamide, cyclosporine, mycophenolate mofetil, methotrexate), methyl prednisolone pulse therapy, IVIg, plasma exchange, cyclophosphamide pulse therapy, tetracycline or minocycline plus nicotinamide, dapsone, and superpotent topical corticosteroids (e.g., clobetasol propionate). This guideline did not differentiate therapies based on the severity of the disease (i.e., moderate, severe, and treatment-resistant BP were grouped together and discussed collectively). Based on the level of evidence (not reported), the strength of recommendations for additional treatments to oral steroids was either labelled as C1, indicating that these therapeutic options "may be implemented," or not reported.

The Italian guideline by Cozzani et al. (2018)[14] recommends several therapeutic options for treatment-resistant BP, despite several weeks of intensive therapy with combined topical and oral steroids. These were immunosuppressants (such as methotrexate, azathioprine, mycophenolate), IVIg, immunoadsorption, rituximab, omalizumab, cyclophosphamide, and plasma exchange. This guideline did not report the strength of the recommendations but provided the level of evidence for each treatment option, ranging from level 1 (highest) to level 5 (lowest). Relevant to this report, recommendations for superpotent topical corticosteroids and plasma exchange were based on level 1 evidence, and recommendations for rituximab, omalizumab, and immunoadsorption were based on level 4 evidence.

Overall, recommendations from 3 guidelines[12-14] for BP showed that IVIg is reserved for treatment-resistant or hard-to-treat cases, and the alternative therapies to IVIg include monoclonal antibodies (e.g.,

rituximab, omalizumab, dupilumab), immunosuppressive drugs (e.g., azathioprine, mycophenolate mofetil, cyclophosphamide, methotrexate), immunoadsorption, and plasma exchange.

Treatment Management of PV and PF

The Taiwanese guideline by Chu et al. (2022)[15] recommends several third-line therapeutic options for patients who did not respond to azathioprine as second-line therapy. These were oral cyclophosphamide, methotrexate, mycophenolate mofetil, immunoadsorption, IVIg, and plasma exchange. This guideline was formulated based on information from previous consensus guidelines, and it did not classify the treatment options based on disease severity. The level of evidence or the strength of the recommendations were not reported.

The European EADV guideline by Joly et al. (2020)[16] listed 3 treatments options that may be recommended as add-on therapy to rituximab or immunosuppressants in patients with severe or refractory pemphigus (PF or PV) who did not respond to rituximab or immunosuppressant therapy. These were IVIg, IV corticosteroid pulse therapy, and immunoadsorption. The strength of the recommendation was labelled as "may be recommended" as the evidence was derived from small RCTs, nonrandomized prospective multicentre or large retrospective multicentre studies.

The Italian guideline by Feliciani et al. (2018)[17] recommended several therapeutic options as adjuvant to systemic corticosteroids in the third-line treatment of treatment-resistant pemphigus. These were IVIg, immunoadsorption, cyclophosphamide, methotrexate, or dapsone. The recommendations were formulated based on an existing French guideline for the management of pemphigus that was published in 2011. This guideline did not report the level of evidence or the strength of the recommendations.

Overall, recommendations from 3 guidelines[15-17] for pemphigus showed that IVIg is used only in third-line treatment or treatment-resistant PV and PF, and the alternative therapies to IVIg include immunosuppressive drugs (e.g., cyclophosphamide, mycophenolate mofetil), immunoadsorption, plasma exchange, IV corticosteroid pulse therapy, methotrexate, and dapsone.

Limitations

The included guidelines had several limitations. First, because of the rarity of the diseases and few clinical studies with high degree of evidence, recommendations were made mostly by expert consensus, relying on their clinical experience and perspectives when supporting evidence was limited or not available. Second, there were some differences in recommendations from different guidelines that reflect incomplete knowledge on the optimal treatment modalities, probably due to the paucity of high-level evidence. For instance, IVIg is reserved for treatment-recalcitrant BP in the EADV guideline,[12] while it is considered when sufficient efficacy cannot be achieved with oral steroids in moderate, severe, or treatment-resistant cases in the Japanese guideline.[13] This would lead to the divergent expert opinion on a number of questions, which would need to be clarified with future studies. Third, the recommendations did not address potential side-effects of the proposed drugs. Also, patient preferences or experiences were not sought and considered while formulating the recommendations. Fourth, there were no clear recommendations for alternative

therapies to IVIg specifically; instead, the drugs or therapies were grouped together with IVIg as therapeutic options for third-line treatment or hard-to-treat cases. This may lead to the assumption that those drugs or therapies are equivalent in treatment efficacy and safety.

Conclusions and Implications for Decision- or Policy-Making

No relevant literature was identified to answer the first 2 research questions; therefore, conclusions could not be provided regarding the clinical effectiveness and safety of alternative therapies to IVIg compared to IVIg or placebo for BP or PV and PF.

Six consensus guidelines were identified, 3 for the treatment of BP[12-14] and 3 for the treatment of PV and PF.[15-17] Recommendations in all included guidelines were in the forms of treatment algorithms in which lists of drugs were classified in a stepladder from first choice to third choice or for hard-to-treat cases. In both BP and PV or PF conditions, IVIg was reserved as a last option in severe or refractory cases. For BP, other therapeutic options to IVIg in the third-line category included monoclonal antibodies (e.g., rituximab, omalizumab, dupilumab), immunosuppressive drugs (e.g., azathioprine, mycophenolate mofetil, methotrexate, cyclophosphamide), immunoadsorption, and plasma exchange. For PV and PF, other therapeutic options to IVIg included immunosuppressive drugs (i.e., cyclophosphamide, mycophenolate mofetil, methotrexate), dapsone, immunoadsorption, plasma exchange, and IV corticosteroid pulse therapy. Although those therapies were listed together with IVIg for third-line treatment, their comparative efficacy and safety with IVIg or among each other remain unclear and have not been addressed in the guidelines. In addition, the methods reporting for these consensus-based guidelines was limited, and the evidence base supporting the recommendations is uncertain. Therefore, extreme caution should be taken when considering any of those therapies as alternatives to IVIg. Safety is the most important factor and should be carefully considered when choosing a therapy to replace IVIg. Future studies are needed to clarify the comparative clinical effectiveness and safety of alternative treatments to IVIg for autoimmune blistering diseases, and to support the development of robust evidence-based guidance for their use.

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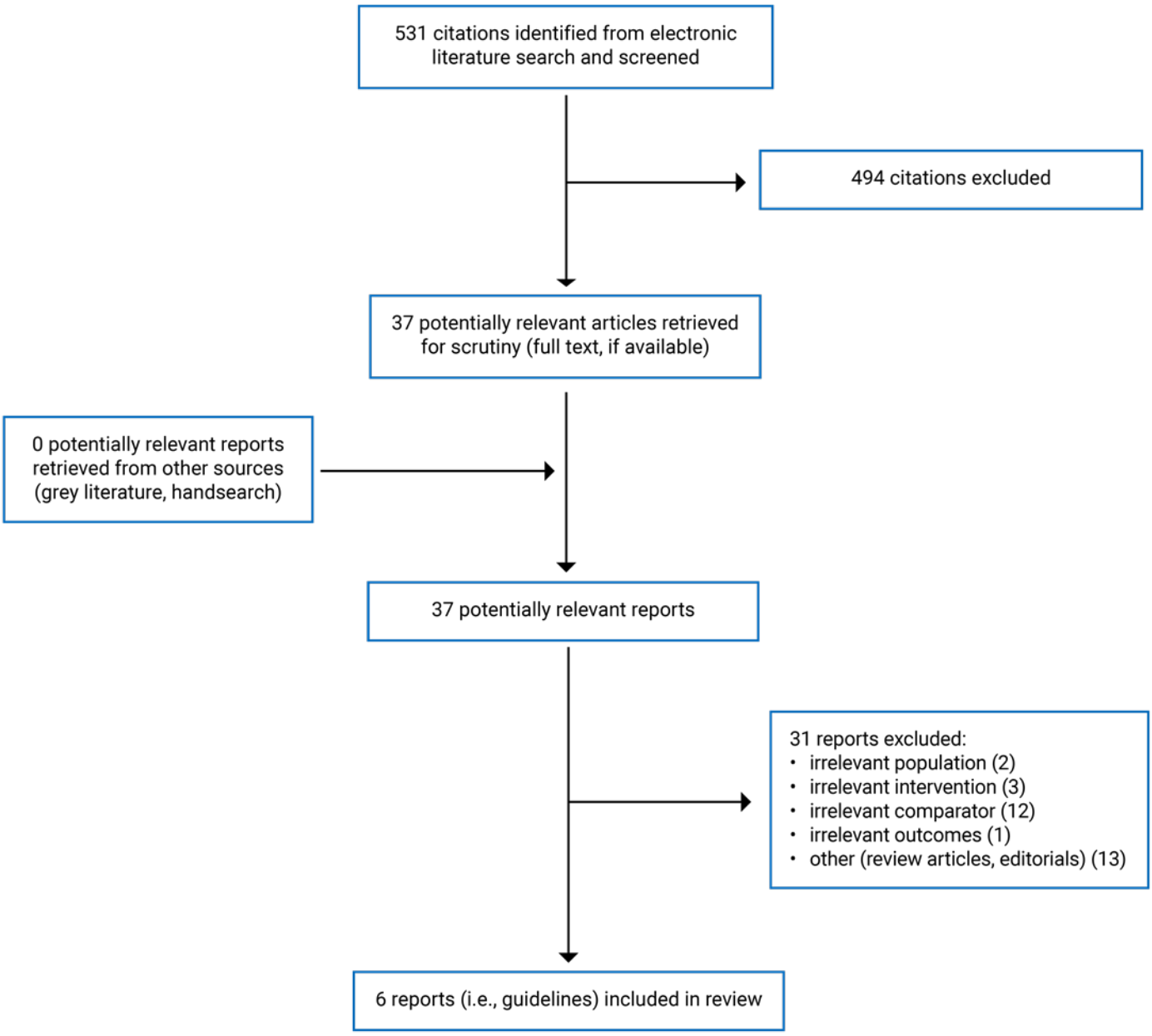
Appendix 1: Selection of Included Studies

Figure 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Guidelines

Intended users, target population	Intervention and practice considered	Major outcomes considered	Evidence collection, selection, and synthesis	Evidence quality assessment	Recommendations development and evaluation	Guideline validation
EADV, Borradori et al. (2022)[12]						
Intended users: Health professionals involved in the patient's management including dermatologists, general practitioners, specialized nurses, and all other specialists. **Target population**: Patients with BP.	Management of BP including diagnostic steps and therapeutic management.	All new relevant knowledge on clinical practice, and evidence about benefits of novel diagnostic and therapeutic interventions and outcomes.	NR	Quality of evidence: NR Strength of recommendation: syntax[a] was used for specific recommendations based on the levels of evidence.	The EADV Task force appointed a writing group to: • revise the first version of the guidelines published in 2015 • assign scores (ranging from 0 to 5 according to the increasing degree of consensus) to each of the recommendation statements • and write subsequent versions of the guidelines, until each of the statements was given a mark greater than 4 by voting group.	The manuscript was revised by different European patient organizations. The revised version was finally passed to the EDF for final consensus. The guideline was published in peer-reviewed journal.
TDA, Chu et al. (2022)[15]						
Intended Users: Health professionals involved in management of pemphigus. **Target Population**: Patients with PV and PF.	Management of pemphigus including assessment of disease severity and therapeutic management.	All outcomes related to diagnosis, treatment, and monitoring of pemphigus.	NR	Quality of evidence: NR Strength of recommendation: NR	A panel of pemphigus experts: • discussed the most recent consensus guidelines (i.e., EDF, EADV, and the International Bullous Diseases Consensus Group)	Published in peer-reviewed journal.

Intended users, target population	Intervention and practice considered	Major outcomes considered	Evidence collection, selection, and synthesis	Evidence quality assessment	Recommendations development and evaluation	Guideline validation
					• formulated a pemphigus consensus with at least a 75% approval on the diagnosis, assessment of disease severity, treatment, monitoring, and prevention and management.	
EADV, Joly et al. (2020)[16]						
Intended Users: Health professionals involved in the patient's management including dermatologists, general practitioners, specialized nurses, and all other specialists whose expertise might be necessary based on the clinical context. **Target Population**: Patients with PV and PF	Management of PV and PF including diagnostic steps and therapeutic management.	All new relevant knowledge on clinical practice, and evidence about benefits of novel diagnostic and therapeutic interventions and outcomes.	NR	Quality of evidence: NR Strength of recommendation: syntax[a] was used for specific recommendations based on the levels of evidence.	The EADV Task force appointed a writing group to: • write the first version of the updated guidelines. • assign scores (ranging from 0 to 5 according to the increasing degree of consensus) to each of the recommendation statements. • and prepare subsequent version of the guidelines, until each of the statements was given a mark greater than 4 by voting group.	The manuscript was revised by different European patient organizations. The revised version was finally passed to the EDF for final consensus. The guideline was published in peer-reviewed journal.
Ujiie et al. (2019)[13]						
Intended Users: Health professionals involved in management of pemphigoid (including epidermolysis bullosa	Management of pemphigoid including diagnostic steps and therapeutic management.	All outcomes related to diagnosis, treatment, and monitoring of pemphigoid.	NR	Quality of evidence: NR Strength of recommendation: labelled as A (strongly recommended); B (recommended); C1	The Committee set clinical questions and described recommendations based on evidence-based medicine derived form Japanese and international sources.	The guideline was published in peer-reviewed journal.

Intended users, target population	Intervention and practice considered	Major outcomes considered	Evidence collection, selection, and synthesis	Evidence quality assessment	Recommendations development and evaluation	Guideline validation
acquisita) **Target Population**: Patients with pemphigoid (including epidermolysis bullosa acquisita)				(may be implemented); C2 (due to scant evidence, not actively recommended); D (recommended not to implement).	The guidelines were established mostly based on the opinions of the Committee. Details of the recommendation development and evaluation were not reported.	
Cozzani et al. (2018)[14]						
Intended Users: Health professionals involved in the patient's management including dermatologists, general practitioners, specialized nurses, and all other specialists. **Target Population**: Patients with BP.	Management of BP including diagnostic steps and therapeutic management.	All outcomes related to diagnosis, treatment, and monitoring of BP.	NR	Quality of evidence: labelled from 1 to 5[b] Strength of recommendation: NR	Not described in published articles.	The guideline was published in peer-reviewed journal.
Feliciani et al. (2018)[17]						
Intended Users: Health professionals involved in the patient's management including dermatologists, general practitioners, specialized nurses, and all other	Management of PV and PF including diagnostic steps and therapeutic management.	All outcomes related to diagnosis, treatment, and monitoring of pemphigus.	NR	Quality of evidence: NR Strength of recommendation: NR	A working group (group of experts): • wrote the first version of the guideline which was based on a recently established French guideline • gave a score (ranging from 0 to 9 according	The revised version was finally passed to the EDF for final consensus of the EDF members. The guideline was published in peer-reviewed journal.

Intended users, target population	Intervention and practice considered	Major outcomes considered	Evidence collection, selection, and synthesis	Evidence quality assessment	Recommendations development and evaluation	Guideline validation
specialists. **Target Population**: Patients with pemphigus (e.g., PV and PF).					to increase degree of consensus) to each of the statements of the first version • then prepared a second version of the guideline.	

BP = bullous pemphigoid; EADV = European Academy of Dermatology and Venereology; EDF = European Dermatology Forum; NR = not reported; PF = pemphigus foliaceus; PV = pemphigus vulgaris; TDA = Taiwanese Dermatological Association.

Note: This table has not been copy-edited.

[a]Syntax used for specific recommendations: "*is recommended*": strong recommendations from large randomized prospective multicentre studies; "*may be recommended*": recommendations from small randomized or non-randomized prospective multicentre or large retrospective multicentre studies; "*may be considered*": recommendations pending from case series, or small retrospective single-centre studies. It also has been used when a consensus could not be reached among experts; "*is not recommended*": negative recommendation.

[b]Level of evidence: Level 1: randomized prospective single-centre or multicentre study. In case that in the latter the intervention is shown effective and not contradicted by other studies, it is considered validated; Level 2: randomized prospective single-centre study (in case of poor methodological quality), retrospective multicentre study; Level 3: case series, retrospective single-centre study; Level 4: anecdotal case reports; Level 5: expert opinion.

Appendix 3: Critical Appraisal of Included Publications

Note that this table has not been copy-edited.

Table 3: Strengths and Limitations of Guidelines Using AGREE II[10]

Item	EADV, Borradori et al. (2022)[12]	TDA, Chu et al. (2022)[15]	EADV, Joly et al. (2020)[16]	Ujiie et al. (2019)[13]	Cozzani et al. (2018)[14]	Feliciani et al. (2018)[17]
Domain 1: scope and purpose						
1. The overall objective(s) of the guideline is (are) specifically described.	Yes	Yes	Yes	Yes	Yes	Yes
2. The health question(s) covered by the guideline is (are) specifically described.	Yes	Yes	Yes	Yes	Yes	Yes
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	Yes	Yes	Yes	Yes	Yes	Yes
Domain 2: stakeholder involvement						
4. The guideline development group includes individuals from all relevant professional groups.	Yes	Yes	Yes	Yes	Yes	Yes
5. The views and preferences of the target population (patients, public, etc.) have been sought.	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
6. The target users of the guideline are clearly defined.	Yes	Yes	Yes	Yes	Yes	Yes
Domain 3: rigour of development						
7. Systematic methods were used to search for evidence.	No	No	No	No	No	No
8. The criteria for selecting the evidence are clearly described.	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
9. The strengths and limitations of the body of evidence are clearly described.	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
10. The methods for formulating the recommendations are clearly described.	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear

Item	EADV, Borradori et al. (2022)[12]	TDA, Chu et al. (2022)[15]	EADV, Joly et al. (2020)[16]	Ujiie et al. (2019)[13]	Cozzani et al. (2018)[14]	Feliciani et al. (2018)[17]
12. There is an explicit link between the recommendations and the supporting evidence.	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
13. The guideline has been externally reviewed by experts before its publication.	Yes	Yes	Yes	Yes	Yes	Yes
14. A procedure for updating the guideline is provided.	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Domain 4: clarity of presentation						
15. The recommendations are specific and unambiguous.	Yes (Treatment algorithm)	Yes (Treatment algorithm)	Yes (Treatment algorithm)	Yes (Treatment algorithm)	Yes (Treatment algorithm)	Yes (Treatment algorithm)
16. The different options for management of the condition or health issue are clearly presented.	Yes	Yes	Yes	Yes	Yes	Yes
17. Key recommendations are easily identifiable.	Yes	Yes	Yes	Yes	Yes	Yes
Domain 5: applicability						
18. The guideline describes facilitators and barriers to its application.	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
20. The potential resource implications of applying the recommendations have been considered.	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
21. The guideline presents monitoring and/or auditing criteria.	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Domain 6: editorial independence						
22. The views of the funding body have not influenced the content of the guideline.	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
23. Competing interests of guideline development group members have been recorded and addressed.	Yes	Yes	Yes	Yes	Yes	Yes

AGREE II = Appraisal of Guidelines for Research and Evaluation II.

Appendix 4: Main Study Findings

Note that this table has not been copy-edited.

Table 4: Summary of Recommendations in Included Guidelines for Bullous Pemphigoid EADV, Borradori et al. (2022)

Recommendations and supporting evidence	Quality of evidence and strength of recommendations
EADV, Borradori et al. (2022)[12]	
Mild and moderate BP (BPDAI < 20 and 20 ≤ BPDAI < 57, respectively)	
First choice	
• In localized BP, apply potent or supper potent topical corticosteroids[a]	Quality of evidence: NR Strength of recommendation: May be considered (recommendation pending)

• In non-localized BP
  ◦ Superpotent topical corticosteroids applied twice a day, or
  ◦ Oral corticosteroids, at initial dose of 0.5 mg/kg/day prednisone or prednisolone[b]
	Quality of evidence: NR
	Strength of recommendation: Is recommended (strong recommendation)

Second choice	Quality of evidence: NR Strength of recommendation: May be recommended (recommendation)
• Doxycycline[c] • Dapsone[c]	
Severe BP (BPDAI ≥ 57)	
• Superpotent topical corticosteroids applied twice a day, or • Oral corticosteroids, at initial dose of 0.5 mg/kg/day prednisone. Note: In patients who do not achieve control within 1 to 3 weeks, dose of prednisone can be increase up to 0.75 mg/kg or add superpotent topical corticosteroids.d	Quality of evidence: NR Strength of recommendation: Is recommended (strong recommendation)
Corticosteroid-dependent or relapsing BP	
Combination with and/or introduction of conventional immunosuppressants[e] • Methotrexate • Azathioprine • Mycophenolate mofetil	Quality of evidence: NR Strength of recommendation: May be considered (recommendation pending)
In patients with poor general condition and/or contraindications to immunosuppressive drugs: • Doxycycline • Dapsone • Omalizumab[f]	Quality of evidence: NR Strength of recommendation: May be considered (recommendation pending)

Recommendations and supporting evidence	Quality of evidence and strength of recommendations
Treatment-recalcitrant BP (resistant to 0.75 mg/kg/day prednisone)	
Combination with and/or introduction of conventional immunosuppressants: • Methotrexate • Azathioprine • Mycophenolate mofetil	Quality of evidence: NR Strength of recommendation: May be considered (recommendation pending)
Other therapeutic options: • Rituximab[g] • Omalizumab • Dupilumab[h] • IVIg[i] • Immunoadsorption[j]	Quality of evidence: NR Strength of recommendation: May be considered (recommendation pending)

BP = bullous pemphigoid; BPDAI = Bullous Pemphigoid Disease Activity Index; EADV = European Academy of Dermatology and Venereology; IVIg = IV immunoglobulin; NR = not reported; RCT = randomized controlled trial.

[a]Topical treatment was supported by 2 RCTs showing that topical corticosteroids improved BP patients' outcome.

[b]A prospective observational multicenter study indicated that a 0.5 mg/kg/day prednisone is effective in patients with mild and moderate BP.

[c]No consensus could be reached among experts regarding the use of doxycycline and dapsone in BP. Dapsone may be considered in patients with contraindications to oral corticosteroids or immunosuppressive treatments, with mild and moderate BP.

[d]Evidence from a multicenter observational study showed that increase the dose of prednisone up to 0.75 mg/kg or add topical corticosteroids in addition to 0.5 mg/kg prednisone is a therapeutic option in patients who do not achieve control within 1 to 3 weeks.

[e]Evidence on immunosuppressive drugs (i.e., methotrexate, azathioprine, mycophenolate) for patients with relapse BP who are not adequately controlled by topical or oral corticosteroids was supported by 3 RCTs and 1 retrospective observational study.

[f]A case study suggested that omalizumab may be considered in patients who are contraindicated to immunosuppressive drugs.

[g]The beneficial effect of rituximab (anti-CD20 monoclonal antibody) in difficult-to-treat cases of BP was demonstrated in 2 case series and 1 retrospective chart review study.

[h]An open retrospective series suggested the potential efficacy of dupilumab in BP.

[i]In an RCT add-on therapy with IVIg, 2 g/kg/day in BP cases with no improvement on prednisolone ≥ 0.4 mg/kg/day showed a trend toward a beneficial effects.

[j]One case series and 1 narrative review provided beneficial evidence of immunoadsorption as adjuvant treatment of severe/refractory BP.

Table 5: Summary of Recommendations in Included Guidelines for Bullous Pemphigoid, Ujiie et al. (2019)

Recommendations and supporting evidence	Quality of evidence and strength of recommendations
Ujiie et al. (2019)[13]	
Mild BP	
Topical therapy (steroid ointment, antibiotic-containing ointment, zinc oxide ointment)[a]	Quality of evidence: NR Strength of recommendation: NR
Tetracycline (500 to 2000 mg/day) or minocycline (100 to 200 mg/day) + nicotinamide (500 to 2000 mg/day)[b]	Quality of evidence: NR Strength of recommendation: C1 (may be implemented)
Dapsone 25 to 100 mg/day, concomitantly used with topical steroid therapy[c]	Quality of evidence: NR Strength of recommendation: C1 (may be implemented)
Oral steroid: 0.2 to 0.3 mg/kg/day prednisolone[c]	Quality of evidence: NR Strength of recommendation: B (recommended)
Moderate, severe and treatment resistant cases[d]	

Recommendations and supporting evidence	Quality of evidence and strength of recommendations
Oral steroid: 0.5 to 1 mg/kg/day prednisolone	Quality of evidence: NR Strength of recommendation: B (recommended)
If sufficient efficacy cannot be achieved with oral steroids, considered additional treatments as followed:	
Immunosuppressants: • Azathioprine: 50 to 150 mg/day • Mizoribine: 150 mg/day • Oral cyclophosphamide: 50 to 100 mg/day • Cyclosporin: 3 to 5 mg/day • Mycophenolate mofetil: 2 g/day • Methotrexate: 2.5 to 7.5 mg/week	Quality of evidence: NR Strength of recommendation: C1 (may be implemented)
Methyl prednisolone pulse therapy: 0.5 to 1 g/day for 3 days.	Quality of evidence: NR Strength of recommendation: C1 (may be implemented)
IVIg therapy: 400 mg/kg/day intravenously for 5 days.	Quality of evidence: NR Strength of recommendation: C1 (may be implemented)
Plasma exchange	Quality of evidence: NR Strength of recommendation: NR
Cyclophosphamide pulse therapy: IV injection once per day (500 to 1000 mg/m^2 body surface area)	Quality of evidence: NR Strength of recommendation: NR
Rituximab	Quality of evidence: NR Strength of recommendation: NR
Tetracycline or minocycline + nicotinamide	Quality of evidence: NR Strength of recommendation: C1 (may be implemented)
Dapsone	Quality of evidence: NR Strength of recommendation: C1 (may be implemented)
Superpotent topical corticosteroid (clobetasol propionate)	Quality of evidence: NR Strength of recommendation: NR

BP = bullous pemphigoid; BPDAI = Bullous Pemphigoid Disease Activity Index; EADV = European Academy of Dermatology and Venereology; IVIg = IV immunoglobulin; NR = not reported; RCT = randomized controlled trial.

[a]An RCT reported that, in mild and moderate cases, the systemic topical application of clobetasol propionate twice a day is effective.

[b]Evidence from a previous guideline suggested that a combination therapy of tetracycline (or minocycline) and nicotinamide was effective in some patients with mild BP. It is standard to use topical steroid in combination.

[c]Evidence supporting dapsone and oral steroid was not reported.

[d]Supporting evidence on treatment recommendations for moderate, severe, and treatment resistant cases was not reported.

Table 6: Summary of Recommendations in Included Guidelines for Bullous Pemphigoid, Cozzani et al. (2018)

Recommendations and supporting evidence	Quality of evidence and strength of recommendations
Cozzani et al. (2018)[14]	
Localized or limited disease with mild activity	
First choice	
• Superpotent topical corticosteroids: clobetasol propionate 10 to 20 g/day[a]	Quality of evidence: Level 1, validated Strength of recommendation: NR
Second choice	
• Tetracyclines: oxytetracycline 2 g/day, doxycycline 200 mg/day + nicotinamide, up to 2 g per day[b] • Methotrexate: up to 15 mg once a week[c] • Dapsone: up to 1.5 mg/kg/day[d]	Quality of evidence: Level 1 to 3, not validated Strength of recommendation: NR
Treatment-resistant BP	
• Immunosuppressants (methotrexate, azathioprine, mycophenolate mofetil)[e]	Quality of evidence: Level 1 to 3 Strength of recommendation: NR
• IVIg[f]	Quality of evidence: Level 3 Strength of recommendation: NR
• Immunoadsorption[g]	Quality of evidence: Level 4 Strength of recommendation: NR
• Rituximab, omalizumab[h]	Quality of evidence: Level 4 Strength of recommendation: NR
• Cyclophosphamide[i]	Quality of evidence: Level 3 Strength of recommendation: NR
• Plasma exchange[j]	Quality of evidence: Level 1 Strength of recommendation: NR

BP = bullous pemphigoid; BPDAI = Bullous Pemphigoid Disease Activity Index; EADV = European Academy of Dermatology and Venereology; IVIg = IV immunoglobulin; NR = not reported; RCT = randomized controlled trial.

[a]Evidence from 2 RCTs suggested that clobetasol propionate was an effective treatment for mild BP.

[b]Two systematic reviews and 1 narrative review provided evidence for the effectiveness of tetracyclines plus nicotinamide for the treatment of BP.

[c]Findings of a retrospective study showed that combination of low-dose methotrexate and superpotent topical steroids may result in protracted control of BP in carefully selected patients.

[d]Findings of a retrospective study support treatment of BP with dapsone.

[e]Two RCTs and 3 retrospective studies provided evidence for the use of immunosuppressants for treatment of BP.

[f]One case series suggested that IVIg may be a useful therapeutic alternative to conventional modalities for selected BP patients.

[g]One case report and 1 narrative review suggested that immunoadsorption might be a safe and effective adjuvant treatment in severe and recalcitrant BP.

[h]Findings of 3 case series suggested that rituximab and omalizumab may be effective in treatment-resistant BP.

[i]Findings of case series suggested that low-dose oral cyclophosphamide might be an effective treatment of BP.

[j]Findings of 1 RCT suggested that plasma exchange allows a substantial saving of corticosteroids in the management of BP.

Table 7: Summary of Recommendations in Included Guidelines for Pemphigus Vulgaris and Pemphigus Foliaceus, TDA, Chu et al. (2022)

Recommendations and supporting evidence	Quality of evidence and strength of recommendations
TDA, Chu et al. (2022)[15]	
First-line treatment	
• Systemic corticosteroids (prednisolone or equivalent): 0.5 to 1.5 mg/kg/day[a] • Rituximab: 2 × 1 g infusion, 2 weeks apart; or may be used concomitantly with corticosteroids[b]	Quality of evidence: NR Strength of recommendation: NR
Second-line treatment	
• Azathioprine: 1 to 3 mg/kg/day; or may be used concomitantly with corticosteroids[c]	Quality of evidence: NR Strength of recommendation: NR
Third-line treatment	
• Cyclophosphamide: 1 to 2 mg/kg; reserved for patients with severe PV[d] • Methotrexate: 10 to 20 mg per week[e] • Mycophenolate mofetil: daily dose may be raised by 1 capsule (500 mg) per week until a final dose of 2 g/day[f] • Immunoadsorption: 2 cycles, 4 weeks apart; used together with immunosuppressive drugs[g] • IVIg: 2 g/kg/cycle for 2 to 5 consecutive days per month[h] • Plasma exchange: an alternative for refractory cases[i]	Quality of evidence: NR Strength of recommendation: NR

EADV = European Academy of Dermatology and Venereology; IVIg = IV immunoglobulin; NR = not reported; PDAI = Pemphigus Disease and Area Index; PF = pemphigus foliaceus; PV = pemphigus vulgaris; TDA = Taiwanese Dermatology Association; RCT = randomized controlled trial.

[a]The use of systemic corticosteroids as one of the first-line therapies was supported by evidence from 2 previous guidelines.

[b]A network meta-analysis showed that rituximab was the most effective of the seven steroid-sparing adjuvants used for pemphigus treatment. One case series and 1 RCT showed that when rituximab was combined with corticosteroids, patients experienced better improvement and had a higher chance of disease improvement with when compared with corticosteroids alone. One systematic review and meta-analysis showed the effectiveness of rituximab in achieving complete remission of pemphigus.

[c]One retrospective observational study suggested that azathioprine could serve as a good choice of maintenance therapy for patients who had received rituximab as first-line or add-on therapy.

[d]Evidence from a previous guideline supported the use of oral cyclophosphamide as alternative to azathioprine or mycophenolate mofetil in refractory cases with second line-treatment. Because of its potential toxicity, it is best reserved for patients with recalcitrant or severe PV.

[e]Evidence from a previous guideline supported the use of methotrexate, an immunomodulatory and corticosteroid-sparing agent, as a third-line treatment.

[f]Evidence from a previous guideline supported the use of mycophenolate mofetil as an alternative to azathioprine.

[g]Evidence from a previous guideline supported the use of immunoadsorption as third-line treatment.

[h]Evidence from a previous guideline supported the use of IVIg in concomitant with immunosuppressive adjuvants for treatment of pemphigus.

[i]Evidence from a previous guideline supported the use of plasma exchange as another alternative in refractory cases.

Table 8: Summary of Recommendations in Included Guidelines for Pemphigus Vulgaris and Pemphigus Foliaceus, EADV, Joly et al. (2020)

Recommendations and supporting evidence	Quality of evidence and strength of recommendations
EADV, Joly et al. (2020)[16]	
Mild PF (PDAI ≤ 15)	
First-line treatment	
• Dapsone: start with 50 to 100 mg/day, up to 1.5 mg/kg, usually combined with topical corticosteroids[a] • Topical corticosteroids (classes III and IV) • Systemic corticosteroids: prednisone 0.5 to 1.0 mg/kg/day[b] • Rituximab: 2 infusions of 1 g 2 weeks apart, alone or in combination with topical corticosteroids or oral prednisone 0.5 mg/kg/day[c]	Quality of evidence: NR Strength of recommendation: May be considered (recommendation pending)
Second-line treatment	
• Rituximab: 2 infusions of 1 g two weeks apart, alone or in combination with topical corticosteroids or oral prednisone 0.5 mg/kg/day in patients previously treated with dapsone or topical corticosteroids • Systemic corticosteroids: prednisone 0.5 to 1.0 mg/kg/day with or without azathioprine, or mycophenolate mofetil or mycophenolate sodium, if rituximab is not available or contraindicated[d]	Quality of evidence: NR Strength of recommendation: May be recommended (recommendation)
Mild PV (PDAI ≤ 15)	
First-line treatment	
• Rituximab: 2 infusions of 1 g 2 weeks apart, alone or in combination with oral prednisone 0.5 mg/kg/day. • Systemic corticosteroids: prednisone 0.5 to 1.0 mg/kg/day with or without azathioprine, or mycophenolate mofetil or mycophenolate sodium	Quality of evidence: NR Strength of recommendation: Is recommended (strong recommendation)
Second-line treatment	
• Add rituximab (2 infusions of 1 g 2 weeks apart) to patients initially treated with prednisone or prednisolone 0.5 to 1.0 mg/kg/day alone. • Increase the dose of prednisone or prednisolone up to 1.0 mg/kg/day in patients initially treated with prednisone or prednisolone 0.5 to 1.0 mg/kg/day plus rituximab.	Quality of evidence: NR Strength of recommendation: Is recommended (strong recommendation)
Moderate and severe types of PV and PF (15 < PDAI ≤ 45 and PDAI > 45, respectively)	
First-line treatment[e]	

Recommendations and supporting evidence	Quality of evidence and strength of recommendations
• Rituximab: 2 infusions of 1 g 2 weeks apart, in combination with oral prednisone 1.0 mg/kg/day. • Systemic corticosteroids: prednisone 1.0 to 1.5 mg/kg/day alone, or in combination with an immunosuppressive drug (azathioprine, mycophenolate mofetil or mycophenolate sodium).	Quality of evidence: NR Strength of recommendation: Is recommended (strong recommendation)
Severe/refractory PV and PF	
• IVIg: 2 g/kg/cycle (over 2 to 5 consecutive days every 4 weeks)[f] • IV corticosteroid pulses: methylprednisolone (0.5 to 1 g/day) or dexamethasone (100 mg/day) over 3 consecutive days in initial intervals of 3 to 4 weeks[g] • Immunoadsorption: minimum 2 cycles over 3 to 4 consecutive days performed 4 weeks apart[h]	Quality of evidence: NR Strength of recommendation: May be recommended (recommendation)

EADV = European Academy of Dermatology and Venereology; IVIg = IV immunoglobulin; NR = not reported; PDAI = Pemphigus Disease and Area Index; PF = pemphigus foliaceus; PV = pemphigus vulgaris; TDA = Taiwanese Dermatology Association; RCT = randomized controlled trial.

[a]Evidence from a report of 9 cases showed that dapsone could be used as initial treatment of mild PF. Dapsone is often combined with topical corticosteroids.

[b]A retrospective cohort study showed that patients relapsed with dapsone alone need a systemic corticosteroid treatment.

[c]Two case series suggested that rituximab alone or associated with oral corticosteroids was an effective treatment for pemphigus.

[d]Evidence from 2 RCTs showed that systemic corticosteroid therapy alone or with an immunosuppressive drug (azathioprine or mycophenolate) as corticosteroid-sparing agent was an effective treatment for pemphigus, particularly in patients with an increased risk of corticosteroid side-effect related to prolonged use of corticosteroids, or there is no possibility to treat with rituximab.

[e]Two RCTs and 1 cost study provided evidence to support for first-line treatment in patients with moderate and severe pemphigus.

[f]An RCT showed that IVIg was an effective and safe treatment for patients with pemphigus who are relatively resistant to systemic steroids.

[g]A case-control study showed that high-dose pulse administration of glucocorticoids is a potentially effective therapy to be considered in the treatment of patients with severe pemphigus vulgaris.

[h]Findings from 2 case series showed that the combination of immunoadsorption with rituximab, pulsed dexamethasone, azathioprine, or mycophenolate mofetil might be effective in treatment of difficult-to-treat pemphigus.

Table 9: Summary of Recommendations in Included Guidelines for Pemphigus Vulgaris and Pemphigus Foliaceus, Feliciani et al. (2018)

Recommendations and supporting evidence	Quality of evidence and strength of recommendations
Feliciani et al. (2018)[17]	
First-line treatment	
• Systemic corticosteroid therapy: prednisone or prednisolone at 0.5 to 1.5 mg/kg/day. • Rituximab: 2 infusions of 1 g 2 weeks apart[a]	Quality of evidence: NR Strength of recommendation: NR
Second-line treatment with adjuvant to systemic corticosteroids	

• Systemic corticosteroids are generally combined with an immunosuppressive adjuvant.
  ◦ Azathioprine: 1 to 3 mg/kg/day.
  ◦ Mycophenolate mofetil: 2 g/day or mycophenolic acid: 1440 mg/day.
	Quality of evidence: NR
	Strength of recommendation: NR

Third-line treatment with adjuvant to systemic corticosteroids	

Recommendations and supporting evidence	Quality of evidence and strength of recommendations
• IVIg: 2 g/kg/month[b] • Immunoadsorption: 2 cycles on 4 consecutive days, 4 weeks apart[c] • Cyclophosphamide: 500 mg as IV bolus or orally at 2 mg/kg/day[d] • Methotrexate: 10 to 20 mg/week[e] • Dapson: 100 mg/day or up to ≤ 1.5 mg/kg/day[f]	Quality of evidence: NR Strength of recommendation: NR

EADV = European Academy of Dermatology and Venereology; IVIg = IV immunoglobulin; NR = not reported; PDAI = Pemphigus Disease and Area Index; PF = pemphigus foliaceus; PV = pemphigus vulgaris; TDA = Taiwanese Dermatology Association; RCT = randomized controlled trial.

[a]Findings of 3 case series and 1 consensus document suggested that rituximab may be an effective treatment of refractory pemphigus.

[b]An RCT found that IVIg was an effective and safe treatment for patients with pemphigus who are relatively resistant to systemic steroids.

[c]One case series, 1 retrospective study and 1 consensus document provided evidence for the effectiveness of immunoadsorption in difficult-to-treat pemphigus.

[d]One prospective cohort study and 1 case report highlighted the potential role of cyclophosphamide therapy for pemphigus.

[e]One retrospective cohort study showed that methotrexate was an effective and safe adjuvant therapy for PV.

[f]An RCT demonstrated a trend to efficacy of dapsone as a steroid-sparing drug in maintenance-phase PV.

Appendix 5: References of Potential Interest

Review Articles

Guignant M, Tedbirt B, Murrell DF, et al. How Do Experts Treat Patients with Bullous Pemphigoid around the World? An International Survey. *JID Innov*. 2022;2(4):100129. PubMed

Khalid SN, Khan ZA, Ali MH, Almas T, Khedro T, Raj Nagarajan V. A blistering new era for bullous pemphigoid: A scoping review of current therapies, ongoing clinical trials, and future directions. *Ann Med Surg (Lond).* 2021;70:102799. PubMed

Zhao W, Wang J, Zhu H, Pan M. Comparison of Guidelines for Management of Pemphigus: a Review of Systemic Corticosteroids, Rituximab, and Other Immunosuppressive Therapies. *Clin Rev Allergy Immunol*. 2021;61(3):351-362. PubMed

Patel PM, Jones VA, Murray TN, Amber KT. A Review Comparing International Guidelines for the Management of Bullous Pemphigoid, Pemphigoid Gestationis, Mucous Membrane Pemphigoid, and Epidermolysis Bullosa Acquisita. *Am J Clin Dermatol*. 2020;21(4):557-565. PubMed