PEMPHIGUS

CHI Formulary Development Project

مجلس الضمان الصحي
Council of Health Insurance

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Related Documents

Related SOPs

- IDF-FR-P-02-01-IndicationsReview&IDFUpdates
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Abbreviations

ACEI	Angiotensin-Converting Enzyme Inhibitor
BP	Bullous Pemphigoid
BSA	Body Surface Area
CADTH	Canadian Agency for Drugs and Technologies in Health
CHI	Council of Health Insurance
DIF	Direct immunofluorescence
DMARD	Disease-Modifying Antirheumatic Drug
ELISA	Enzyme-Linked Immunosorbent Assay
HAS	Haute Autorité de Santé
HTA	Health Technology Assessment
IDF	Insurance Drug Formulary
IgA	Immunoglobulin A
IIF	Indirect immunofluorescence
IQWIG	Institute for Quality and Efficiency in Health Care
IV	Intravenous
IVIG	Intravenous immunoglobulins
MMF	Mycophenolate Mofetil
NICE	National Institute for Health and Care Excellence
NUDT15	Nudix hydrolase 15
PDAI	Pemphigus Disease and Area Index
PF	Pemphigus Foliaceus
PV	Pemphigus Vulgaris
SFDA	Saudi Food and Drug Authority
TMTP	Thiopurine Methyl Transferase

Executive Summary

Pemphigus refers to a group of rare, autoimmune, life-threatening mucocutaneous blistering disorders. It is characterized by acantholysis (loss of keratinocyte-to-keratinocyte adhesion), which results in the formation of intraepithelial blisters in mucous membranes and skin.[1] Acantholysis is induced by the binding of circulating immunoglobulin G (IgG) autoantibodies to intercellular adhesion molecules. Patients with pemphigus develop mucosal and skin erosion, flaccid bullae, or pustules. Significant morbidity and mortality are associated with pemphigus, its complications, and its treatments.

Four major types of pemphigus exist: pemphigus vulgaris (PV), pemphigus foliaceus (PF), immunoglobulin A (IgA) pemphigus and paraneoplastic pemphigus. These different types are distinguished by their clinical features, associated autoantigens, and laboratory findings.

- **PV:** characterized by mucosal only or mucosal and cutaneous involvement, suprabasal acantholytic blisters, and IgG autoantibodies against desmoglein (Dsg) 3 or both Dsg 1 and Dsg 3. Clinical variants include pemphigus vegetans and pemphigus herpetiformis.
- **PF:** characterized by cutaneous involvement only, subcorneal acantholytic blisters, IgG autoantibodies against Dsg 1. Clinical variants include endemic pemphigus foliaceus (fogo selvagem), pemphigus erythematosus (Senear-Usher syndrome) and pemphigus herpetiformis.
- **IgA pemphigus**: characterized by grouped vesicles or pustules and erythematous plaques with crusts, subcorneal or intraepidermal acantholytic blisters, and autoantibodies against desmocollin 1 in subcorneal pustular dermatosis-type IgA pemphigus. Subtypes of the disease are subcorneal pustular dermatosis-type IgA pemphigus (distinct from classic subcorneal pustular dermatosis (Sneddon-Wilkinson disease)) and intraepidermal neutrophilic IgA dermatosis.
- **Paraneoplastic pemphigus**: characterized by extensive, intractable stomatitis and variable cutaneous findings with multiform exanthems, associated neoplastic disease, suprabasal acantholytic blisters, and autoantibodies against desmoplakins or other desmosomal antigens.

Pemphigus is a rare disease. The most common form worldwide is PV. It is rare in itself, but incidence varies with geographic regions. For instance, incidence ranges between 0.76 per million per year in Finland and 16.1 per million per year in Israel. Higher rates exist in certain populations, such as Ashkenazi jews, people from India, Southeast Europe, or the Middle East.[2] In certain locations, such as North Africa, Turkey and South America, the prevalence of PF exceeds that of PV.[3] Endemic PF

contributes to the higher rate of PF in some of these countries. Pemphigus usually occurs in adults, and the sex ratio for PF and PV seems to be equivalent.[4]

The prevalence of pemphigus in Middle Eastern countries, including the Kingdom of Saudi Arabia, has not been extensively studied in terms of the epidemiological figures and clinical patterns. To address this gap, one epidemiologic study was conducted in 2001 by Tallab et al. in the southern region of Saudi Arabia. In this study, incidence of pemphigus in the southern region of Saudi Arabia was 0.16/100 000. Incidence was higher among adults over 20 years of age (0.27/100 000), and the male to female ratio was 2.2:1. Mean age of onset was 43.2 years, and PV was the most common type, followed by pemphigus erythematosus.[5]

The diagnosis of pemphigus is based on the presence of consistent clinical, histologic, and direct immunofluorescence (DIF) findings, as well as the detection of circulating IgG and IgA autoantibodies against cell surface antigens in serum. This diagnostic work-up is useful for distinguishing pemphigus from other blistering and erosive diseases. The following tests are required:

- A lesional skin or mucosal biopsy for routine hematoxylin and eosin (H&E) staining;
- A perilesional skin or mucosal biopsy for DIF;
- Serum collection for detection of autoantibodies by enzyme-linked immunosorbent assay (ELISA) and/or indirect immunofluorescence (IIF).

Clinical evaluation includes:

- A thorough physical examination of mucosae (eyes, mouth, nose, ears, genital mucosa) and skin;
- Assessment of functional symptoms (pain, pruritus, dysphagia, ocular and ear, nose, and throat symptoms, dysuria, anogenital problems; and weight loss), contraindications of systemic treatments, contraception and pregnancy plans in women of childbearing age;
- Medication history, with special attention to causes of drug-induced pemphigus (D-penicillamine, angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers, and cephalosporins);
- Psychologic tolerance of possible side effects due to treatment, especially corticosteroid treatment;
- Impact of disease burden on quality of life.

In general, systemic glucocorticoids and rituximab are the mainstays of therapy for PV and PF and are usually highly effective for obtaining control of disease. Other immunomodulatory agents, such as azathioprine and mycophenolate mofetil (MMF), are commonly prescribed in conjunction with systemic glucocorticoids in

order to minimize the risk for adverse effects of long-term, high-dose glucocorticoid therapy. Other treatments, such as intravenous immunoglobulins (IVIG), immunoadsorption and cyclophosphamide are typically reserved for patients with refractory disease.

There is no consensus regarding pemphigus treatment in the Arab countries. Therapeutic regimens differ according to countries.

This report compiles all clinical and economic evidence related to pemphigus according to the relevant sources. The ultimate objective of issuing pemphigus guidelines by the Council of Health Insurance is to update the IDF (CHI Drug Formulary) with the best available clinical and economic evidence related to drug therapies, ensuring timely and safe access to pemphigus patients in Saudi Arabia. The focus of the review was on Saudi, American, European, and international guidelines issued within the last five years.

Several classes and drugs can be used for the management of pemphigus and are summarized in the table below.

Table 1. SFDA-Registered Drugs for the Management of Pemphigus

Drug	Indication	Dose	Level of evidence and HTA recommendation
Rituximab	First-line or second-line treatment for PV and PF	1g IV twice 2 weeks apart Then at month 6: - Complete remission + severe pemphigus and/or high rate of anti-Dsg antibodies at month 3: 500mg-1g IV - No complete remission: 2g IV once or 1g 2 weeks apart Then 500mg IV at months 12 and 18	Level B (1+); moderate evidence. HAS: favorable opinion on the maintenance of reimbursement in the treatment of moderate to severe PV in adults.
Azathioprine	First-line or second-line treatment for PV and PF Usually started with systemic corticosteroids Cortico-sparing agent	1 to 2.5 mg/kg/d orally	Level B (1+); moderate evidence. There are no recommendations issued by the HTA bodies for azathioprine.
Mycophenolate mofetil (MMF)	First-line or second-line treatment for PV and PF	2g/d orally	Level B (1+); moderate evidence.

	Usually started with systemic corticosteroids Cortico-sparing agent		There are no recommendations issued by the HTA bodies for MMF.
Mycophenolate sodium	First-line or second-line treatment for PV and PF Usually started with systemic corticosteroids Cortico-sparing agent	1440 mg/d orally	Level of evidence: none available There are no recommendations issued by the HTA bodies for mycophenolate sodium.
Cyclophosphamide	Third-line treatment in recalcitrant pemphigus	50 mg/day orally or 500–750 mg/month IV	Level D (3); conflicting evidence. There are no recommendations issued by the HTA bodies for cyclophosphamide.
Intravenous immunoglobulin (IVIG)	Severe, refractory pemphigus	2 g/kg/cycle (over 2–5 consecutive days every 4 weeks)	Level B (2++); moderate evidence. CADTH: IVIG may be used as a third-line treatment for severe or refractory cases.
CORTICOSTEROIDS			
Prednisone	First-line or second-line treatment for PV and PF	0.5-1.0 mg/kg/day PO in mild PV and PF 1 to 1.5 mg/kg/day PO in moderate to severe pemphigus	Level B (1+); moderate evidence. There are no recommendations issued by the HTA bodies for prednisone.
Prednisolone	First-line or second-line treatment for PV and PF	0.5-1.0 mg/kg/day PO in mild PV and PF	Level B (1+); moderate evidence.

		1 to 1.5 mg/kg/day PO in moderate to severe pemphigus	There are no recommendations issued by the HTA bodies for prednisolone.
	Moderate to severe PV and PF initially treated with rituximab and prednisone, with no disease control at week 3-4	IV pulses: methylprednisolone 0.5–1 g/day over 3 consecutive days in initial intervals of 3–4 weeks	Level D (4); conflicting evidence. There are no recommendations issued by the HTA bodies for prednisolone.
Dexamethasone	Moderate to severe PV and PF initially treated with rituximab and prednisone, with no disease control at week 3-4	IV pulses: dexamethasone 100 mg/day over 3 consecutive days in initial intervals of 3–4 weeks	Level D (4); conflicting evidence. There are no recommendations issued by the HTA bodies for dexamethasone.
Topical high-potency corticosteroids (e.g. clobetasol propionate, betamethasone valerate, triamcinolone acetate)	First-line treatment in mild PF Adjuvant with rituximab or dapsone	Twice daily	None available HAS: potent topical corticosteroids can be (rarely) used alone, in pemphigus with few lesions and when circulating antibodies titers are low or null.
Intralesional corticosteroids (e.g. triamcinolone acetonide)	Recalcitrant individual lesions	High concentrations (e.g. 20 microgram/L)	None available There are no recommendations issued by the HTA bodies for intralesional corticosteroids.

Non SFDA registered drugs

Dapsone, a sulfone drug, is used as a first-line treatment in mild PF. Starting dose is 50 to 100 mg/day, up to 1.5 mg/kg body weight, usually combined with topical corticosteroids. If disease control is achieved, it may be continued at a dose of 1.5 mg/kg body weight. If disease control is not achieved, rituximab, prednisone, prednisolone, azathioprine, MMF or mycophenolate sodium may be started. It is important to assess the presence of sulfamide allergy, glucose-6-phosphate-dehydrogenase deficiency, anemia or methemoglobinemia before starting the treatment.

It is important to emphasize that these treatment approaches serve as general recommendations. The appropriate treatment plan for each patient should be determined based on the specific type of pemphigus, as well as their overall health status. To provide a concise overview, the report will feature in section 3 a synthesis of key recommendations, focusing on the relevant drugs that align with these guidelines.

Section 1.0 Summary of Reviewed Clinical Guidelines and Evidence

1.1 KSA Guidelines

To date, there are no guidelines issued by Saudi bodies for the management of pemphigus.

1.2 European Guidelines

1.2.1 European Academy of Dermatology and Venereology (EADV) Updated S2K Guidelines on the Management of Pemphigus Vulgaris and Foliaceus (2020)

The *Autoimmune blistering diseases* Task Force of the European Academy of Dermatology and Venereol-ogy (EADV) initiated a throughout update of the guideline for the management of patients with pemphigus, and as a result, the guidelines for the management of pemphigus were updated, and the degree of consent among all taskforce members was included. The final version of the guideline was consented by the European Dermatology Forum (EDF) and several patient organizations.[6]

Mild pemphigus

Definition: mild pemphigus is defined as PF with involved body surface area (BSA) <5%, or PV with involved BSA <5% and limited oral lesions not impairing food intake or requiring analgesics, or a Pemphigus Disease and Area Index (PDAI) ≤ 15.

a. Mild pemphigus foliaceus

Treatment options for mild PF are presented in figure 1.

First-line treatment

- Dapsone: starting dose of 50 to 100 mg/day, adjusted to clinical response up to 1.5 mg/kg bodyweight.[7] It is usually combined with class III or IV topical corticosteroids.[8] However, around 50% of patients who start with dapsone without oral corticosteroids will experience a relapse and subsequently require systemic corticosteroids. Finally, dapsone failed to demonstrate a corticosparing effect in a randomized control trial.[9]
- Topical corticosteroids (class III, IV): alone if there are only very limited lesions.
- Systemic corticosteroids with prednisone 0.5–1.0 mg/ kg/day

- Rituximab: two infusions of 1 g two weeks apart. Rituximab may be given alone, or associated with topical corticosteroids[10], or oral corticosteroids (prednisone 0.5 mg/kg/day)[11] with a rapid decrease in order to stop corticosteroids after 3 to 4 months.

Second-line treatment

In patients who have been initially treated with dapsone and/or topical corticosteroids and have persistent active lesions and detection of anti-Dsg1 serum antibodies and significant impact on quality of life (ABQOL or DLQI scores), the following treatments may be recommended:

- Rituximab: two infusions of 1 g two weeks apart. It may be used alone or associated with oral corticosteroids (prednisone 0.5 mg/kg/day) with a rapid decrease in order to stop corticosteroids after 3 or 4 months.[12]
- If rituximab is contraindicated or not available: systemic corticosteroid therapy with prednisone 0.5–1.0 mg/kg/day with or without azathioprine (1 to 2.5 mg/kg/day), or mycophenolate mofetil (MMF) 2 g/day or mycophenolate sodium 1,440 mg/day.[13]

In patients who have been initially treated with oral corticosteroid therapy alone and have persistent active lesions, add rituximab.

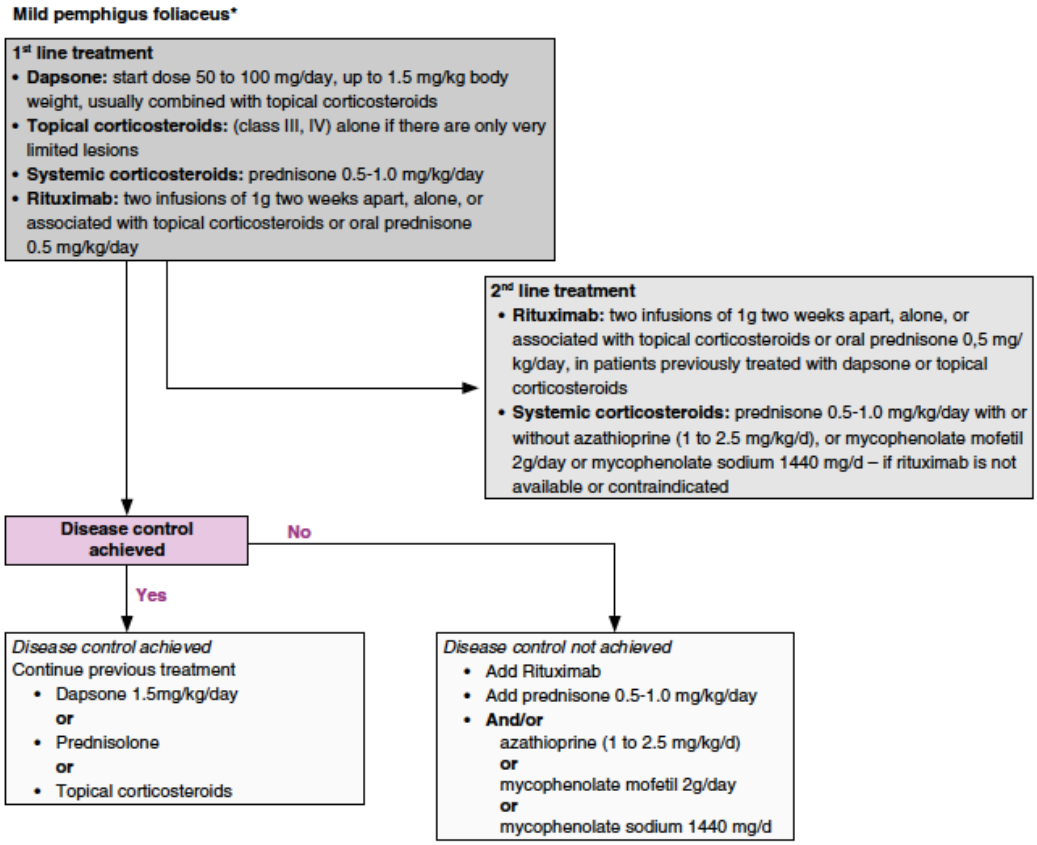

Figure 1. *Treatment algorithm for mild pemphigus foliaceus.*

Retrieved from Joly P, Horvath B, Patsatsi A, Uzun S, Bech R, Beissert S, Bergman R, Bernard P, Borradori L, Caproni M, Caux F, Cianchini G, Daneshpazhooh M, De D, Dmochowski M, Drenovska K, Ehrchen J, Feliciani C, Goebeler M, Groves R, Guenther C, Hofmann S, Ioannides D, Kowalewski C, Ludwig R, Lim YL, Marinovic B, Marzano AV, Mascaró JM Jr, Mimouni D, Murrell DF, Pincelli C, Squarcioni CP, Sárdy M, Setterfield J, Sprecher E, Vassileva S, Wozniak K, Yayli S, Zambruno G, Zillikens D, Hertl M, Schmidt E. Updated S2K guidelines on the management of pemphigus vulgaris and foliaceus initiated by the european academy of dermatology and venereology (EADV). J Eur Acad Dermatol Venereol. 2020 Sep;34(9):1900-1913. doi: 10.1111/jdv.16752. Epub 2020 Aug 24. PMID: 32830877.

b. Mild pemphigus vulgaris

Treatment options for mild PV are presented in Figure 2.

<u>First-line treatment</u>

- Systemic corticosteroid therapy with prednisone 0.5–1.0 mg/kg/day with or without azathioprine (2.0 mg/kg/day), or MMF 2 g/day or mycophenolate sodium 1,440 mg/day.
- Rituximab (two infusions of 1 g two weeks apart) alone or associated with oral corticosteroids (prednisone 0.5 mg/kg/day) with a rapid decrease in order to stop corticosteroids after 3 or 4 months.[11]

Second-line treatment

In patients initially treated with prednisone/prednisolone 0.5–1.0 mg/kg/day alone who have persistent active lesions, and in patients with CS side-effect or contraindication to conventional immunosuppressant, and detection of anti-Dsg3 serum antibodies and significant impact on quality of life (ABQOL or DLQI scores):

- Addition of rituximab: two infusions of 1 g two weeks apart, with a rapid decrease of oral prednisolone in order to stop corticosteroids after 3 to 4 months.

In patients initially treated with prednisone/prednisolone 0.5–1.0 mg/kg/day plus rituximab, who have persistent active lesions, it is recommended to increase the dose of prednisone/prednisolone up to 1 mg/kg/day.

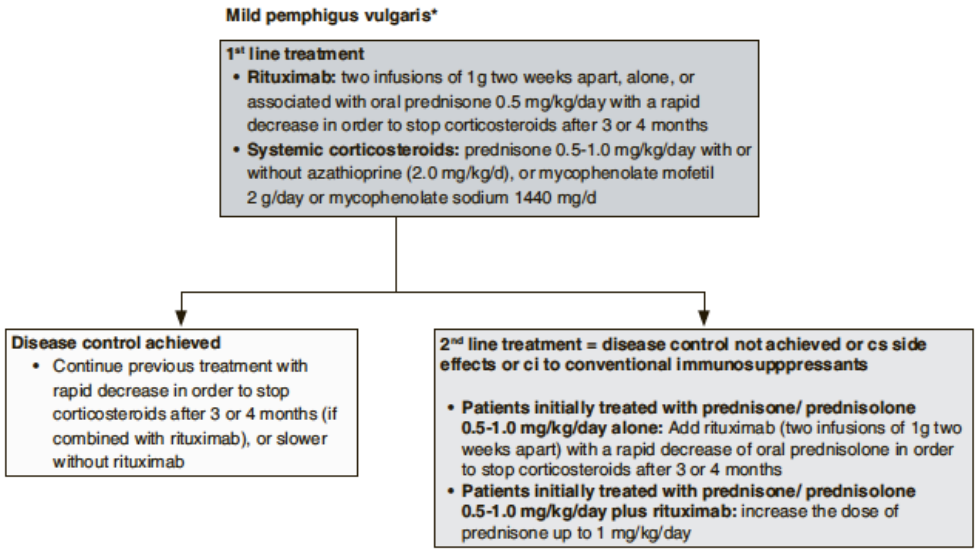

Figure 2. *Treatment algorithm for mild pemphigus vulgaris.*

Retrieved from Joly P, Horvath B, Patsatsi A, Uzun S, Bech R, Beissert S, Bergman R, Bernard P, Borradori L, Caproni M, Caux F, Cianchini G, Daneshpazhooh M, De D, Dmochowski M, Drenovska K, Ehrchen J, Feliciani C, Goebeler M, Groves R, Guenther C, Hofmann S, Ioannides D, Kowalewski C, Ludwig R, Lim YL, Marinovic B, Marzano AV, Mascaró JM Jr, Mimouni D, Murrell DF, Pincelli C, Squarcioni CP, Sárdy M, Setterfield J, Sprecher E, Vassileva S, Wozniak K, Yayli S, Zambruno G, Zillikens D, Hertl M, Schmidt E. Updated S2K guidelines on the management of pemphigus vulgaris and foliaceus initiated by the european academy of dermatology and venereology (EADV). J Eur Acad Dermatol Venereol. 2020 Sep;34(9):1900-1913. doi: 10.1111/jdv.16752. Epub 2020 Aug 24. PMID: 32830877.

Moderate and severe types of pemphigus (PV and PF)

Definition:

- *Multiple mucosal involvement of PV: oral, nasopharyngeal, conjunctival, genital*
- *Severe oral lesions or dysphagia with weight loss*
- *Significant pain*
- *And/or skin lesions >5% BSA.*

Moderate pemphigus: PDAI score> 15 and ≤ 45

Severe pemphigus: PDAI score > 45 [14]

Treatment options for moderate and severe types of PV and PF are presented in figure 3.

<u>First-line treatment of moderate and severe types of pemphigus</u>

- Rituximab: two infusions of 1 g two weeks apart, associated with systemic corticosteroids (prednisone 1 mg/kg/day) with a progressive tapering to stop corticosteroids after 6 months.[11]

NB: In patients with absolute contraindication to systemic corticosteroid therapy, Rituximab can be administered as a monotherapy or associated with topical corticosteroids.[10,12]

- If rituximab is contraindicated or not available: systemic corticosteroid therapy (oral prednisone 1 to 1.5 mg/kg/day) alone or associated with an immunosuppressive drug as corticosteroid-sparing agent (azathioprine 1 to 2.5 mg/kg/day or MMF 2 g/day or mycophenolate sodium 1,440 mg/day), particularly in patients with an increased risk of severe corticosteroid side-effect related to an expected prolonged use of corticosteroids, or if there is no possibility to treat the patient with rituximab.[13,15]

Clinicians should be cautious for side-effects, relative and absolute contraindication of systemic corticosteroid therapy.

In paraneoplastic pemphigus or other type of pemphigus associated with cancer, consultation with an oncologist is recommended before use of Rituximab.

<u>Maintenance treatment after the initial cycle of rituximab</u>

Patients' status 6 months after the first cycle of rituximab (month 6)

- In patients who are in complete remission on/off therapy at month 6, and initially presented with a severe pemphigus and/or still have a high rate of anti-Dsg antibodies at month 3, it may be considered to perform an infusion

of 500 mg or 1 g of rituximab at month 6.[16,17] The optimal dose (500 mg to 1 g) has not been determined yet.

- In patients without complete remission on/off therapy at month 6, it may be recommended to perform two infusions of 1g two weeks apart (2 g in total).

Months 12 and 18 after the first cycle (M12 and M18)

- In patients in complete remission on/off therapy, it is recommended to perform one infusion of rituximab (500 mg) at month 12 and another infusion of 500 mg at month 18, particularly in patients with still positive anti-Dsg antibodies.[17]
- There is no sufficient evidence to recommend systematic infusions of rituximab after month 18 in patients in complete remission.[18] Monitoring of circulating anti-Dsg antibody ELISA values is necessary at least every six months.
- Additional infusions of rituximab as maintenance therapy after month 18 may be performed in patients with a re-increase of anti-Dsg antibodies after their initial disappearance following the initial infusions of rituximab.

Absence of initial disease control (after 3 to 4 weeks of treatment) in patients initially treated with rituximab and prednisone

- Increase the prednisone dose up to 1.5 mg/kg/day
- Or start intravenous corticosteroid pulses: methylprednisolone 0.5–1 g/day or dexamethasone 100 mg/day over 3 consecutive days in initial intervals of 3–4 weeks.[19]

In patients initially treated with systemic corticosteroids alone, at an initial dose of prednisone 1.0mg/kg/day

- Increase the prednisone dose to 1.5 mg/kg/day and add rituximab (1 g twice),
- If there is no possibility to use rituximab, an immunosuppressant may be used (azathioprine 1 to 2.5 mg/kg/day or MMF 2 g/day or mycophenolate sodium 1,440 mg/day).

In patients treated with systemic corticosteroids alone, at an initial dose of prednisone 1.5 mg/kg/day

- If there is no possibility to use rituximab, add a corticosteroid-sparing agent (azathioprine 1 to 2.5 mg/kg/day or MMF 2 g/day or mycophenolate sodium 1,440 mg/day). Cyclophosphamide is less frequently used due to its potentially severe side-effects.

In patients with severe/refractory pemphigus

The following treatments may be recommended may be used in addition to rituximab, or if there is no response to rituximab, or in addition to an immunosuppressant if there is no possibility to use rituximab:

- Intravenous immunoglobulins (IVIG) 2 g/kg/cycle, over 2–5 consecutive days every 4 weeks[20], or over several days to avoid headache and nausea. A rare but serious side-effect of IVIG is aseptic meningitis, which should be considered in patients with frequent migraine. Complete IgA deficiency is a contraindication for IVIG treatment.
- Intravenous corticosteroid pulses: methylprednisolone 0.5–1 g/day or dexamethasone 100 mg/day over 3 consecutive days in initial intervals of 3–4 weeks.[19]
- Immunoadsorption: minimum of 2 cycles over 3–4 consecutive days, performed 4 weeks apart. Contraindications include severe cardiovascular diseases, hypersensitivity against components of the immunoadsorption column, treatment with ACEI, severe systemic infections, and extensive hemorrhagic diathesis.[21,22]

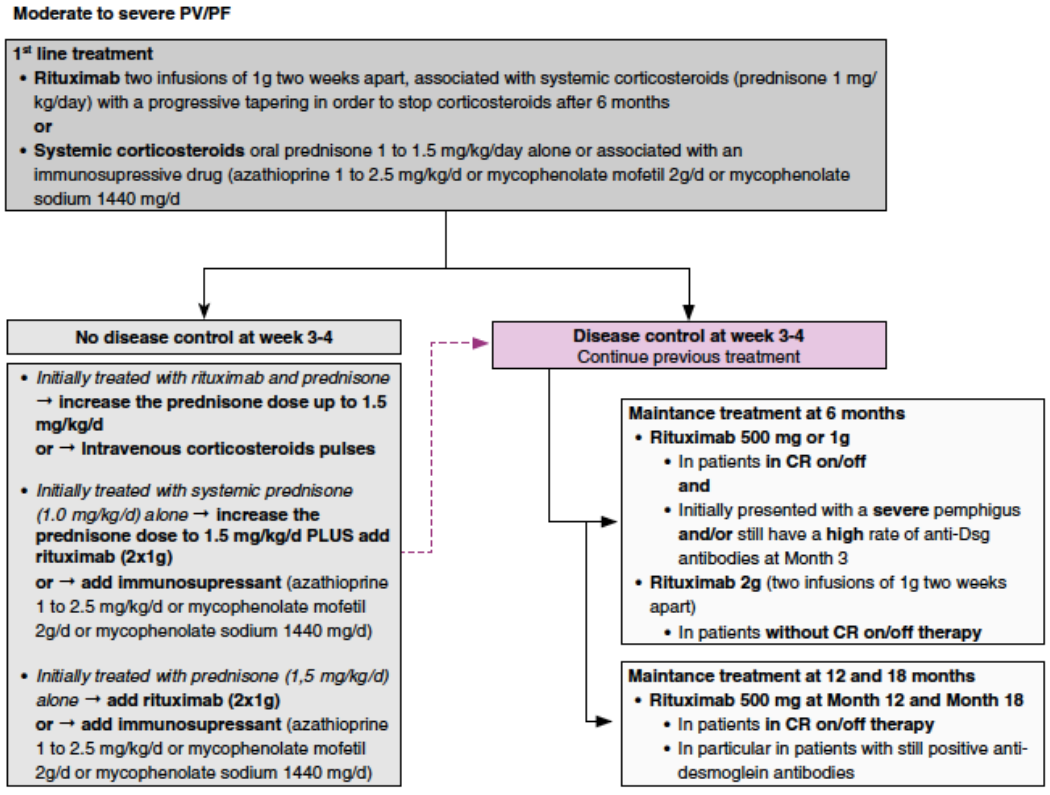

Figure 3. *Treatment algorithm for moderate and severe pemphigus vulgaris and pemphigus foliaceus.*

Retrieved from Joly P, Horvath B, Patsatsi A, Uzun S, Bech R, Beissert S, Bergman R, Bernard P, Borradori L, Caproni M, Caux F, Cianchini G, Daneshpazhooh M, De D, Dmochowski M, Drenovska K, Ehrchen J, Feliciani C, Goebeler M, Groves R, Guenther C, Hofmann S, Ioannides D, Kowalewski C, Ludwig R, Lim YL, Marinovic B, Marzano AV, Mascaró JM Jr, Mimouni D, Murrell DF, Pincelli C, Squarcioni CP, Sárdy M, Setterfield J, Sprecher E, Vassileva S, Wozniak K, Yayli S, Zambruno G, Zillikens D, Hertl M, Schmidt E. Updated S2K guidelines on the management of pemphigus vulgaris and foliaceus initiated by the european academy of dermatology and venereology (EADV). J Eur Acad Dermatol Venereol. 2020 Sep;34(9):1900-1913. doi: 10.1111/jdv.16752. Epub 2020 Aug 24. PMID: 32830877.

Conventional immunosuppressive adjuvant

The main conventional immunosuppressive adjuvants used at first-line treatments in pemphigus are azathioprine and MMF.[23] Their use is considered as first-line when rituximab is not available, or not permitted as first line, or in patients with contraindications to rituximab.

- Azathioprine at a dose of 1–2.5 mg/kg/day. Start first week 50 mg/day to detect idiosyncratic reactions (and in case stop immediately), and then raise to desired dose. Though not predictive for idiosyncratic reactions, thiopurine methyl transferase (TMTP) activity should be monitored prior to treatment: recommendations for azathioprine dosing vary based upon TPMT activity.[23] Adults with pemphigus and high TPMT activity are treated with normal doses of azathioprine (up to 2.5 mg/kg/day), those with intermediate or low TPMT activity are treated with a lower maintenance dose (up to 0.5 to 1.5 mg/kg/ day) depending on level of enzyme activity, and those with lack of TPMT activity should not be treated with azathioprine.
- MMF at a dose of 2 g/day or mycophenolic acid at a dose of 1,440 mg/day. In case of MMF, consider raising daily dose by 1 capsule (500 mg) per week until the final dose of 2 g/day for better gastrointestinal tolerance.[13]
- Methotrexate and cyclosporine are not recommended.

If those conventional immunosuppressants fail as first-line therapy, rituximab may be applied as second line.

- Cyclophosphamide 50 mg/day per os or 500–750 mg/ month IV. It may be considered as third-line treatment in recalcitrant cases of pemphigus due its potentially severe side-effects.

Additional supportive treatment

- Intralesional injections of corticosteroids (triamcinolone acetonide) may be considered for isolated lesions of oral mucosa, lips and skin.
- Topical adjuvant treatment with super-potent corticosteroids (clobetasol propionate or triamcinolone acetonide gel), directly applied to oral erosions, may be considered in some patients in combination with systemic therapy.

- Baths containing antiseptics such as chlorhexidine may be recommended in patients with extensive skin lesions.
- It is recommended to cover erosive lesions with low adhesive wound dressings or local emollients, and compresses.
- Analgesics (paracetamol, metamizol and opioids), if required for pain management.
- Gels containing local anesthetics may be recommended for application at the mucosal surfaces.
- Proper dental care is recommended.
- Extensive dental surgery (e.g. dental implants) is not recommended before the healing of oral lesions.
- Nutritional management with the help of a dietician or a nutritionist is recommended if malnutrition is related to oral involvement or systemic corticosteroid therapy.

Measures in prolonged corticosteroid therapy

The following measures are recommended:

- Use of vitamin D and calcium supplementation at initiation of glucocorticoid treatment to prevent osteoporosis.
- Use of bisphosphonates (i.e. alendronate, risedronate) in patients at risk (postmenopausal women, men > 50 years, with pathological initial osteoporosis screening) to prevent osteoporosis.
- Regular ophthalmologic evaluations during treatment with systemic corticosteroids may be considered.
- Use of systemic antifungal, antiviral and antibiotic treatments only when clinically indicated.
- Use of H2 blockers or proton pump inhibitors may be considered to prevent gastric/duodenal ulcers. Due to insufficient evidence, the decision should be individualized to the patient, for example in case of additional treatment with non-steroidal anti-inflammatory drugs.
- Psychological support if required, and attention to signs of depression, sometimes induced by corticosteroid treatment.
- Physiotherapy may be considered if prolonged corticosteroid therapy is required.

- Use of antithrombotic prophylaxis may be considered in case of high risk of thrombosis.

Vaccinations

Adjuvant immunosuppressants and rituximab contraindicate the use of live vaccines.

It is recommended that patients receiving oral corticosteroids or immunosuppressive therapy are vaccinated against seasonal influenza and pneumococci. It is recommended to be up to date with other standard vaccinations (tetanus, diphtheria, pertussis, polio, etc.).

Monitoring

Pemphigus often shows a chronic, relapsing course which requires close monitoring of clinical symptoms and of potential side-effects inherent to chronic immunosuppressive treatment. Thus, a multidisciplinary approach is commonly required.

Approach to be maintained after consolidation phase

If systemic corticosteroids are used with rituximab, tapering is recommended over the next 4–6 months.[11] The following tapering regimen may be recommended:

Table 2. Corticosteroid Tapering

	Mild pemphigus	Moderate/severe pemphigus
Month 1	0.5 mg/kg	1 mg/kg
Month 2	0.3 mg/kg	0.75 mg/kg
Month 3	0.2 mg/kg	0.5 mg/kg
Month 4	± 0.1 mg/kg	0.3 mg/kg
Month 5		0.2 mg/kg
Month 6		0.1 mg/kg

Beyond the last month of corticosteroid treatment (0.1 mg/kg/day), the attitude is not clearly defined. Three options may be considered:

a. stopping corticosteroid treatment after performing an ACTH test;

b. slow tapering (mg per mg every month or more slowly);

c. maintaining a minimal dose of corticosteroids (usually between 3 and 6 mg/day), especially in patients with persistent significant levels of circulating anti-Dsg antibodies.

If systemic corticosteroids are used without rituximab, it is recommended to taper the corticosteroids according to the clinical response.

There is no clear consensus on the best corticosteroid tapering regimen: decrease prednisone dose by 10% - 25% every 2- 3 weeks until 15–25 mg/day; then, there is no consensus on the best way of tapering prednisone from 1 mg every 3 to 4 weeks to a more rapid tapering using 5 mg steps. It may be recommended to taper the prednisolone dose even slower as the rate of anti-Dsg 1 > 50 IU/mL (higher risk of skin relapse). The persistence of high levels of anti-Dsg1 antibodies by ELISA has a positive predictive value for skin relapses, while the persistence of anti-Dsg3 IgG does not necessarily predict a mucosal relapse (except if > 130 IU/mL).[24]

Treatment of relapse

In patients initially treated with rituximab and systemic corticosteroids

- Relapse during tapering of prednisone between month 0 and month 4: it is recommended to re-increase oral corticosteroids (depending on the severity of relapse).
- Relapse during tapering of prednisone between month 4 and month 6: it is recommended to perform an additional cycle of 2 g of rituximab. In this case, a maintenance infusion of rituximab will not be performed at month 6.
- Relapse after stopping prednisone (after the month 6 maintenance infusion of rituximab): evaluation by an expert in the field of pemphigus is recommended due to few evidence-based data.

In patients not initially treated with rituximab

- Relapse during tapering of the corticosteroid: apply rituximab 1 g two weeks apart.
- In patients with contraindications to rituximab or when rituximab is not available, it is recommended to re-increase the corticosteroids dose and add azathioprine (1 to 2.5 mg/kg/day), or MMF (2 g/day) or mycophenolate sodium (1,440 mg/day) until disease control is achieved, before tapering of systemic corticosteroids.

Scheduling and content of consultations

Evaluation of the efficacy of treatment is primarily based on clinical symptoms.

The frequency of disease management (physical examination, additional examinations) must be adapted to the patient's clinical condition, severity and disease course during treatment and therapeutics used (monitoring, tolerance, side-effects). Follow-up visits are recommended every 2–4 weeks until disease control is achieved, then every 4–8 weeks until corticosteroids have been stopped. Thereafter,

follow-up visits are recommended every 8–16 weeks until complete remission off therapy is achieved and serum anti-Dsg antibodies are normalized.

Clinical examination

A complete physical examination to determine if the disease is clinically controlled (mucosal, mucocutaneous, or cutaneous lesions) and to uncover treatment-related adverse effects, such as:

- diabetes mellitus, high blood pressure or cardiac insufficiency, related to corticosteroids;
- respiratory disorders, anemia or hepatitis, related to dapsone and methotrexate;
- infections, notably respiratory, hepatitis or cytomegalovirus (CMV) reactivation, related to corticosteroids and immunosuppressants;
- mental disorders related to corticosteroids;
- myopathy, osteoporosis, avascular bone necrosis, glaucoma or cataract, related to glucocorticoids;
- hematological abnormalities (leucopenia) related to immunosuppressants.

Serological monitoring of disease activity

Determining the level of serum autoantibodies is recommended at the initiation of treatment, after 3 months and every 3 to 6 months based on the evolution, or in case of relapse by ELISA: anti-Dsg1 and/or Dsg3 IgG. If ELISA is not available, indirect immunofluorescence (IIF) microscopy utilizing monkey esophagus or Dsg 1/3-expressing cells can be used.

Serum concentrations of anti-Dsg1 IgG and, to a lesser degree, anti-Dsg3 IgG correlate with the clinical activity of pemphigus and may help in therapeutic decision- making. Anti-Dsg3 Abs have poor specificity and should be used with caution for the management of pemphigus, since only high titers are good predictor for the occurrence of a relapse.[16,17]

- *Discontinuation of treatment*

Discontinuation of treatment is primarily based on the clinical symptoms in combination with findings of Dsg ELISA and/or IIF microscopy.[8,24]

Discontinuation of systemic corticosteroids may be considered after performing an ACTH test in patients in complete remission on minimal therapy (prednisolone or equivalent at ≤ 10 mg/day) with negative circulating anti-Dsg antibodies.

It is recommended to omit the corticosteroid-sparing adjuvants 6–12 months after achieving complete remission on therapy.

Possible sequelae

Sequelae are the result of the lesions involving skin and conjunctivae, oral, pharyngeal, laryngeal, esophageal, anogenital and anal mucosa, but also of treatments adverse events.

Information for patients and their families

Patients should receive proper education about their disease, its clinical course, prognosis, treatment options, signs of relapse and side effects of therapies. The EADV website provides written information about disease and patient support groups. It is recommended to inform patients about the existence of those groups, because they promote knowledge about the disease, provide comfort, enable daily-life experience sharing between patients and information dissemination. They may contribute to a better overall management of the disease by promoting cooperation between patients, patient associations, and health professionals. Patients should also be informed about referrals centers, and be educated about triggers (drugs, operations, radiation, infections, sun exposure). Dietary restrictions are not recommended.

1.3 International Guidelines

1.3.1 Diagnosis and Management of Pemphigus: Recommendations of an International Panel of Experts (2020)

Following the development of management guidelines for pemphigus by the European Dermatology Forum and the European Academy of Dermatology and Venereology, an international group of experts participated in a Delphi process to broaden the generalizability of the recommendations. This international consensus includes intravenous CD20 inhibitors as a first-line therapy option for moderate-to-severe pemphigus.[25]

Suggested work-up before treatment

Work-up before corticosteroid or immunosuppressive therapy:

- Complete blood count
- Creatinine, blood electrolyte levels
- Transaminases, g-glutamyltransferase, alkaline phosphatase levels
- Total serum protein, albumin level
- Fasting serum glucose level
- Hepatitis B, hepatitis C, and HIV

- Quantiferon gold or PPD level is recommended

Recommended, on indication or optional:

- Serum IgA deficiency should be ruled out prior to IVIG treatment
- Analysis of TPMT activity is recommended when azathioprine is considered in countries where genetic polymorphisms for decreased TMPT activity levels are more common
- Chest radiograph if Quantiferon gold or PPD level is abnormal
- ß-HCG test is recommended to exclude pregnancy in women of childbearing potential
- Osteodensitometry is recommended prior to corticosteroid treatment
- Ocular examination (glaucoma, cataract) is recommended

First-line treatment

First-line treatment includes corticosteroids and anti-CD20 monoclonal antibodies.

Corticosteroids

Systemic corticosteroid therapy: prednisone/prednisolone at 0.5 mg to 1.5 mg/kg/d

- Systemic corticosteroids may be taken orally or in IV pulses. They can be combined with an immunosuppressive adjuvant at the onset of therapy, especially in cases of increased risk of corticosteroid therapy, expected prolonged use (>4 months), or dose dependency above minimal therapy (>10 mg/d). Evidence that the addition of adjuvants is superior to treatment with corticosteroids alone is still limited.
- Limited evidence has not shown IV corticosteroid pulses to have an additional benefit on top of that of conventional treatment with oral prednisone/prednisolone and immunosuppressive adjuvants. Steroid pulse therapy in addition to conventional treatment should be reserved for refractory cases of pemphigus.
- Treat with the smallest dose for the shortest time possible to minimize risk of adverse events.

Anti-CD20 monoclonal antibodies

- First-line treatment in new-onset moderate-to-severe pemphigus and/or for patients who do not achieve clinical remission with systemic corticosteroids and/or immunosuppressive adjuvants.
- Enables more rapid tapering of corticosteroids
- Major corticosteroid-sparing effect.

- A course of IV rituximab consists of 2 x 1000 mg (2 weeks apart) or 4 x 375 mg/m2 (1 week apart).
- Course can be repeated in cases of clinical relapse or as early as 6 months after treatment. Lower doses are sometimes used for retreatment.
- Combine with short-term (< 4 months) systemic corticosteroids and long-term (> 12 months) immunosuppressive treatment (although the need for immunosuppressive adjuvants in rituximab therapy remains unclear).

Corticosteroid-sparing agents

First-line corticosteroid-sparing agents

1. **Azathioprine**

Dosage: 1-3 mg/kg/d per os

Start 50 mg/d the first week to detect idiosyncratic reactions (sudden-onset fevers, oral ulcers, elevated liver function tests and/or drug reaction with eosinophilia and systemic symptoms). In that case, stop immediately.

Then raise to desired dose.

TPMT evaluation: TPMT activity should be evaluated in countries/ethnicities where there is a higher incidence of polymorphisms before starting azathioprine, although it is not predictive for idiosyncratic reactions. Recommended azathioprine doses vary depending on TPMT activity:

- adults with pemphigus and high TPMT activity: normal doses of azathioprine (≥ 2.5 mg/kg/d).
- patients with intermediate or low TPMT activity: lower maintenance dose (≥ 0.5 to 1.5 mg/kg/d) depending on level of enzyme activity.
- patients who lack TPMT activity should avoid treatment with azathioprine.

2. **Mycophenolate mofetil**

Dosage: 30 mg/kg-45 mg/kg/d

3. **Mycophenolic acid**

Dosage: 1440 mg/d

Other corticosteroid-sparing agents

1. **IVIG**

Dosage: 2g/kg over 2-5 d/month

Generally combined with systemic corticosteroids (initially) and immunosuppressive adjuvants.

Treatment should be performed over several days to avoid side effects.

Aseptic meningitis: rare but important side effect.

Although uncommon, patients with IgA deficiency should receive IgA-depleted IVIG treatment.

2. **Immunoadsorption**

First-line treatment option in emergency situations where available

Second-line corticosteroid-sparing agent where available

Contraindications: severe systemic infections, severe cardiovascular diseases, hypersensitivity against components of the immunoadsorption column, treatment with ACEI and extensive hemorrhagic diathesis.

3. ***Cyclophosphamide***

Use is reserved for cases of limited resources or in severe cases that have not responded to other treatments.

Drug of last resort due to its long-term side effects.

Supportive treatment

Supportive treatment includes proper dental care; intralesional injections of corticosteroids (triamcinolone acetonide) for isolated lesions, topical treatment with potent corticosteroids (clobetasol propionate) or calcineurin inhibitors applied directly to the lesions, and oral topical corticosteroids (such as triamcinolone acetonide gel) applied directly to oropharyngeal erosions for use in combination with systemic therapy; antiseptic baths; covering erosive lesions, if present, using low adhesive wound dressings or local emollients and compresses; analgesics (over-the-counter analgesics and opioids), gels containing local anesthetics for application at the mucosal surfaces; nutritional management with the help of a dietician or a nutritionist if malnutrition is related to oral involvement or systemic corticosteroid therapy.

Prophylaxis against side effects in prolonged corticosteroid therapy

- Osteoporosis baseline screening and prophylaxis
- Ophthalmologic evaluation
- Vitamin D and calcium supplementation at initiation of corticosteroid treatment
- Treatment with bisphosphonates (eg, alendronate, risedronate) in patients at risk of developing osteoporosis (postmenopausal women and men older than

50 years who will be undergoing corticosteroid treatment for more than 3 months)

- Systemic antifungal, antiviral, and antibiotic treatment should be used when clinically indicated
- H2-blockers or proton pump inhibitor use should be individualized to the patients, given the lack of sufficient evidence
- Antithrombotic prophylaxis in cases of high risk of thrombosis
- Psychologic support if required
- Physiotherapy if prolonged corticosteroid therapy is required

Vaccinations

- Adjuvant immunosuppressants and intravenous CD20 inhibitors contraindicate the use of live vaccines.
- Patients on oral corticosteroids or immunosuppressive treatments may be vaccinated against seasonal influenza, H1N1, tetanus, and pneumococci.
- The level of protection during systemic immunosuppression is questionable.

Monitoring

Monitoring aims to evaluate the efficacy and safety of treatments, and to plan the gradual reduction of immunosuppressive treatment and the duration of maintenance therapy or its discontinuation.

Definitions for disease outcome parameters[26]

Table 3. Definitions for Disease Outcome Parameters

Disease outcome parameter	Definition
Control of disease activity	The time at which new lesions cease to form and established lesions begin to heal.
End of consolidation phase	The time at which no new lesions have developed for a minimum of 2 weeks and approximately 80% of lesions have healed (usually beginning of steroids tapering).
Complete remission during therapy	The absence of new or established lesions while the patient is receiving minimal therapy.

Complete remission off therapy	The absence of new and/or established lesions while the patient has not received any systemic therapy for at least 2 months
Relapse/flare	Appearance of 3 or more new lesions in a month that do not heal spontaneously within 1 week, or by the extension of established lesions, in a patient who has achieved disease control
Minimal therapy	Prednisolone (or the equivalent) at a dose of 10 mg/d or less and/or minimal adjuvant therapy for at least 2 months

Adapted from Murrell DF, Daniel BS, Joly P, et al. Definitions and outcome measures for bullous pemphigoid: recommendations by an international panel of experts. J Am Acad Dermatol. 2012;66(3): 479-485.

Approach to be maintained after consolidation phase

- Clinical improvement is usually slow, often requiring a period of 1 to 3 months for complete healing of lesions. Steroids should be tapered as soon as disease control is reached or until the end of the consolidation phase: prednisone/prednisolone should be decreased by 25% every 2 weeks, until 20 mg/d. Once a dose of 20 mg/d has been reached, prednisone/prednisolone should be decreased by 2.5 mg/week, and when 10 mg/d has been reached, by 1 mg/d thereafter.
- If more than 3 lesions recur during the tapering of oral corticosteroids, last dose should be reinitiated.
- In case of relapse (i.e., the appearance of 3 or more new lesions in a month that do not heal spontaneously within 1 week, or if there is extension of established lesions): oral corticosteroid dose should be increased by going back to the second-to-last dose until control of the lesions is achieved within 2 weeks. Tapering resumes afterwards.
- If disease control is still not reached despite this, the initial dose should be given again.
    - If oral corticosteroids are given alone, an immunosuppressant should be added (especially in cases of early-stage relapse occurring despite continued high-dose corticosteroid treatment).
    - If oral corticosteroids are already combined with an immunosuppressant, another immunosuppressant should be considered.

Scheduling and content of consultations

Scheduling and content of consultations depend on the patient's clinical condition, comorbidities, severity, and course of disease during treatment, drug used (monitoring required, tolerance, side effects), level of disease activity. Initial follow-up visits should be done every 2 weeks until clinical disease control is achieved. During consolidation phase, visits should take place every 1 to 2 weeks to determine how soon steroid tapering can be started. Then, during the tapering phase, monthly clinical follow-ups are recommended for the next 3 months. Once the patient is in partial or complete remission while receiving minimal therapy, visits can be reduced to every 3 months.

Clinical evaluation

Clinical follow-up aims to determine the level of disease control, presence of therapeutic adverse effects (diabetes, high blood pressure, cardiac insufficiency, myopathy, osteoporosis, avascular bone necrosis, glaucoma, cataract due to corticosteroids), infections (respiratory infections), hepatitis or hematologic abnormalities (leukopenia) due to immunosuppression, or mental health disorders.

Serologic monitoring of disease activity

Serum autoantibodies should be determined at the initiation of treatment, after 3 months, and every 3 to 6 months according to evolution or in cases of relapse, as follows:

- ELISA: anti-Dsg1and/or Dsg3 IgG
- If ELISA not available: IIF microscopy using monkey esophagus

Serum concentrations of IgG autoantibodies against Dsg1 and Dsg3 correlate with the clinical activity of pemphigus and may help in therapeutic decision making. Persistence of high levels of anti-Dsg1 by ELISA has a positive predictive value for skin relapses, whereas the persistence of anti- Dsg3 IgG does not necessarily indicate a mucosal relapse.

Discontinuation of treatment

Discontinuation of treatment essentially depends on the clinical symptoms. It may also be supported by the findings of anti-Dsg autoantibodies using ELISA, IIF microscopy, and/or a negative result of DIF microscopy of a skin biopsy. Discontinuation of systemic corticosteroids is proposed when complete remission is obtained while on minimal therapy (prednisone/prednisolone **≤** 10 mg/d). Adjuvants can be stopped 6 to 12 months 6 to 12 months after achievement of complete remission during minimal therapy with adjuvants only.

Possible sequelae

Sequelae are the result of the lesions involving skin and mucosae, but also of the treatment side effects. Immunosuppressive therapy increases the risk of side effects.

Information for patients and their families

Patients should receive proper education about their disease, its clinical course, prognosis, treatment options, signs of relapse and side effects of therapies. Self-support groups exist and are helpful for more information about the disease, providing comfort, sharing experiences of daily life. They also contribute to a better overall management of the disease by promoting cooperation between patients, patient associations, and health professionals. Patients should also be informed about referrals centers, and be educated about disease triggers (certain drugs, operations, radiation, physical trauma). Due to insufficient evidence to date, dietary restrictions are not necessary.

1.3.2 Taiwanese Dermatological Association (TDA) Consensus for the Management of Pemphigus (2022)

A panel of seven dermatology experts from the Taiwanese Dermatological Association (TDA) and one rheumatology expert convened to develop a consensus for the management of pemphigus. The meeting reviewed the available consensus statements from international dermatology groups, including the European Dermatology Forum (EDF), the European Academy of Dermatology and Venereology (EADV), and the International Bullous Diseases Consensus Group.[27] The therapeutic management of pemphigus is summarized in table 4.

Table 4. Treatment Algorithm for Pemphigus

First-line treatment	Comments
Prednisolone (or equivalent)	Initial dose of prednisolone 1 mg/kg per day (or equivalent) in most cases, 0.5-1 mg/kg in milder cases. If used alone, the dosage can be increased to 1.5 mg/kg per day for 3 weeks. If blistering persists, dosing may be increased in 50-100% increments every 5-7 days. Taper dose once remission is induced and achieved, with the absence of new blisters and healing of most lesions. Aim is to reduce the dosage to 10 mg/ day or less.
Rituximab	2 x 1 g infusion, 2 weeks apart

	May be used concomitantly with corticosteroid
Second-line treatment	**Comments**
Azathioprine	1-3 mg/kg/day 50 mg/day is given for the first week to detect idiosyncratic reactions Up to 3 mg/kg (if *NUDT15* is normal) May be used concomitantly with corticosteroid
Third-line treatment	**Comments**
Cyclophosphamide	1-2 mg/kg Best reserved for patients with severe pemphigus vulgaris (PV)
Methotrexate	10-20 mg per week May be used concomitantly with corticosteroid
Mycophenolate mofetil (MMF)	2 g/day or 1440 mg/day if in the form of mycophenolic acid. In the form of MMF, the daily dose may be raised by 1 capsule (500 mg) per week until a final dose of 2 g/day is reached.
Immunoadsorption	Used together with immunosuppressive drugs 2 cycles, 4 weeks apart; one cycle consists of 4 treatment on 4 consecutive days
Intravenous immunoglobulin (IVIG)	2 g/kg/cycle for 2-5 consecutive days per month Patients with total IgA deficiency should not receive IVIG therapy
Plasmapheresis or plasma exchange	An alternative to refractory cases Not to be used in newly presenting patients

1.3.3 Brazilian Society of Dermatology Consensus on the Treatment of Autoimmune Bullous Dermatoses: Pemphigus Vulgaris and Pemphigus Foliaceus (2019)

I. Pemphigus Vulgaris (PV)

The treatment of autoimmune bullous dermatoses, including PV is usually based on systemic medications, because they comprise a severe group of mucosal and cutaneous diseases with significant morbidity and mortality. Treatment should be started as early as possible, and its goal is to achieve and maintain disease remission.

Thus, the treatment is often prolonged and can last many years (average 5 to 10 years).

Evaluation before starting treatment

Clinical evaluation: weight, height, and blood pressure

Laboratory tests: blood count; electrolytes; hepatic and renal function; blood glucose and glycated hemoglobin; vitamin D; lipids; serologies for hepatitis B and C, syphilis, and HIV; urine I; pregnancy test if applicable; chest x-ray; and bone densitometry (should be repeated after 6 months and then annually).

Ophthalmological evaluation: initial and then annually.

Systemic treatment

1. Corticosteroids

Oral administration: Prednisone is the most used oral corticosteroid, followed by prednisolone and deflazacort. Dosage typically starts at 40 to 60 mg/day of prednisone for patients with mild PV and up to 100 mg/day for severe cases. Doses are increased as needed, with full doses in the 1 to 2 mg/kg/day range. Extremely high dosages of 3 to 4 mg/kg/day have been shown to be disadvantageous due to their frequent and severe side effects.

Pulse therapy: Corticosteroids can also be administered as pulse therapy for cases in which control with prednisone at dosages of over 1mg/kg/day is not achieved. To this end, methylprednisolone 1g/day IV and dexamethasone 300mg/day IV are used, both for 3 consecutive days. The advantage of pulse therapy is that it allows for a faster reduction in the prednisone dose, minimizing its side effects.

Adjuvant drugs

Adjuvant or corticosteroid-sparing agents are incorporated when the condition is not controlled solely with corticosteroids or when the patients has clinical contraindications to high-dose corticosteroids.

1. Azathioprine

The recommended dosage of azathioprine in PV is 100 to 200mg/ day (1 to 3mg/kg/day), orally, divided into 2 doses. Its therapeutic effect begins after 4 to 6 weeks, which restricts its use as monotherapy. Three months of use should elapse before replacing it with another adjuvant when there is no satisfactory clinical response.

2. Mycophenolate mofetil (MMF)

The recommended dosage of MMF in PV is 2-3 g/day, divided into 2 doses. Its main side effects are altered bowel habits, neutropenia, lymphopenia, and myalgia.

Therapeutic failure should be considered only after 3 months of use at a dosage of 3 g/day.

3. Rituximab

Rituximab should be administered IV as a slow infusion (4 to 6 hours). There are no standardized protocols for the use of rituximab in autoimmune bullous diseases, but studies have been published using the lymphoma protocol (375mg/m2 , 1x/week for 4 weeks) and that for rheumatoid arthritis (1000mg with an interval of 2 weeks; can be repeated after 6 months).

4. Cyclophosphamide

Cyclophosphamide can be administered orally at a dose of 1 to 3mg/kg/day, or intravenously, with or without dexamethasone IV, in the form of pulse therapy. In such cases, dexamethasone is administered at 100mg/day IV for 3 days, with cyclophosphamide 500mg/day IV being administered on the first day. This pulse therapy is repeated every 2 to 4 weeks, between which an oral dose of cyclophosphamide 50mg/day and prednisone 1mg/kg/day is maintained. Treatment failure should be considered after 3 months of use at 2mg/kg/day.

5. Methotrexate

Methotrexate can be added as an adjuvant in PV at 10 to 20mg per week in cases of therapeutic failure to other adjuvants.

6. Dapsone

Dapsone has anti-inflammatory and anti-TNF activity and can be attempted as adjuvant medication in PV at 50 to 200 mg/day orally.

7. Cyclosporine

Cyclosporine has been shown to be effective as an adjuvant treatment at dosages of 3 to 5 mg/kg/day, either orally or intravenously.

8. Intravenous immunoglobulin (IVIG)

IVIG is used in cases of PV that do not respond to other treatments or those that present with severe side effects, and it is effective in certain cases at a dosage of 0.4g/kg/day for 5 days, always as an adjunct to corticosteroid therapy once per month.

9. Anti-TNF drugs

Case reports with the use of infliximab and etanercept have suggested its efficacy in PV, but further studies are needed.

10. Plasmapheresis/immunoadsorption

Plasmapheresis is an exceptional alternative for severe cases of PV that are unresponsive to other therapeutic modalities. Immunoadsorption is a more selective method that does not remove other antibodies or plasma components from circulation, unlike plasmapheresis. Performed in cycles of 4 consecutive days every 4 weeks, it has fewer side effects than plasmapheresis.

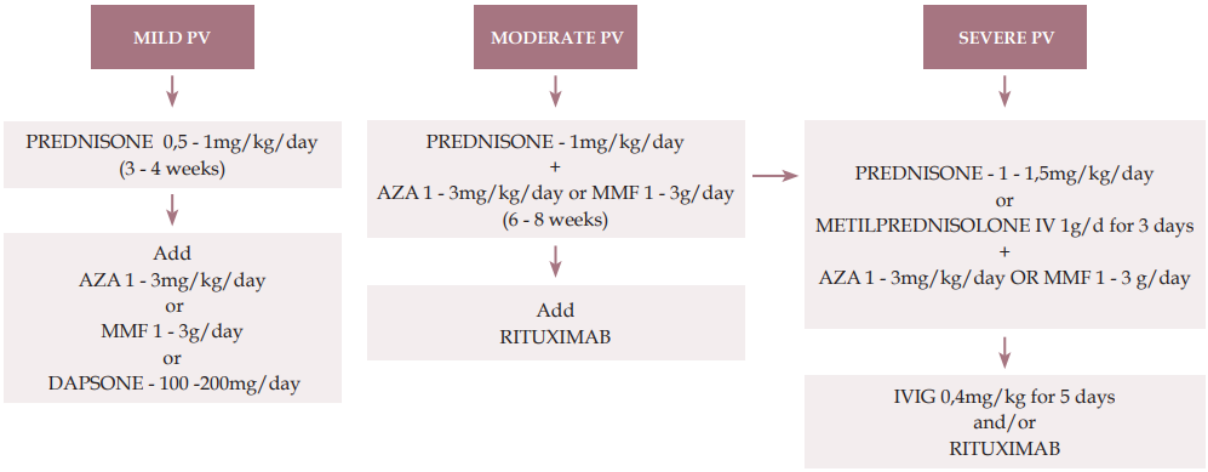

Figure 4. *Treatment algorithm for pemphigus vulgaris (retrieved from the Brazilian Society of Dermatology 2019 guideline)*

II. Pemphigus Foliaceus (PF)

Treatment is indicated from the outset of symptoms in PF, even if the clinical manifestation is mild. The goal is to induce rapid control of the disease and complete remission, minimizing treatment-related adverse effects.

Prior to initiation of therapy, complete blood count, creatinine, sodium, potassium, transaminases, gamma-glutamyl transferase (gGT), alkaline phosphatase, total proteins and protein fractions, fasting glycemia, serology for hepatitis B and C and human immunodeficiency virus (HIV), and chest x-ray should be examined.

Corticosteroids

In localized forms, with a limited number of lesions (up to 1% of body area), topical (moderate to high potency) or intralesional corticosteroid therapy (triamcinolone acetonide 2 to 3mg/ml) is used. Associated with topical therapy, dapsone 50 to 100mg/day can be prescribed.

Systemic corticosteroid therapy (prednisone/prednisolone) is prescribed when topical treatment does not control the disease or if the cutaneous condition worsens, as evidenced by an increase in lesion number, at a dosage of 0.5mg/kg/day. In severe disseminated forms (above 10% of body area), the dosage of prednisone/prednisolone is 1mg/kg/day. Systemic corticosteroid therapy remains the

most widely used, recognized, and established treatment option, due to its high efficacy and rapid control.

Adjuvant drugs

1. Azathioprine

Azathioprine is used at 1-3mg/kg/d (beginning at 50mg/d, increasing progressively until the total daily dose is reached).

2. Mycophenolate mofetil (MMF)

MMF is administered at a dosage of 2g/d (starting dosage of 1g/d, with a gradual increase of 500mg/day to improve gastric tolerance).

3. Methotrexate

Methotrexate is used at 7.5 to 25mg/week, administered over 1 or 2 consecutive days. After 24 hours, folic acid should be prescribed at a dose of 5mg.

4. Dapsone

For less extensive forms, dapsone 100mg/d or up to 1.5mg/kg/d can be attempted because it has also corticosteroid-sparing effects. However, glucose-6-phosphate dehydrogenase (G6PD) activity should be evaluated beforehand. Considering that pemphigus is an antibody-mediated disease, dapsone use is controversial.

Newer therapies

Rituximab is indicated when the patient is refractory to conventional therapy or if prednisone is required at dosages of higher than 10mg/d in combination with an immunosuppressant for more than 6 months.

IVIG is indicated for very severe, refractory patients, those who present with significant adverse effects, and severe and disseminated forms of pemphigus that require a more rapid clinical response.

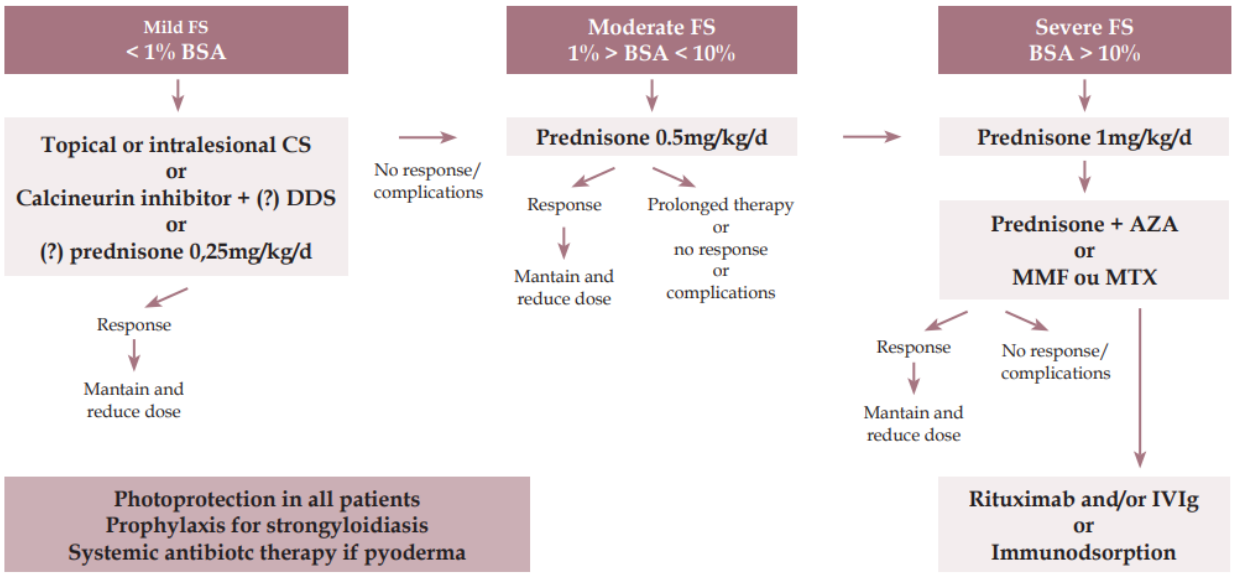

Figure 5. *Treatment algorithm for pemphigus foliaceus (retrieved from the Brazilian Society of Dermatology 2019 guideline)*

FS – fogo selvagem; BSA – body surface area (1% means the sum of injured areas corresponding to the palm area); CS – corticosteroid; DDS – diamino-diphenil-sulfone or dapsone; AZA – azathioprine; MMF – mycophenolate mofetil; MTX – methotrexate; IVIg – intravenous immunoglobulin.

1.3.4 Current Biologics in Treatment of Pemphigus Foliaceus: A Systematic Review (*Front. Immunol.*, 2023)

Treatment of PF is not isolated from the treatment of PV. This systematic review aims to provide information regarding the use of current biological therapy, specifically in PF. It included 41 studies, with 105 patients in total.[28]

Results

- The majority of patients had PF that was nonresponsive to conventional immunosuppressive therapies with significant side effects.
- RTX treatment resulted in complete remission in 63.2%, a relapse rate of 39.5%, an infection rate of 19.7%, and a mortality rate of 3.9%.
- IVIg resulted in complete remission in 62.5% of patients, with no relapses or infections.
- Treatment with both biologics led to better outcomes when RTX was first administered, then followed by IVIg.

- Follow-up durations for patients receiving RTX, IVIg, and both were 22.1, 24.8, and 35.7 months, respectively.

Discussion

In PF patients nonresponsive to conventional immunosuppressive therapy or with significant side effects, RTX and IVIg appear to be useful agents. In comparison to PV patients, profile of clinical response, relapse, infection, and mortality rates in PF patients treated with RTX were similar. This review indicates that protocols specific for PF may lead to better clinical outcomes, less adverse effects, and improved quality of life.

1.4 Systematic Reviews/Meta-Analyses

Table 5. Systematic Reviews/Meta-Analyses

Author (year)	Study title	Primary objective	Results
Etesami et al. (2022)[29]	Topical care in pemphigus wounds: A systematic review of the literature	Determine various topical wound care options for pemphigus patients, the advantage of each alternative, and to compare their efficacy, safety, and feasibility	Findings were divided into the following categories: silver-containing dressings, paraffin-embedded tulle nets, topical insulin, EPIFIBROIN 0039, platelet gel, and Biobrane®. The most used topical care in pemphigus patients was silver-containing dressings in six studies. All the included studies reported acceptable outcomes without any severe adverse effects. **Due to the few available studies in this field, a definite suggestion cannot be made.**

Section 2.0 Drug Therapy

2.1 Corticosteroids

2.1.1 Prednisolone

Information on Prednisolone is detailed in the table below.[30]

Table 6. Prednisolone Drug Information

SCIENTIFIC NAME PREDNISOLONE	
SFDA Classification	Prescription
SFDA	N/A
US FDA	N/A
EMA	Yes
MHRA	Yes
PMDA	N/A
Indication (ICD-10)	L10
Drug Class	CORTICOSTEROIDS FOR SYSTEMIC USE, PLAIN
Drug Sub-class	GLUCOCORTICOIDS
ATC Code	H02AB06 (tablet), H02AB04 (IV)
Pharmacological Class (ASHP)	Glucocorticoids, Adrenals
DRUG INFORMATION	
Dosage Form	Tablet, effervescent tablet, syrup
Route of Administration	Oral
Dose (Adult) [DDD]*	- 0.5-1.0 mg/kg/day PO in mild PV and PF; 1 to 1.5 mg/kg/day PO in moderate to severe pemphigus
Maximum Daily Dose Adults*	80 to 100 mg/day
Dose (pediatrics)	0.1 to 2 mg/kg/day in divided doses 1 to 4 times daily.
Maximum Daily Dose Pediatrics*	N/A
Adjustment	No dosage adjustment is necessary for altered kidney of hepatic function.
Prescribing edits*	**CU, ST**
AGE (Age Edit):	N/A

CU (Concurrent Use Edit):	May be administered with azathioprine, MMF, mycophenolate sodium, rituximab
G (Gender Edit):	N/A
MD (Physician Specialty Edit):	N/A
PA (Prior Authorization):	N/A
QL (Quantity Limit):	N/A
ST (Step Therapy):	Prednisolone is used in mild or moderate to severe PV and PF, as first-line or as second-line therapy.
EU (Emergency Use Only):	N/A
PE (Protocol Edit):	N/A
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	Adrenal suppression (tertiary adrenal insufficiency), cardiovascular effects (hypertension and dyslipidemia), CNS and psychiatric/behavioral effects, cushingoid features/Cushing syndrome, hyperglycemia, infection, neuromuscular and skeletal effects (osteoporosis), ocular effects (glaucoma)
Drug Interactions	**Category X:** • Aldesleukin • Brivudine • Cladribine • Desmopressin • Disulfiram • Mifamurtide • Natalizumab • Pimecrolimus • Ruxolitinib • Tacrolimus (topical) • Tertomotide • Vaccines like Mumps- Rubella- or Varicella-Containing Live Vaccines
Special Population	Pediatric, older patients
Contraindications	Hypersensitivity to prednisolone, administration of live or live attenuated vaccines with immunosuppressive

	doses of prednisolone; systemic fungal infections.
Monitoring Requirements	• Blood pressure • Serum glucose and electrolytes • Growth in pediatric • Bone mineral density • Hypothalamus-pituitary axis suppression (ACTH stimulation test, morning plasma cortisol test, urinary free cortisol test) • Occult blood loss
Precautions	Cardiovascular, ocular and thyroid diseases; diabetes; hepatic or renal impairment; myasthenia gravis; perforation risk in patients with GI diseases; osteoporosis
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

A search for clinical economic recommendations from the HTA bodies didn't yield any guidance for prednisolone in pemphigus.

CONCLUSION STATEMENT – Prednisolone

Prednisolone is a synthetic glucocorticoid derived from cortisone, used to treat various diseases with anti-inflammatory or immunosuppressive effects. It may be used for pemphigus treatment, in mild PV and PF or moderate to severe cases, as first-line or as second-line therapy. Typically, oral prednisolone is prescribed at a dosage of 0.5-1.0 mg/kg/day PO in mild PV and PF, or 1 to 1.5 mg/kg/day PO in moderate to severe pemphigus. It may also be used intravenously in moderate to severe PV and PF initially treated with rituximab and prednisone, with no disease control at week 3-4, at a dosage of 0.5–1 g/day IV over 3 consecutive days in initial intervals of 3–4 weeks. However, it's crucial to note that the use of prednisolone should be carefully monitored by a healthcare professional, as corticosteroids can have potential side effects, particularly when used over an extended period or at high doses. There are no recommendations issued by the HTA bodies for prednisolone.

2.1.2 Prednisone

Information on Prednisone is detailed in the table below.

Table 7. Prednisone Drug Information

SCIENTIFIC NAME PREDNISONE	
SFDA Classification	Prescription
SFDA	N/A
US FDA	N/A
EMA	N/A
MHRA	N/A
PMDA	N/A
Indication (ICD-10)	L10
Drug Class	CORTICOSTEROIDS FOR SYSTEMIC USE, PLAIN
Drug Sub-class	GLUCOCORTICOIDS
ATC Code	H02AB07
Pharmacological Class (ASHP)	Glucocorticoids, Adrenals
DRUG INFORMATION	
Dosage Form	Tablet
Route of Administration	Oral use
Dose (Adult) [DDD]*	0.5-1.0 mg/kg/day PO in mild PV and PF; 1 to 1.5 mg/kg/day PO in moderate to severe pemphigus
Maximum Daily Dose Adults*	80 to 100 mg/day
Dose (pediatrics)	0.1 to 2 mg/kg/day in divided doses 1 to 4 times daily.
Maximum Daily Dose Pediatrics*	N/A
Adjustment	No dosage adjustment is necessary for altered kidney of hepatic function.
Prescribing edits*	**CU, ST**
AGE (Age Edit):	N/A
CU (Concurrent Use Edit):	May be administered with azathioprine, MMF, mycophenolate sodium, rituximab
G (Gender Edit):	N/A

MD (Physician Specialty Edit):	N/A
PA (Prior Authorization):	N/A
QL (Quantity Limit):	N/A
ST (Step Therapy):	Prednisone is used in mild or moderate to severe PV and PF, as first-line or as second-line therapy.
EU (Emergency Use Only):	N/A
PE (Protocol Edit):	N/A
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	Adrenal suppression (tertiary adrenal insufficiency), cardiovascular effects (hypertension and dyslipidemia), CNS and psychiatric/behavioral effects, cushingoid features/Cushing syndrome, hyperglycemia, infection, neuromuscular and skeletal effects (osteoporosis), ocular effects (glaucoma).
Drug Interactions	**Category X:** • Aldesleukin • BCG Products • Brivudine • Cladribine • Desmopressin • Disulfiram • Methotrimeprazine • Mifamurtide • Nadofaragene Firadenovec • Natalizumab • Ornidazole • Pimecrolimus • Ritlecitinib • Ruxolitinib • Secnidazole • Tacrolimus (topical) • Tertomotide • Vaccines like mumps-rubella, typhoid, yellow fever, dengue

	tetravalent vaccine or varicella-containing live vaccines
Special Population	Pediatric, older patients
Contraindications	Hypersensitivity to prednisone, administration of live or live attenuated vaccines with immunosuppressive doses of prednisone; systemic fungal infections.
Monitoring Requirements	• Blood pressure • Serum glucose and electrolytes • Growth in pediatric • Bone mineral density • Hypothalamus-pituitary axis suppression (ACTH stimulation test, morning plasma cortisol test, urinary free cortisol test) • Occult blood loss
Precautions	Cardiovascular, ocular and thyroid diseases; diabetes; hepatic or renal impairment; myasthenia gravis; perforation risk in patients with GI diseases; osteoporosis
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

A search for clinical economic recommendations from the Health Technology Assessment (HTA) bodies didn't yield any guidance for prednisone in pemphigus.

CONCLUSION STATEMENT- Prednisone

Prednisone is a synthetic glucocorticoid derived from cortisone, used to treat various diseases with anti-inflammatory or immunosuppressive effects. It may be used for pemphigus treatment, in mild PV and PF or moderate to severe cases, as first-line or as second-line therapy. Typically, oral prednisone is prescribed at a dosage of 0.5-1.0 mg/kg/day PO in mild PV and PF, or 1 to 1.5 mg/kg/day PO in moderate to severe pemphigus. It may also be used intravenously in moderate to severe PV and PF initially treated with rituximab and prednisone, with no disease control at week 3-4, at a dosage of 0.5–1 g/day IV over 3 consecutive days in initial intervals of 3–4 weeks. However, it's crucial to note that the use of prednisone should be carefully monitored by a healthcare professional, as corticosteroids can have

potential side effects, particularly when used over an extended period or at high doses. There are no recommendations issued by the HTA bodies for prednisone.

2.1.3 Dexamethasone

Information on Dexamethasone is detailed in the table below.[31]

Table 8. Dexamethasone Drug Information

SCIENTIFIC NAME DEXAMETHASONE	
SFDA Classification	Prescription
SFDA	N/A
US FDA	N/A
EMA	N/A
MHRA	Yes
PMDA	N/A
Indication (ICD-10)	L10
Drug Class	CORTICOSTEROIDS FOR SYSTEMIC USE, PLAIN
Drug Sub-class	GLUCOCORTICOIDS
ATC Code	H02AB02
Pharmacological Class (ASHP)	Glucocorticoids, Adrenals
DRUG INFORMATION	
Dosage Form	Solution
Route of Administration	IV use
Dose (Adult) [DDD]*	IV pulses: dexamethasone 100 mg/day over 3 consecutive days in initial intervals of 3–4 weeks in moderate to severe PV and PF initially treated with rituximab and prednisone, with no disease control at week 3-4
Maximum Daily Dose Adults*	40 mg/day
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	No dosage adjustment necessary for altered kidney or hepatic function.
Prescribing edits*	**CU, ST**
AGE (Age Edit):	N/A

CU (Concurrent Use Edit):	May be administered with azathioprine, MMF, mycophenolate sodium, rituximab
G (Gender Edit):	N/A
MD (Physician Specialty Edit):	N/A
PA (Prior Authorization):	N/A
QL (Quantity Limit):	N/A
ST (Step Therapy):	Moderate to severe PV and PF initially treated with rituximab and prednisone, with no disease control at week 3-4
EU (Emergency Use Only):	N/A
PE (Protocol Edit):	N/A
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	Adrenal suppression (tertiary adrenal insufficiency), cardiovascular effects (hypertension and dyslipidemia), CNS and psychiatric/behavioral effects, cushingoid features/Cushing syndrome, hyperglycemia, infection, neuromuscular and skeletal effects (osteoporosis), ocular effects (glaucoma).
Drug Interactions	**Category X:** • Aldesleukin • BCG Products • Brivudine • Cladribine • Desmopressin • Disulfiram • Fexinidazole • Fusidic Acid (Systemic) • Lapatinib • Methotrimeprazine • Mifamurtide • Nadofaragene Firadenovec • Natalizumab • Ornidazole • Pimecrolimus • Rilpivirine

	• Ritlecitinib • Ruxolitinib • Secnidazole • Tacrolimus (topical) • Tertomotide • Vaccines like mumps-rubella, typhoid, yellow fever, dengue tetravalent vaccine or varicella-containing live vaccines
Special Population	Pediatric, older patients
Contraindications	Hypersensitivity to dexamethasone, administration of live or live attenuated vaccines with immunosuppressive doses of prednisone; systemic fungal infections.
Monitoring Requirements	• Blood pressure • Serum glucose and potassium • Weight and height in children • Intraocular pressure • Occult blood loss
Precautions	Cardiovascular, ocular and thyroid diseases; diabetes; hepatic or renal impairment; myasthenia gravis; perforation risk in patients with GI diseases; osteoporosis
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA):

A search for clinical economic recommendations from the Health Technology Assessment (HTA) bodies didn't yield any guidance for dexamethasone in pemphigus.

CONCLUSION STATEMENT- Dexamethasone

Dexamethasone is a synthetic glucocorticoid derived from cortisone, used to treat various diseases with anti-inflammatory or immunosuppressive effects. It may be used for moderate to severe PV and PF initially treated with rituximab and prednisone, with no disease control at week 3-4. Typically, dexamethasone is given IV at a dosage of 100 mg/day over 3 consecutive days in initial intervals of 3–4 weeks. However, it's crucial to note that the use of prednisolone should be carefully monitored by a healthcare professional, as corticosteroids can have potential side

effects, particularly when used over an extended period or at high doses. There are no recommendations issued by the HTA bodies for dexamethasone.

2.1.4 Clobetasol Propionate

Information on Clobetasol propionate is detailed in the table below.[32]

Table 9. Clobetasol Propionate Drug Information

SCIENTIFIC NAME CLOBETASOL PROPIONATE	
SFDA Classification	Prescription
SFDA	N/A
US FDA	N/A
EMA	N/A
MHRA	N/A
PMDA	N/A
Indication (ICD-10)	L10
Drug Class	CORTICOSTEROID
Drug Sub-class	GLUCOCORTICOID
ATC Code	D07AD01
Pharmacological Class (ASHP)	Adrenals
DRUG INFORMATION	
Dosage Form	Cream or ointment
Route of Administration	Topical
Dose (Adult) [DDD]*	Once to twice daily
Maximum Daily Dose Adults*	Twice daily
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics	N/A
Adjustment	There are no dosage adjustments necessary in renal or hepatic impairment
Prescribing edits	CU, ST
AGE (Age Edit):	N/A
CU (Concurrent Use Edit):	May be added to systemic therapy
G (Gender Edit):	N/A
MD (Physician Specialty Edit):	N/A
PA (Prior Authorization):	N/A

QL (Quantity Limit):	N/A
ST (Step Therapy):	First-line treatment in mild PF Adjuvant with rituximab or dapsone Adjunct to systemic therapy for persistent, active, hard-to-treat pemphigus lesions
EU (Emergency Use Only):	N/A
PE (Protocol Edit):	N/A
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	- Endocrine and metabolic: HPA-axis suppression - Dermatologic: eczema, erythema, folliculitis, hypopigmentation, pruritus, skin atrophy, skin fissure, stinging of skin, telangiectasia, xeroderma - Local: application site reaction, local irritation - Nervous system: headache, localized burning, local discomfort, numbness of fingers - Respiratory: nasopharyngitis, streptococcal pharyngitis, upper respiratory tract infection
Drug Interactions	Category X: none
Special Population	N/A
Contraindications	Canadian labeling: - hypersensitivity to clobetasol, other corticosteroids, or any component of the formulation; - primary infections of the scalp; - treatment of rosacea, acne vulgaris, perioral dermatitis, or perianal and genital pruritus; - viral (eg, herpes or varicella) lesions of the skin, bacterial or fungal skin infections, parasitic infections, skin manifestations relating to tuberculosis or

	syphilis, eruptions following vaccinations; - ulcerous wounds; - application to eyes or eyelids; - children <2 years of age (shampoo, spray); children <1 year of age (cream, ointment, scalp application).
Monitoring Requirements	- Adrenal suppression with extensive/prolonged use: ACTH stimulation test, morning plasma cortisol test, urinary free cortisol test - Response to treatment - Ocular changes
Precautions	- Pediatric: use of augmented formulations in patients <13 years of age is not recommended. - Do not use if there is atrophy at the treatment site
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

A search for clinical economic recommendations from the HTA bodies didn't yield any guidance for topical Clobetasol propionate in pemphigus.

CONCLUSION STATEMENT – Topical Clobetasol propionate

Topical Clobetasol propionate is a synthetic glucocorticoid derived from cortisone, used topically to treat various diseases with anti-inflammatory or immunosuppressive effects. It may be used for pemphigus treatment, as a first-line treatment in mild PF, as an adjuvant with rituximab or dapsone, or in adjunction to systemic therapy for persistent, active, hard-to-treat lesions. It is formulated as a cream or an ointment, applied once or twice daily on lesions. Topical corticosteroids can have local side effects, such as skin atrophy and telangiectasia, and HPA axis suppression in high dose use. There are no recommendations issued by the HTA bodies for topical Clobetasol propionate.

2.1.5 Betamethasone Valerate

Information on Betamethasone valerate is detailed in the table below.[33]

Table 10. Betamethasone Valerate Drug Information

SCIENTIFIC NAME BETAMETHASONE	
SFDA Classification	Prescription
SFDA	N/A
US FDA	N/A
EMA	N/A
MHRA	N/A
PMDA	N/A
Indication (ICD-10)	L10
Drug Class	CORTICOSTEROID
Drug Sub-class	GLUCOCORTICOID
ATC Code	D07AC01
Pharmacological Class (ASHP)	Adrenals
DRUG INFORMATION	
Dosage Form	Cream
Route of Administration	Topical
Dose (Adult) [DDD]*	Once to twice daily
Maximum Daily Dose Adults*	Twice daily
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics	N/A
Adjustment	There are no dosage adjustments necessary in renal or hepatic impairment
Prescribing edits	CU, ST
AGE (Age Edit):	N/A
CU (Concurrent Use Edit):	May be added to systemic therapy
G (Gender Edit):	N/A
MD (Physician Specialty Edit):	N/A
PA (Prior Authorization):	N/A
QL (Quantity Limit):	N/A
ST (Step Therapy):	First-line treatment in mild PF Adjuvant with rituximab or dapsone

EU (Emergency Use Only):	N/A
PE (Protocol Edit):	N/A
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	- Local: application-site reaction (atrophy, burning, irritation, pain, pruritus, stinging) - Dermatologic: acne vulgaris, alopecia, pruritus, xeroderma - Nervous system: Paresthesia - Ophthalmic: Conjunctivitis
Drug Interactions	Category X: none
Special Population	N/A
Contraindications	- Hypersensitivity to betamethasone, another corticosteroid, or any component of the formulation. - Canadian labeling: treatment of rosacea, acne vulgaris, perioral dermatitis, or pruritus without inflammation (foam); viral diseases (eg, herpes simplex, chicken pox, vaccina); untreated bacterial, fungal, parasitic, syphilis, and tubercular infection involving the skin; eruptions following vaccinations (patch); application to eyes (foam); <18 years of age (patch).
Monitoring Requirements	- HPA axis suppression and adrenal insufficiency, especially in children or with augmented formulation use; - Ocular symptoms. - Foam, gel, lotion, and ointment: reassess if no improvement after 2 weeks of treatment.
Precautions	Pediatric: Use of augmented formulations in patients <13 years of age is not recommended.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

A search for clinical economic recommendations from the HTA bodies didn't yield any guidance for topical betamethasone valerate in pemphigus.

CONCLUSION STATEMENT – Topical betamethasone valerate

Topical betamethasone valerate is a synthetic glucocorticoid derived from cortisone, used topically to treat various diseases with anti-inflammatory or immunosuppressive effects. It may be used for pemphigus treatment, as a first-line treatment in mild PF, as an adjuvant with rituximab or dapsone, or in adjunction to systemic therapy for persistent, active, hard-to-treat lesions. It is formulated as a cream, applied once or twice daily on lesions. Topical corticosteroids can have local side effects, such as skin atrophy and telangiectasia, and HPA axis suppression in high dose use. There are no recommendations issued by the HTA bodies for topical betamethasone valerate.

2.1.6 Triamcinolone Acetonide Intralesional Injection

Information on triamcinolone acetonide is detailed in the table below.[34]

Table 11. Triamcinolone Acetonide Drug Information

SCIENTIFIC NAME TRIAMCINOLONE ACETONIDE	
SFDA Classification	Prescription
SFDA	N/A
US FDA	N/A
EMA	N/A
MHRA	N/A
PMDA	N/A
Indication (ICD-10)	L10
Drug Class	CORTICOSTEROID
Drug Sub-class	GLUCOCORTICOID
ATC Code	H02AB08
Pharmacological Class (ASHP)	Adrenals
DRUG INFORMATION	
Dosage Form	Suspension for injection
Route of Administration	Intralesional injection
Dose (Adult) [DDD]*	N/A

Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics	N/A
Adjustment	There are no dosage adjustments necessary in renal or hepatic impairment
Prescribing edits	ST
AGE (Age Edit):	N/A
CU (Concurrent Use Edit):	N/A
G (Gender Edit):	N/A
MD (Physician Specialty Edit):	N/A
PA (Prior Authorization):	N/A
QL (Quantity Limit):	N/A
ST (Step Therapy):	For recalcitrant individual lesions
EU (Emergency Use Only):	N/A
PE (Protocol Edit):	N/A
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	Described for topical formulations: - Dermatologic: acneiform eruption, allergic contact dermatitis, atrophic striae, desquamation, folliculitis, hypertrichosis, hypopigmentation, local dryness, maceration of the skin, miliaria, perioral dermatitis, skin atrophy, skin blister - Endocrine and metabolic: cushing syndrome, glycosuria, HPA-axis suppression, hyperglycemia - Infection: secondary infection
Drug Interactions	Category X: none
Special Population	N/A
Contraindications	Hypersensitivity to triamcinolone or any component of the formulation
Monitoring Requirements	Skin atrophy HPA axis suppression

Precautions	N/A
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

A search for clinical economic recommendations from the HTA bodies didn't yield any guidance for intralesional triamcinolone acetonide in pemphigus.

CONCLUSION STATEMENT – Topical betamethasone valerate

Intralesional triamcinolone acetonide is a synthetic glucocorticoid derived from cortisone, used as intralesional injections to treat various diseases with anti-inflammatory or immunosuppressive effects. It may be used for pemphigus treatment in recalcitrant individual lesions. Topical corticosteroids can have local side effects, such as skin atrophy and telangiectasia, and HPA axis suppression in high dose use. There are no recommendations issued by the HTA bodies for intralesional triamcinolone acetonide.

2.2 Immunosuppressive agents

2.2.1 Mycophenolate Mofetil (MMF)

Information on mycophenolate mofetil is detailed in the table below.[35]

Table 12. Mycophenolate Mofetil Drug Information

SCIENTIFIC NAME MYCOPHENOLATE MOFETIL	
SFDA Classification	Prescription
SFDA	N/A
US FDA	N/A
EMA	N/A
MHRA	N/A
PMDA	N/A
Indication (ICD-10)	L-10
Drug Class	IMMUNOSUPPRESSANTS
Drug Sub-class	IMMUNOSUPPRESSANTS
ATC Code	L04AA06
Pharmacological Class (ASHP)	Immunosuppressive agents

DRUG INFORMATION	
Dosage Form	Tablet
Route of Administration	Oral
Dose (Adult) [DDD]*	2g/d per os
Maximum Daily Dose Adults*	2g/d per os
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics	N/A
Adjustment	- Renal impairment: if glomerular filtration rate < 25 mL/min/1.73m^{2,} not to exceed 1g/12h. - There are no dosage adjustments necessary in hepatic impairment.
Prescribing edits	CU, ST
AGE (Age Edit):	N/A
CU (Concurrent Use Edit):	May be started with prednisone, prednisolone, dexamethasone
G (Gender Edit):	N/A
MD (Physician Specialty Edit):	N/A
PA (Prior Authorization):	N/A
QL (Quantity Limit):	N/A
ST (Step Therapy):	- First-line or second-line treatment for PV and PF - Cortico-sparing agent
EU (Emergency Use Only):	N/A
PE (Protocol Edit):	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	- Acute inflammatory syndrome - Bone marrow suppression (anemia, leucopenia, thrombocytopenia) - Gastro-intestinal effects (diarrhea, abdominal pain, nausea, vomiting) - Infections - Lymphoproliferative disorders and skin cancers - Pure red cell aplasia (when used with corticosteroids)

	- Cardiovascular effects: edema, hypertension, hypotension, tachycardia - Dermatologic effects: cellulitis, ecchymosis, rash - Endocrine & metabolic (such as acidosis, hypercholesterolemia, hyperglycemia) - Hematuria, urinary infection - Renal effects (such as increase in creatinine) - Neurologic effects (such as confusion) - Hepatic effects (such as hepatitis or liver function tests alteration)
Drug Interactions	Category X : - Abrocitinib - Baricitinib - BCG products - Bile Acid Sequestrants - Brivudine - Cholestyramine Resin - Cladribine - Deucravacitinib - Etrasimod - Filgotinib - Nadofaragene Firadenovec - Natalizumab - Pimecrolimus - Ritlecitinib - Ruxolitinib - Tacrolimus (topical) - Talimogene Laherparepvec - Tertomotide - Tofacitinib - Upadacitinib - Vaccines, such as Dengue Tetravalent live vaccine, Mumps-Rubella or Varicella-containing live vaccines, Poliovirus vaccine

	(Live/Trivalent/Oral), Typhoid vaccine, Yellow Fever vaccine
Special Population	Older adults
Contraindications	- Hypersensitivity to mycophenolate mofetil, mycophenolic acid, mycophenolate sodium, or any component of the formulation - IV formulation: contraindicated in patients who are allergic to polysorbate 80 (Tween) - *Canadian labeling : p*regnancy; women of childbearing age not using highly effective contraceptive methods; women of childbearing age not providing a pregnancy test result; breastfeeding.
Monitoring Requirements	- Complete blood count (weekly for first month, twice monthly during months 2 and 3, then monthly thereafter through the first year) - Renal and liver function - In HBV and HCV + patients: monitor for signs of viral reactivation - Pregnancy test (immediately prior to initiation and 8 to 10 days later in patients who may become pregnant, followed by repeat tests during therapy) - Skin check-up (skin cancers)
Precautions	Women of childbearing potential are advised to choose a safer option if available, and to use 2 forms of reliable contraception during treatment course and 6 weeks after discontinuation
Black Box Warning	Increased risk of infection (bacterial, viral, fungal, protozoal, opportunistic infections and viral reactivation)

	Increased risk of lymphoma, skin cancer Risk of first trimester miscarriage and congenital malformations
REMS	FDA: exposure to mycophenolate during pregnancy is associated with an increased risk of first trimester pregnancy loss and congenital malformations

HEALTH TECHNOLOGY ASSESSMENT (HTA):

A search for clinical economic recommendations from the HTA bodies didn't yield any guidance for MMF in pemphigus.

CONCLUSION STATEMENT - Mycophenolate mofetil

MMF is an immunosuppressant used as a first-line or second-line treatment for PV and PF. It may be started with prednisone, prednisolone, or dexamethasone. It is considered a cortico-sparing agent. It is given orally at a dosage of 2g/d per os. Main adverse effects include acute inflammatory syndrome, bone marrow suppression (anemia, leucopenia, thrombocytopenia), gastro-intestinal effects (diarrhea, abdominal pain, nausea, vomiting), infections, lymphoproliferative disorders and skin cancers, pure red cell aplasia (when used with corticosteroids), and hepatic disturbance (such as hepatitis or liver function tests alteration), among others. Monitoring of complete blood count, renal and hepatic tests is required during treatment. Practitioners should also be aware of signs of viral reactivation in HCV and HBV positive patients. A pregnancy test is recommended immediately prior to initiation of MMF and 8 to 10 days later in patients who may become pregnant, followed by repeat tests during therapy. Skin check-up for skin cancers are recommended as well. Women of childbearing age are advised to choose a safer option if available, and to use 2 forms of reliable contraception during treatment course and 6 weeks after discontinuation. MMF has a black box warning for Increased risk of infection, lymphoma, skin cancer, and first trimester miscarriage and congenital malformations.

2.2.2 Mycophenolate Sodium

Information on Mycophenolate sodium is detailed in the table below.[35]

Table 13. Mycophenolate Sodium Drug Information

SCIENTIFIC NAME MYCOPHENOLATE SODIUM	
SFDA Classification	Prescription
SFDA	N/A
US FDA	N/A
EMA	N/A
MHRA	N/A
PMDA	N/A
Indication (ICD-10)	L-10
Drug Class	IMMUNOSUPPRESSANTS
Drug Sub-class	IMMUNOSUPPRESSANTS
ATC Code	L04AA06
Pharmacological Class (ASHP)	Immunosuppressive agents
DRUG INFORMATION	
Dosage Form	Tablet
Route of Administration	Oral
Dose (Adult) [DDD]*	1440 mg/d per os
Maximum Daily Dose Adults*	1440 mg/d per os
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics	N/A
Adjustment	- Renal impairment: if glomerular filtration rate < 25 mL/min/1.73m^{2,} not to exceed 1g/12h. - There are no dosage adjustments necessary in hepatic impairment.
Prescribing edits	CU, ST
AGE (Age Edit):	N/A
CU (Concurrent Use Edit):	May be started with prednisone, prednisolone, dexamethasone
G (Gender Edit):	N/A
MD (Physician Specialty Edit):	N/A
PA (Prior Authorization):	N/A

QL (Quantity Limit):	N/A
ST (Step Therapy):	- First-line or second-line treatment for PV and PF - Cortico-sparing agent
EU (Emergency Use Only):	N/A
PE (Protocol Edit):	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	- Acute inflammatory syndrome - Bone marrow suppression (anemia, leucopenia, thrombocytopenia) - Gastro-intestinal effects (diarrhea, abdominal pain, nausea, vomiting) - Infections - Lymphoproliferative disorders and skin cancers - Pure red cell aplasia (when used with corticosteroids) - Cardiovascular effects: edema, hypertension, hypotension, tachycardia - Dermatologic effects: cellulitis, ecchymosis, rash - Endocrine & metabolic (such as acidosis, hypercholesterolemia, hyperglycemia) - Hematuria, urinary infection - Renal effects (such as increase in creatinine) - Neurologic effects (such as confusion) - Hepatic effects (such as hepatitis or liver function tests alteration)
Drug Interactions	Category X : - Abrocitinib - Baricitinib - BCG products - Bile Acid Sequestrants - Brivudine

	- Cholestyramine Resin - Cladribine - Deucravacitinib - Etrasimod - Filgotinib - Nadofaragene Firadenovec - Natalizumab - Pimecrolimus - Ritlecitinib - Ruxolitinib - Tacrolimus (topical) - Talimogene Laherparepvec - Tertomotide - Tofacitinib - Upadacitinib - Vaccines, such as Dengue Tetravalent live vaccine, Mumps-Rubella or Varicella-containing live vaccines, Poliovirus vaccine (Live/Trivalent/Oral), Typhoid vaccine, Yellow Fever vaccine
Special Population	Older adults
Contraindications	- Hypersensitivity to mycophenolate mofetil, mycophenolic acid, mycophenolate sodium, or any component of the formulation - IV formulation: contraindicated in patients who are allergic to polysorbate 80 (Tween) - *Canadian labeling : p*regnancy; women of childbearing age not using highly effective contraceptive methods; women of childbearing age not providing a pregnancy test result; breastfeeding.
Monitoring Requirements	- Complete blood count (weekly for first month, twice monthly during months 2 and 3, then

	monthly thereafter through the first year) - Renal and liver function - In HBV and HCV + patients: monitor for signs of viral reactivation - Pregnancy test (immediately prior to initiation and 8 to 10 days later in patients who may become pregnant, followed by repeat tests during therapy) - Skin check-up (skin cancers)
Precautions	Women of childbearing potential are advised to choose a safer option if available, and to use 2 forms of reliable contraception during treatment course and 6 weeks after discontinuation
Black Box Warning	Increased risk of infection (bacterial, viral, fungal, protozoal, opportunistic infections and viral reactivation) Increased risk of lymphoma, skin cancer Risk of first trimester miscarriage and congenital malformations
REMS	FDA: exposure to mycophenolate during pregnancy is associated with an increased risk of first trimester pregnancy loss and congenital malformations

HEALTH TECHNOLOGY ASSESSMENT (HTA):

A search for clinical economic recommendations from the HTA bodies didn't yield any guidance for mycophenolate sodium in pemphigus.

CONCLUSION STATEMENT-Mycophenolate sodium

Mycophenolate sodium is an immunosuppressant used as a first-line or second-line treatment for PV and PF. It may be started with prednisone, prednisolone or dexamethasone. It is considered a cortico-sparing agent. It is given orally at a dosage of 1440 mg/d per os. Main adverse effects include acute inflammatory syndrome, bone marrow suppression (anemia, leucopenia, thrombocytopenia), gastro-intestinal effects (diarrhea, abdominal pain, nausea, vomiting), infections, lymphoproliferative disorders and skin cancers, pure red cell aplasia (when used with corticosteroids),

and hepatic disturbance (such as hepatitis or liver function tests alteration), among others. Monitoring of complete blood count, renal and hepatic tests is required during treatment. Practitioners should also be aware of signs of viral reactivation in HCV and HBV positive patients. A pregnancy test is recommended immediately prior to initiation of mycophenolate sodium and 8 to 10 days later in patients who may become pregnant, followed by repeat tests during therapy. Skin check-up for skin cancers are recommended as well. Women of childbearing age are advised to choose a safer option if available, and to use 2 forms of reliable contraception during treatment course and 6 weeks after discontinuation. Mycophenolate sodium has a black box warning for Increased risk of infection, lymphoma, skin cancer, and first trimester miscarriage and congenital malformations.

2.2.3 Azathioprine

Information on Azathioprine is detailed in the table below.[36]

Table 14. Azathioprine Drug Information

SCIENTIFIC NAME AZATHIOPRINE	
SFDA Classification	Prescription
SFDA	N/A
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	N/A
Indication (ICD-10)	L-10
Drug Class	IMMUNOSUPPRESSANTS
Drug Sub-class	DMARDs, IMMUNOMODULATORS
ATC Code	L04AX01
Pharmacological Class (ASHP)	Immunosuppressive agents, Immunomodulatory Agents, DMARDs
DRUG INFORMATION	
Dosage Form	Tablet
Route of Administration	Oral
Dose (Adult) [DDD]*	1 to 2.5 mg/kg/d per os
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics	N/A

Adjustment	Renal impairment: - CrCl ≥30 mL/minute: no dosage adjustment necessary - CrCl 10 to <30 mL/minute: administer 75% to 100% of the usual indication-specific dose. If the initial dose is a dose range, then it is recommended to begin with the lowest end of the dose range. - CrCl <10 mL/minute: administer 50% to 100% of the usual indication-specific dose. If the initial dose is a dose range, then it is recommended to begin with the lowest end of the dose range. - Hemodialysis and peritoneal dialysis: administer 50% to 100% of the indication-specific dose There are no dosage adjustments necessary in hepatic impairment.
Prescribing edits	CU, ST
AGE (Age Edit):	N/A
CU (Concurrent Use Edit):	Usually started with systemic corticosteroids
G (Gender Edit):	N/A
MD (Physician Specialty Edit):	N/A
PA (Prior Authorization):	N/A
QL (Quantity Limit):	N/A
ST (Step Therapy):	- First-line or second-line treatment for PV and PF. - Cortico-sparing agent
EU (Emergency Use Only):	N/A
PE (Protocol Edit):	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	- Gastro-intestinal effects (diarrhea, nausea, vomiting)

	- Hematologic toxicity (leukopenia, thrombocytopenia, macrocytic anemia, pancytopenia) - Infections - Liver dysfunction: cholestatic, hepatocellular, or mixed type hepatotoxicity - Lymphoproliferative disorders, neoplasms and skin cancers - Pancreatitis
Drug Interactions	Category X : - Abrocitinib - Baricitinib - BCG products - Brivudine - Cladribine - Deucravacitinib - Dipyrone - Etrasimod - Febuxostat - Fexinidazole - Filgotinib - Mercaptopurine - Nadofaragene Firadenovec - Natalizumab - Pimecrolimus - Ritlecitinib - Ruxolitinib - Tacrolimus (topical) - Talimogene Laherparepvec - Tertomotide - Tofacitinib - Upadacitinib - Vaccines, such as Dengue Tetravalent live vaccine, Mumps-Rubella or Varicella-containing live vaccines, Poliovirus vaccine (Live/Trivalent/Oral), Typhoid vaccine, Yellow Fever vaccine
Special Population	TPMT and nudix hydrolase 15 (nucleotide diphosphatase; NUDT15)

	deficient patients: develop severe bone marrow toxicities and may require dose reduction or discontinuation.
Contraindications	- Hypersensitivity to azathioprine or any component of the formulation - Pregnancy - History of rheumatoid arthritis treated with alkylating agents (prohibitive risk of malignancy with azathioprine)
Monitoring Requirements	- Complete blood count (weekly for first month, twice monthly for months 2 and 3, then monthly thereafter) - Total bilirubin, LFTs (every 3 months) - Creatinine clearance - Regular skin check-up and avoidance of sun exposure in patients taking azathioprine for a prolonged time period. - In case of severe bone marrow toxicities: TPMT genotyping or phenotyping and NUDT15 genotyping. The American Gastroenterological Association suggests routine TPMT testing.
Precautions	Pregnancy category D
Black Box Warning	Increased risk of neoplasms, mutations and hematologic toxicities.
REMS	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA):

A search for clinical economic recommendations from the HTA bodies didn't yield any guidance for azathioprine in pemphigus.

CONCLUSION STATEMENT-Azathioprine

Azathioprine is an immunosuppressant used as a first-line or second-line treatment for PV and PF. It is usually started with systemic corticosteroids, and is considered a cortico-sparing agent. Azathioprine is given orally at a dosage of 1 to 2.5 mg/kg/d per

os. Main adverse effects include pancreatitis, diarrhea, nausea, vomiting, hematologic toxicity (leukopenia, thrombocytopenia, macrocytic anemia, pancytopenia), infections, liver dysfunction (cholestatic, hepatocellular, or mixed type hepatotoxicity) and lymphoproliferative disorders, neoplasms and skin cancers. Monitoring is required and includes a complete blood count (weekly for first month, twice monthly for months 2 and 3, then monthly thereafter), total bilirubin, LFTs (every 3 months), creatinine clearance, and regular skin check-up. Avoidance of sun exposure in patients taking azathioprine for a prolonged time period is recommended. In case of severe bone marrow toxicities, TPMT genotyping or phenotyping and NUDT15 genotyping are recommended. Azathioprine has a black box warning for an increased risk of neoplasms, mutations and hematologic toxicities.

2.2.4 Cyclophosphamide

Information on Cyclophosphamide is detailed in the table below.[37]

Table 15. Cyclophosphamide Drug Information

SCIENTIFIC NAME CYCLOPHOSPHAMIDE	
SFDA Classification	Prescription
SFDA	N/A
US FDA	N/A
EMA	N/A
MHRA	N/A
PMDA	N/A
Indication (ICD-10)	L-10
Drug Class	ANTINEOPLASTIC, ALKYLATING
Drug Sub-class	DMARDs, IMMUNOMODULATOR
ATC Code	L01AA01
Pharmacological Class (ASHP)	Antineoplastic agent
DRUG INFORMATION	
Dosage Form	Tablet, powder for solution for injection
Route of Administration	Oral, IV
Dose (Adult) [DDD]*	50 mg/day per os or 500–750 mg/month IV
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	N/A

Maximum Daily Dose Pediatrics	N/A
Adjustment	Renal impairment: - CrCl ≥30 mL/minute: No dosage adjustment necessary. - CrCl 10 to 29 mL/minute: administer 75% or 100% of normal dose. - CrCl <10 mL/minute: administer 50%, 75%, or 100% of normal dose. - Hemodialysis : administer 50% or 75% of the normal dose. - Peritoneal dialysis: administer 75% of the normal dose Hepatic impairment: Krens 2019: - Mild or moderate impairment: dosage adjustment is not likely needed. - Severe impairment: use is not recommended due to risk of reduced efficacy. Floyd 2006: - Serum bilirubin 3.1 to 5 mg/dL or transaminases >3 times upper limit of normal: administer 75% of dose. - Serum bilirubin >5 mg/dL: avoid use.
Prescribing edits	CU, MD, ST
AGE (Age Edit):	N/A
CU (Concurrent Use Edit):	To be used concurrently with antiemetics and appropriate hydration
G (Gender Edit):	N/A
MD (Physician Specialty Edit):	To be prescribed by a physician specialized in the treatment of pemphigus and the use of immunosuppressants
PA (Prior Authorization):	N/A

QL (Quantity Limit):	N/A
ST (Step Therapy):	Third-line treatment in recalcitrant pemphigus
EU (Emergency Use Only):	N/A
PE (Protocol Edit):	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	- Bone marrow suppression (anemia, leucopenia, thrombocytopenia) - Cardiotoxicity (such as arrhythmias, heart failure, myocarditis) - Hemorrhagic cystitis - Hepatotoxicity (hepatic sinusoidal obstruction syndrome) - Pulmonary toxicity (such as pneumonitis, pulmonary fibrosis, pulmonary veno-occlusive disease, and acute respiratory distress syndrome) - Secondary primary malignant neoplasm
Drug Interactions	Category X : - Abrocitinib - Baricitinib - BCG (Intravesical) and BCG products - Brivudine - Cladribine - Deucravacitinib - Dipyrone - Etanercept - Etrasimod - Fexinidazole - Filgotinib - Nadofaragene Firadenovec - Natalizumab - Pimecrolimus - Ritlecitinib - Ruxolitinib

	- Tacrolimus (topical) - Talimogene Laherparepvec - Tertomotide - Tofacitinib - Upadacitinib - Vaccines, such as Dengue Tetravalent live vaccine, Mumps-Rubella or Varicella-containing live vaccines, Poliovirus vaccine (Live/Trivalent/Oral), Typhoid vaccine, Yellow Fever vaccine - Voclosporin
Special Population	N/A
Contraindications	- History of severe hypersensitivity to cyclophosphamide, its metabolites, or any component of the formulation - Urinary outflow obstruction. - Severe immunosuppression - *Canadian labeling:* severe myelosuppression, severe renal or hepatic impairment, active infection (especially varicella zoster), severe immunosuppression.
Monitoring Requirements	- Complete blood count - BUN - Serum electrolytes - Serum creatinine - Urinalysis - Pregnancy test prior to initiation - American Society of Clinical Oncology: HBV screening
Precautions	Women of childbearing age: effective contraception during treatment for up to 1 year after completion of treatment.
Black Box Warning	N/A
REMS	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA):

A search for clinical economic recommendations from the HTA bodies didn't yield any guidance for cyclophosphamide in pemphigus.

CONCLUSION STATEMENT-Cyclophosphamide

Cyclophosphamide is an antineoplastic agent, used as a DMARD as a third-line treatment in recalcitrant pemphigus. It is given orally at a dosage of 50 mg/day or intravenously at a dosage of 500–750 mg/month. Adverse effects include bone marrow suppression, cardiotoxicity, hemorrhagic cystitis, hepatotoxicity, pulmonary toxicity and secondary primary malignant neoplasm. Monitoring includes a pregnancy test prior to initiation, a complete blood count, serum electrolytes, urea and creatinine dosage, and a urinalysis. Women of childbearing age are recommended to use an effective contraception during treatment for up to 1 year after completion of treatment.

2.3 Immune Globulins

2.3.1 Intravenous Immunoglobulin (IVIG)

Information on IVIG is detailed in the table below.[38]

Table 16. IVIG Drug Information

SCIENTIFIC NAME IVIG	
SFDA Classification	Prescription
SFDA	N/A
US FDA	N/A
EMA	N/A
MHRA	N/A
PMDA	Yes
Indication (ICD-10)	L-10
Drug Class	BLOOD PRODUCT DERIVATIVE; IMMUNE GLOBULIN
Drug Sub-class	IMMUNE GLOBULIN
ATC Code	J06BA01, J06BA02
Pharmacological Class (ASHP)	N/A
DRUG INFORMATION	
Dosage Form	Solution for infusion

Route of Administration	IV
Dose (Adult) [DDD]*	2 g/kg/cycle (over 2–5 consecutive days every 4 weeks, or over several days to avoid headache and nausea)
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics	N/A
Adjustment	N/A
Prescribing edits	CU, MD, ST
AGE (Age Edit):	N/A
CU (Concurrent Use Edit):	To be used concurrently with appropriate pre-medication
G (Gender Edit):	N/A
MD (Physician Specialty Edit):	To be prescribed by a physician specialized in the treatment of pemphigus and the use of immunosuppressants
PA (Prior Authorization):	N/A
QL (Quantity Limit):	N/A
ST (Step Therapy):	Severe, refractory pemphigus
EU (Emergency Use Only):	N/A
PE (Protocol Edit):	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	- Aseptic meningitis - Cardiovascular: chest pain, bradycardia, tachycardia, hypertension, hypotension - Dermatologic : dermatitis - Gastrointestinal: abdominal pain, diarrhea, nausea, viral gastroenteritis, vomiting - Hematologic and oncologic: anemia, hemolysis, positive direct Coombs test, thrombosis - Hepatic: increased serum alanine aminotransferase, increased serum alkaline phosphatase, increased serum bilirubin

	- Immunologic: antibody development - Locally at injection site: bruising, erythema, edema, pain, irritation, nodule or pruritus - Neuromuscular and skeletal: asthenia, back pain, limb pain, myalgia - Respiratory: asthma, bronchitis, cough, epistaxis, nasal congestion, nasopharyngitis, pharyngitis, rhinitis, sinusitis, upper respiratory tract infection, wheezing - Fever
Drug Interactions	Category X : N/A
Special Population	Older adults (may be at increased risk for renal dysfunction/failure and thromboembolic events)
Contraindications	- Complete IgA deficiency - Hypersensitivity to immune globulin or any component of the formulation
Monitoring Requirements	- Renal function (prior to initial infusion and at appropriate intervals) - Urine output - IgG concentrations - Hemoglobin and hematocrit, platelets (in patients with ITP) - Infusion- or injection-related adverse reactions, anaphylaxis, signs and symptoms of thrombosis, signs and symptoms of hemolysis; - Blood viscosity (in patients at risk for hyperviscosity); - Presence of antineutrophil antibodies (if TRALI is suspected); - Volume status;

	- Neurologic or pulmonary symptoms - Blood pressure (prior to, during, and following infusion); - Clinical response. - For patients at high risk of hemolysis (dose ≥2 g/kg, given as a single dose or divided over several days, and non-O blood type): hemoglobin or hematocrit prior to and 36 to 96 hours post-infusion and again at 7 to 10 days post-infusion.
Precautions	- Patients with IgA deficiency should receive IgA-depleted IVIG treatment. - Risk of immune globulin-induced renal dysfunction: rate of infusion and concentration of solution should be minimized. Discontinue if renal function deteriorates during treatment. - Fluid overload: high-dose regimens (1g/kg for 1 to 2 days) are not recommended for individuals with fluid overload or where fluid volume may be of concern.
Black Box Warning	FDA: risk of thrombosis in a number of potential predisposing states, such as advanced age, prolonged immobilization, hypercoagulable conditions, etc.
REMS	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of pemphigus treatment options by the following agencies/institutes/authorities: NICE, CADTH, HAS and IQWIG as applicable. The recommendations below are for IVIG.

Table 17. IVIG HTA Analysis

MEDICATION	AGENCY	HTA RECOMMENDATION
IVIG	CADTH	29 May 2023 - No evidence regarding the clinical effectiveness and safety of alternative treatments to IVIG compared to IVIG or placebo for bullous pemphigoid (BP) or PV and PF that met inclusion criteria for this review. - Identification of 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 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.
	NICE	N/A
	HAS	N/A
	IQWIG	N/A
	PBAC	N/A

CONCLUSION STATEMENT-IVIG

IVIG therapy is reserved for severe, refractory pemphigus. It consists of immune globulin (derived from human blood) given intravenously at a dosage of 2 g/kg/cycle (over 2–5 consecutive days every 4 weeks, or over several days to avoid headache and nausea). It is contraindicated in case of complete IgA deficiency or hypersensitivity to immune globulin. Monitoring includes mainly renal function, complete blood count, blood viscosity, blood pressure and volume status surveillance. The FDA issued a black box warning regarding the risk of thrombosis in a number of potential predisposing states, such as advanced age, prolonged immobilization, hypercoagulable conditions, etc.

2.4 Antineoplastic agents

2.4.1 Rituximab

Information on Rituximab is detailed in the table below.[39]

Table 18. Rituximab Drug Information

SCIENTIFIC NAME RITUXIMAB	
SFDA Classification	Prescription
SFDA	N/A
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	L-10
Drug Class	MONOCLONAL ANTIBODIES FOR SYSTEMIC USE
Drug Sub-class	DISEASE-MODIFYING ANTIRHEUMATIC DRUGS (DMARDs), ANTI-CD20 MONOCLONAL ANTIBODY
ATC Code	L01XC02
Pharmacological Class (ASHP)	Antineoplastic agents, DMARDs
DRUG INFORMATION	
Dosage Form	Concentrate for solution for infusion
Route of Administration	IV
Dose (Adult) [DDD]*	1g IV twice 2 weeks apart, Then at month 6: - Complete remission + severe pemphigus and/or high rate of anti-Dsg antibodies at month 3: 500mg-1g IV - No complete remission: 2g IV once or 1g 2 weeks apart Then 500mg IV at months 12 and 18
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A

Adjustment	No dosage adjustment necessary for altered kidney of hepatic function.
Prescribing edits*	**CU, ST**
AGE (Age Edit):	N/A
CU (Concurrent Use Edit):	May be used with prednisone, prednisolone, dexamethasone
G (Gender Edit):	N/A
MD (Physician Specialty Edit):	N/A
PA (Prior Authorization):	N/A
QL (Quantity Limit):	N/A
ST (Step Therapy):	First-line or second-line treatment for PV and PF
EU (Emergency Use Only):	N/A
PE (Protocol Edit):	N/A
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	• Infusion-related reactions (angioedema, bronchospasm, cough, hypotension, hypoxia, throat irritation, urticaria, acute respiratory distress syndrome, pulmonary infiltrates, acute myocardial infarction, ventricular fibrillation, and cardiogenic shock) • Mucocutaneous reactions • Hepatitis B virus reactivation • Progressive multifocal leukoencephalopathy • Hypogammaglobulinemia and Infection • Cardiovascular • Gastrointestinal • Respiratory
Drug Interactions	**<u>Category X:</u>** Abrocitinib Anifrolumab Baricitinib Belimumab DMARDs

	Brivudine Cladribine Deucravacitinib Dipyrone Etrasimod Fexinidazole Filgotinib Nadofaragene Firadenovec Natalizumab Pimecrolimus Ritlecitinib Ruxolitinib (topical) Tacrolimus (Topical) Talimogene Laherparepvec Tertomotide Tofacitinib Upadacitinib Live vaccines, such as Yellow Fever vaccine, Dengue Tetravalent vaccine, Mumps-Rubella or Varicella-containing live vaccines, Poliovirus vaccine (Live/Trivalent/Oral), Typhoid vaccine
Special Population	Older adult
Contraindications	Canadian labeling: known type 1 hypersensitivity or anaphylactic reaction to murine proteins, Chinese Hamster Ovary cell proteins, or any component of the formulation; patients who have or have had progressive multifocal leukoencephalopathy; patients with severe, active infections.
Monitoring Requirements	• Blood pressure and vital signs • Pregnancy status • Screening for latent infections (HCV, HBV, HIV, tuberculosis) • Infusion-related reactions • Signs/symptoms of bowel obstruction/perforation • Mucocutaneous skin reactions • Signs/symptoms of progressive multifocal leukoencephalopathy;

Precautions	Bowel obstruction/perforation Cytopenias Renal toxicity (oncology) Tumor lysis syndrome (oncology)
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of pemphigus treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS) and Institute for Quality and Efficiency in Health Care (IQWIG) as applicable. The recommendations below are for rituximab.

Table 19. Rituximab HTA Analysis

MEDICATION	AGENCY	HTA RECOMMENDATION
Rituximab	HAS	19 April 2023 The new data confirm the role of MABTHERA (rituximab) in combination with brief systemic corticosteroid therapy, in the first-line treatment of moderate to severe PV in adults. 1 Phase III study (ML22196): of a short course (3-6 months) of the combination rituximab + prednisone at a low dose, compared to prednisone alone at a standard dose for a prolonged course (12-18 months), in terms of complete remission after 24 months, in adults with moderate to severe pemphigus vulgaris (PV) (89.5% vs 27.8%, p < 0.0001), despite the methodological weaknesses of the study (open study, with no control of alpha risk, analysis of a subgroup of patients) 2 New phase III study (PEMPHIX): good quality methodology, comparative versus mycophenolate mofetil (MMF), in combination with brief corticosteroid therapy in each group, in adults with active moderate to severe PV requiring oral corticosteroid therapy. The study demonstrated:

		- the superiority of rituximab compared to MMF after 52 weeks of treatment with regard to the percentage of patients obtaining a complete response (with discontinuation of corticosteroid therapy) maintained for at least 16 weeks with a significant effect: 40.3% vs 9.5% respectively (p <0.0001), - the superiority of rituximab compared with MMF after 52 weeks of treatment, with also a significant effect, on the following hierarchical endpoints: cortisone sparing, number of relapses during treatment, time period until the first relapse, time period until complete lasting remission obtained, - the superiority of rituximab compared to MMF with regard to the variation in the DLQI (quality of life) score, although the difference observed is not clinically relevant (-2.87 points); 3 Unchanged tolerance profile, marked mainly by the reactions associated with the infusion and infections; In view of these 3 elements, the Committee considers that MABTHERA 100 mg and 500 mg (rituximab) now provides moderate clinical added value (CAV III) in the management of moderate to severe pemphigus vulgaris in adults, which comprises long-term corticosteroid therapy and short-term corticosteroid therapy combined with an immunosuppressant (mycophenolate mofetil, methotrexate or azathioprine).
	NICE	N/A
	CADTH	N/A
	IQWIG	N/A
	PBAC	N/A

CONCLUSION STATEMENT- Rituximab

Rituximab is a monoclonal antibody approved for first-line or second-line treatment of mild, moderate or severe PV and PF. It is a systemic treatment that has proven its superiority to MMF in the treatment of pemphigus and allowed cortisone sparing. It is given intravenously in the following regimen: 1g IV twice 2 weeks apart, then at month 6:

- Complete remission + severe pemphigus and/or high rate of anti-Dsg antibodies at month 3: 500mg-1g IV
- No complete remission: 2g IV once or 1g 2 weeks apart

An additional dose of 500mg IV is giver at months 12 and 18.

It is necessary to monitor a few parameters when treating pemphigus with Rituximab, notably: pregnancy status and screening for latent infections (HCV, HBV, HIV, tuberculosis) before initiation of treatment; during infusion, blood pressure and vital signs should be monitored. Surveillance is also necessary for infusion-related reactions, signs/symptoms of bowel obstruction/perforation, mucocutaneous skin reactions and signs/symptoms of progressive multifocal leukoencephalopathy.

In 2023, HAS has provided a favorable opinion on the maintenance of reimbursement in the treatment of moderate to severe PV in adults.

2.5 Other Therapeutic Options

2.5.1 Dapsone

Dapsone is a sulfone drug, classified as an antibiotic. The S2K updated EADV guidelines of 2020 recommend its use as a first-line treatment in mild pemphigus foliaceus. It is taken orally as a tablet. Starting dose is 50 to 100 mg/day, up to 1.5 mg/kg body weight according to clinical response. It is usually combined with topical corticosteroids. If disease control is achieved, it may be continued at a dose of 1.5 mg/kg body weight. Around 50% of patients who start with dapsone without oral corticosteroids will experience a relapse and subsequently require systemic corticosteroids. Moreover, a randomized controlled trial by Werth et al showed that dapsone does not have a cortico-sparing effect.[9] If disease control is not achieved, rituximab, prednisone, prednisolone, azathioprine, MMF or mycophenolate sodium may be started. There are no dose adjustments necessary in case of renal or hepatic impairment.

It is important to assess the presence of sulfamide allergy, glucose-6-phosphate-dehydrogenase deficiency, anemia or methemoglobinemia before starting the treatment. Indeed, significant adverse effects include hemolysis and methemoglobinemia, described in 1 to 10% of cases. Hepatic injury is also described, ranging from mild increased serum transaminases to fulminant hepatic failure.

Hyperbilirubinemia may occur more frequently in G6PD deficient patients. Hepatotoxicity is most often associated with signs of hypersensitivity, as part of drug rash with eosinophilia and systemic symptoms. Other serious cutaneous adverse reactions include Stevens-Johnson syndrome/toxic epidermal necrolysis, as well as acute generalized exanthematous pustulosis.

2.5.2 Immunoadsorption

Immunoadsorption is a selective apheresis method that aims to remove specific antibodies and immunes complexes from plasma. This technique is used in patients with severe and/or refractory pemphigus, as recommended by the S2K updated EADV guidelines of 2020 (in addition to rituximab, or if there is no response to rituximab, or in addition to an immunosuppressant if there is no possibility to use rituximab). A minimum of 2 cycles over 3–4 consecutive days is recommended, performed 4 weeks apart. In their international panel of experts of 2020, Murrell et al. also designate immunoadsorption as a first-line treatment option in emergency situations and as a second-line corticosteroid-sparing agent, where available.

Contraindications include severe cardiovascular diseases, hypersensitivity against components of the immunoadsorption column, treatment with ACEI, severe systemic infections, and extensive hemorrhagic diathesis.

A retrospective study by Dietze et al. showed immunoadsorption for the treatment of PV to be safe and effective.[40] Nine patients with, resistant to standard treatments, were treated either by immunoadsorption on two consecutive days every two weeks, or by immunoadsorption on four consecutive days every four weeks. Treatment duration was 17.5 months. Improvement was measured clinically and the reduction of autoantibodies in serum measured by IIF immunofluorescence and ELISA. Tolerability was evaluated using a visual analog scale. Retrospective analysis showed an 80% reduction of serum autoantibodies concentration after 6 months, with clinical improvement when added to classical immunosuppression. Immunoadsorption allowed for steroid tapering by 50% after 30 and 75% after 90 days. Total response rate was 89%, with 56% of patients in partial and 33% in complete remission. The bi-weekly treatment regimen was subjectively preferred by patients. The authors concluded that immunoadsorption is a safe, effective, and well tolerated treatment for PV, especially when performed every two weeks.

Section 3.0 Key Recommendations Synthesis

Pemphigus is group of rare, autoimmune, life-threatening mucocutaneous blistering disorders. It is characterized by acantholysis on histology, due to the binding of circulating IgG to intercellular adhesion molecules, resulting in the formation of intraepithelial blisters in mucous membranes and skin. Patients develop mucosal and skin erosions, flaccid bullae, or pustules. Significant morbidity and mortality are associated with pemphigus, its complications, and its treatments. There are four major types of pemphigus: PV, the most common, PF, IgA pemphigus and paraneoplastic pemphigus. These different types are distinguished by their clinical features, associated autoantigens, and laboratory findings. Pemphigus diagnosis is based on the presence of consistent history, clinical, histologic, and direct immunofluorescence (DIF) findings, as well as the detection of circulating IgG and IgA autoantibodies against cell surface antigens in serum. The following diagnostic tests are recommended:

- A lesional skin or mucosal biopsy for routine hematoxylin and eosin (H&E) staining
- A perilesional skin or mucosal biopsy for DIF
- Serum collection for detection of autoantibodies by ELISA and/or indirect immunofluorescence (IIF)
- Impact of disease burden on quality of life.

Therapeutic guidelines have recently emerged, notably by the EADV.

- Systemic **glucocorticoids** and **rituximab** are the mainstays of therapy for PV and PF and are usually highly effective for obtaining control of disease.
- Other immunomodulatory agents, such as **azathioprine** and **MMF**, are commonly prescribed in conjunction with systemic glucocorticoids in order to minimize the risk for adverse effects of long-term, high-dose glucocorticoid therapy.
- **IVIG**, **immunoadsorption** and **cyclophosphamide** are typically reserved for patients with refractory disease.
- Topical corticosteroids are used in adjunction to systemic treatments or for mild disease.
- Intralesional injections of corticosteroids (triamcinolone acetonide) may be considered for isolated lesions of oral mucosa, lips, and skin.
- Additional therapies, such as baths containing antiseptics, covering of erosive lesions with low adhesive wound dressings or local emollients and

compresses, analgesics, anesthetic gels, proper dental care, and nutritional management are recommended when appropriate.

Section 4.0 Conclusion

The recommendations provided in this report are intended to assist in the management of pemphigus. These recommendations should be used to support and not supplant decisions in individual patient management.

Section 5.0 References

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Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

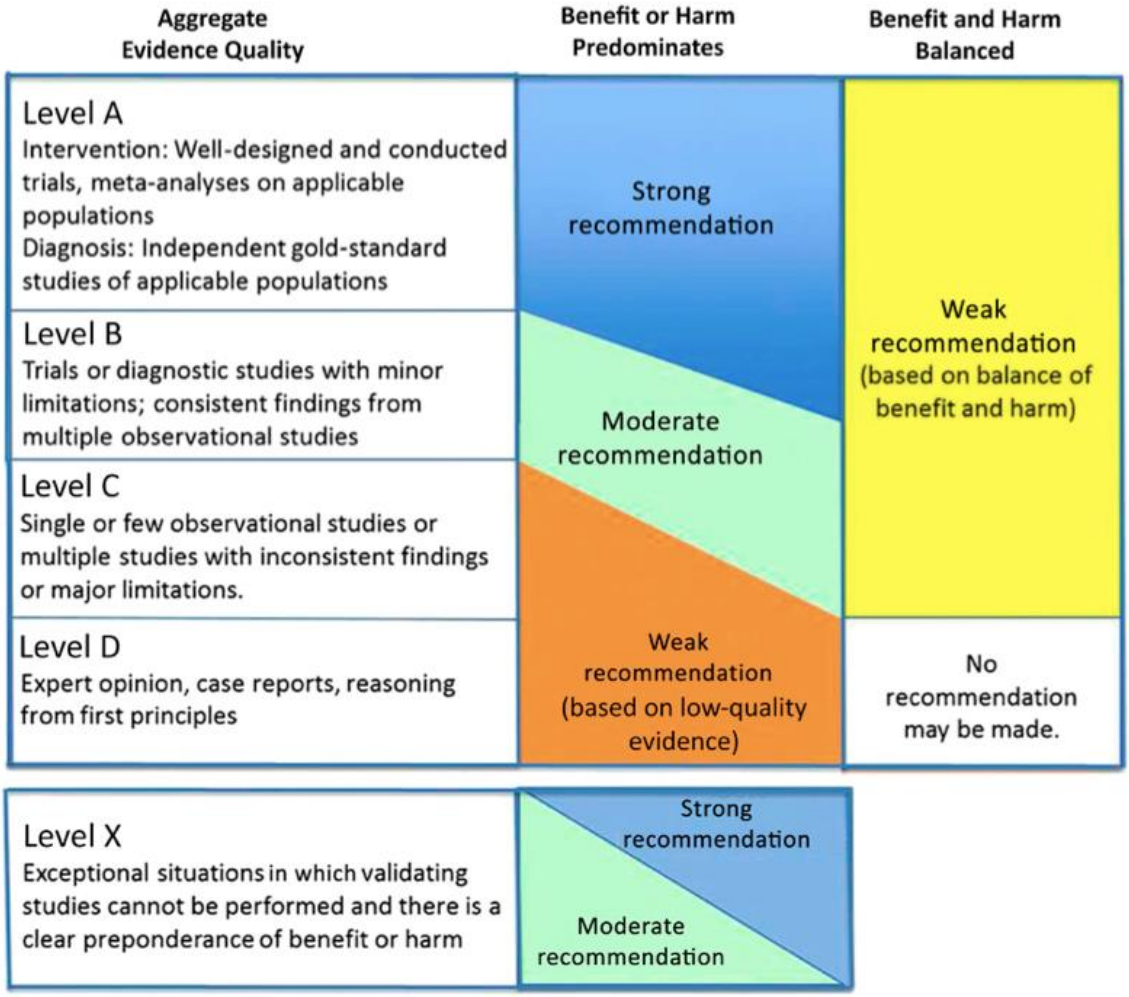
Some covered drugs may have additional requirements, rules, or limits on coverage. These requirements and limits may include:

Prescribing edits Tools	Description
AGE (Age):	Coverage may depend on patient age
CU (Concurrent Use):	Coverage may depend upon concurrent use of another drug
G (Gender):	Coverage may depend on patient gender
MD (Physician Specialty):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limits):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another drug
EU (Emergency Use only):	This drug status on Formulary is only for emergency use
PE (Protocol Edit):	Use of drug is dependent on protocol combination, doses and sequence of therapy

Appendix B. PubMed Search Methodology Terms

Query	Filters	Search Details	Results
(((((((((benign familial pemphigus[MeSH Terms]) OR (Benign Familial Pemphigus[Title/Abstract])) OR (Familial Pemphigus, Benign[Title/Abstract])) OR (Chronic Benign Familial Pemphigus[Title/Abstract])) OR (Benign Chronic Pemphigus[Title/Abstract])) OR (Familial Benign Chronic Pemphigus[Title/Abstract])) OR (Hailey-Hailey Disease[Title/Abstract])) OR (Hailey Hailey Disease[Title/Abstract])) OR (Familial pemphigus vulgaris[Title/Abstract])) OR (Endemic pemphigus foliaceus[Title/Abstract])	In the last 5 years	("pemphigus, benign familial"[MeSH Terms] OR "benign familial pemphigus"[Title/Abstract] OR (("familialities"[All Fields] OR "familiality"[All Fields] OR "familially"[All Fields] OR "familials"[All Fields] OR "familie"[All Fields] OR "family"[MeSH Terms] OR "family"[All Fields] OR "Familial"[All Fields] OR "families"[All Fields] OR "family s"[All Fields] OR "familys"[All Fields]) AND "pemphigus benign"[Title/Abstract]) OR "chronic benign familial pemphigus"[Title/Abstract] OR "benign chronic pemphigus"[Title/Abstract] OR "familial benign chronic pemphigus"[Title/Abstract] OR "hailey hailey disease"[Title/Abstract] OR "hailey hailey disease"[Title/Abstract] OR "familial pemphigus vulgaris"[Title/Abstract] OR "endemic pemphigus foliaceus"[Title/Abstract]) AND (y_5[Filter])	199

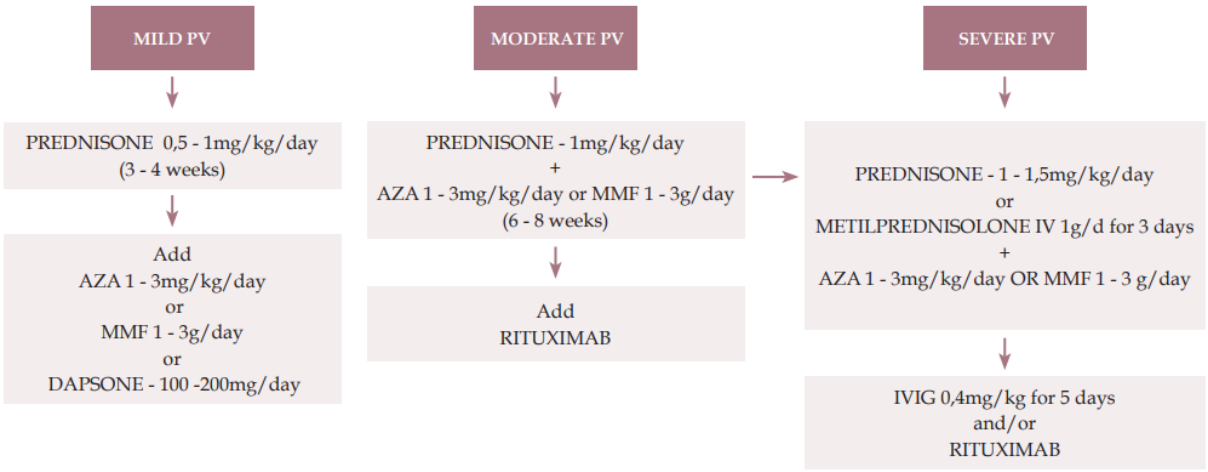
Appendix C. Level of Evidence



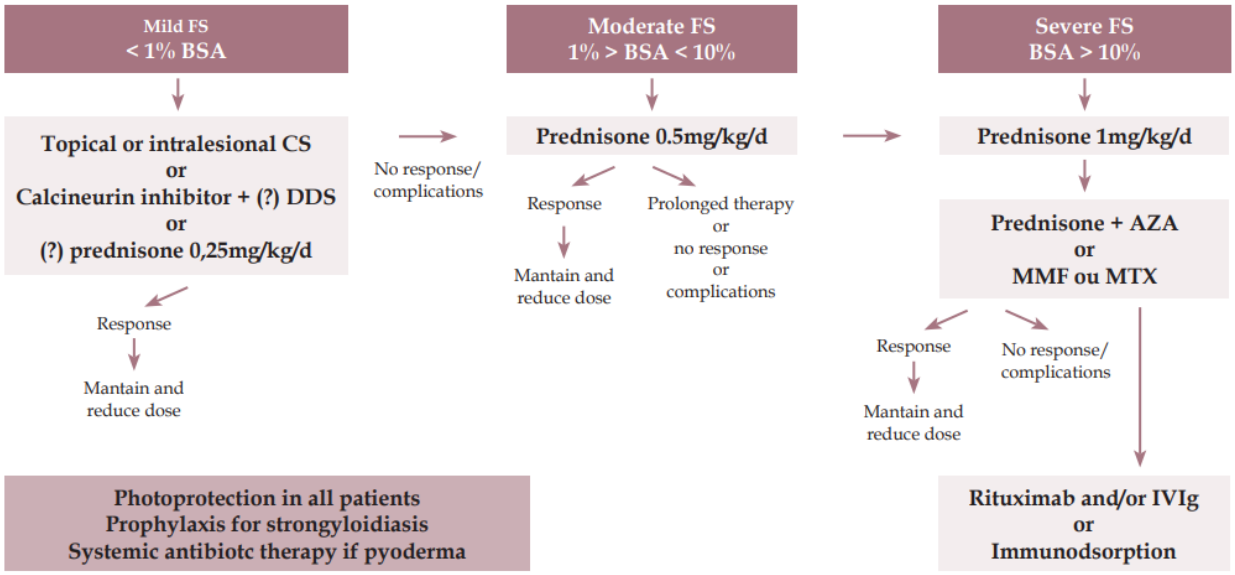
Statement	Definition	Implication
Strong recommendation	A particular action is favored because anticipated benefits clearly exceed harms (or vice versa), and quality of evidence is excellent or unobtainable.	Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.
Moderate recommendation	A particular action is favored because anticipated benefits clearly exceed harms (or vice versa), and the quality of evidence is good but not excellent (or is unobtainable).	Clinicians would be prudent to follow a moderate recommendation but should remain alert to new information and sensitive to patient preferences.
Weak recommendation (based on low-quality evidence)	A particular action is favored because anticipated benefits clearly exceed harms (or vice versa), but the quality of evidence is weak.	Clinicians would be prudent to follow a weak recommendation but should remain alert to new information and sensitive to patient preferences.
Weak recommendation (based on balance of benefits and harms)	A weak recommendation is provided when the aggregate database shows evidence of both benefit and harm that appears to be similar in magnitude for any available courses of action.	Clinicians should consider the options in their decision-making, but patient preference may have a substantial role.

Appendix D. Treatment Algorithm

Treatment algorithm for pemphigus vulgaris (retrieved from the Brazilian Society of Dermatology 2019 guideline)



Treatment algorithm for pemphigus foliaceus (retrieved from the Brazilian Society of Dermatology 2019 guideline)



FS – fogo selvagem; BSA – body surface area (1% means the sum of injured areas corresponding to the palm area); CS – corticosteroid; DDS – diamino-diphenil-sulfone or dapsone; AZA – azathioprine; MMF – mycophenolate mofetil; MTX – methotrexate; IVIg – intravenous immunoglobulin.