Guideline

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S2k guidelines for the treatment of pemphigus vulgaris/foliaceus and bullous pemphigoid: 2019 update

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Introduction

The present S2K guidelines are an update of the most recent edition of the German guidelines from 2015 [1, 2]. The complete guidelines (including methodology) are available at www.awmf.org. As this is an update, some sections from the previous version have been adopted without any changes.

In the "diagnosis" section, the present revision contains only one significant change. Apart from spironolactone, phenothiazines with aliphatic side chains and loop diuretics,

it is now also recommended to inquire whether patients with bullous pemphigoid take dipeptidyl peptidase 4 (DPP-4) inhibitors (gliptins). Consequently, the chapter "Possible triggers of bullous pemphigoid" now contains the recommendation to switch patients to other antidiabetic agents instead of DPP 4 inhibitors. The present article focuses on the comprehensive changes that have been made in the guidelines' "treatment" section. The most important changes include:

- Clinical classification of pemphigus vulgaris/foliaceus based on severity: 1) localized disease, 2) mild disease and 3) moderate-to-severe disease.
- Specific treatment recommendations based on clinical severity. For mild pemphigus foliaceus, the recommendation to treat patients with dapsone in combination with corticosteroids is now stronger than before ("is recommended" instead of "may be recommended"). For initial treatment of moderate-to-severe pemphigus vulgaris/foliaceus, recommended treatment options now include rituximab (anti-CD20 antibody) in combination with corticosteroids (in the 2015 version, this immunosuppressant was recommended only for treatment-resistant disease).
- For systemic maintenance therapy of pemphigus vulgaris/foliaceus, a distinction is now made between treatment with and without anti-CD20 antibodies. While the recommendations for maintenance therapy without anti-CD20 antibodies has remained unchanged, four new consensus-based recommendations have been introduced for maintenance therapy with anti-CD20 antibodies.
- With respect to induction therapy in patients with bullous pemphigoid, the strengths of recommendation, the various therapeutic agents as well as the order in which they are recommended has remained unchanged. However, there are now two new recommendations regarding the use of rituximab for systemic maintenance therapy.
- For both bullous pemphigoid and pemphigus vulgaris/foliaceus, there are now two new recommendations aimed at patient information and patient support groups.

Methods

The methodology of this update of the most recent version of these S2k guidelines (2015) follows the specifications issued by the Association of the Scientific Medical Societies in Germany (Arbeitsgemeinschaft Wissenschaftlicher Medizinischer Fachgesellschaften, AWMF) [3]. The level of development remains unchanged (S2k). Using a structured nominal group process (consensus conferences), the recommendations

Table 1 Gradation of the strength of recommendations – wording, symbols and interpretation (modified after Kaminski-Hartenthaler et al. 2014).

Strength of recommendations	Wording	Symbol	Interpretation
Strong recommendation *for* a measure	"is recommended" or "... shall ..."	↑↑	We believe that all or nearly all individuals appropriately informed would make this decision. Clinicians require less time with the patient for decision making. In most clinical situations, the recommendation can be adopted as a generally accepted approach.
Weak recommendation *for* a measure	"may be recommended" or "... should ..."	↑	We believe that most individuals appropriately informed would make this decision, but there is a substantial percentage of individuals who would not. Clinicians and other health care providers will need to devote more time to ensure that the choice of the intervention along with the consequences potentially associated therewith reflects the values and preferences of the individual patient. Decision-making processes in the health care system require thorough discussions and the involvement of various stakeholders.
No recommendation with respect to a measure	"... may be considered ..."	o	For specific reasons, no recommendation in favor or against a specific intervention can be made at present (e.g., lack of evidence available, unclear or unfavorable risk-benefit ratio, and others)
Recommendation *against* a measure	"is not recommended" "... shall not ..."	↓	We believe that all or nearly all individuals appropriately informed would make this decision.

contained in these guidelines were developed by a representative interdisciplinary group of experts.

The present update is valid until Dec 31, 2022.

This article is a short version of the updated guidelines. The long version (see AWMF guideline registry) includes additional information. This includes information on the group of experts, on how to use these guidelines, on target audience and objectives, financial support, implementation and circulation, as well as on the handling of conflicts of interests (www.awmf.org).

Uniform wording was used in an effort to standardize the guideline recommendations (Table 1).

Treatment of pemphigus vulgaris (PV)/ foliaceus (PF)

Severity-based treatment

General treatment recommendation for pemphigus vulgaris/foliaceus

Recommendation	Strength	Agreement
For the treatment of pemphigus vulgaris/foliaceus, systemic immunosuppressive/immunomodulatory treatment in combination with topical antiseptic agents and, if required, topical corticosteroids is recommended.	↑↑	Strong consensus (100 %)*
Only in patients with localized disease and mild disease severity may monotherapy with topical corticosteroids or, alternatively, with topical calcineurin inhibitors** be considered.	o	Strong consensus (100 %)*

*No new vote, as this recommendation was adopted from the previous guideline version; **off-label use.

Classification of pemphigus vulgaris/foliaceus based on severity

(1) Localized pemphigus vulgaris/foliaceus
- ≤ 1 cm^2 of mucous membranes affected (only in pemphigus vulgaris)
- ≤ 1 % of normal skin affected
- no pain, no significant impairment of quality of life

(2) Mild pemphigus vulgaris/foliaceus
- PDAI score ≤ 15

(3) Moderate-to-severe pemphigus vulgaris/foliaceus
- PDAI score > 15
- severe pain and significant impairment of quality of life

The differentiation between mild and moderate-to-severe pemphigus is based on the cutoff value between the first and the second quartile of the PDAI score in a large prospective multicenter study of 96 newly diagnosed PV und PF patients [4].

Systemic induction therapy

Systemic induction therapy in patients with mild pemphigus vulgaris/foliaceus

Recommendation	Strength	Agreement
For initial treatment of pemphigus vulgaris/foliaceus, systemic corticosteroid therapy is recommended at a dose of 1.0–1.5 mg/kg/day of prednisolone equivalent, depending on disease severity, patient age, and possible comorbidities.	↑↑	Strong consensus (100 %)**
As an alternative to daily oral administration of corticosteroids, IV pulse therapy may be recommended (e.g., dexamethasone 100 mg/day [or 500–1,000 mg/day of prednisolone equivalent] on three consecutive days), initially at 3–4-week intervals, subsequently every 6–8 weeks.	↑	Strong consensus (100 %) *Abstention:* patient representative
If the initial dose proves to be inadequate to control disease activity* after 1–2 weeks, a higher corticosteroid dose (usually up to 2 mg/kg/day of prednisolone equivalent) may be recommended.	↑	Consensus (90 %)**
Subsequently, it is recommended to gradually taper the initial corticosteroid dose based on clinical presentation (see maintenance therapy).	↑↑	Consensus (90 %)**
It is recommended to combine corticosteroids with an immunosuppressive agent (see recommended regimens for induction therapy). - Azathioprine (2.0–2.5 mg/kg/day; normal TPMT levels required) - Mycophenolate mofetil*** (2 g/day) - Mycophenolic acid*** (1,440 mg/day) - Dapsone (up to 1.5 mg/kg/day; only for pemphigus foliaceus)	↑↑	Strong consensus (100 %) *Abstention:* patient representative

*Control of disease activity is defined as absence of new lesions concurrent with improvement of existing lesions; **no new vote, as this recommendation was adopted from the previous guideline version; ***off-label use.

Besides our own experience, the recommendation for dapsone is based on a case series of nine patients and a dozen individual case reports of patients with pemphigus foliaceus [5–7]. In the aforementioned case series, five patients showed complete remission after 2 weeks [8]. In the various case reports, approximately 70 % of patients received dapsone monotherapy, which resulted in a good clinical response and/or complete remission [5–7].

Systemic induction therapy in patients with moderate-or-severe pemphigus vulgkaris/foliaceus

Recommendation	Strength	Agreement
For initial treatment of moderate-to-severe pemphigus vulgaris/foliaceus, systemic therapy, it is recommended to use: ▸ Anti-CD20 antibodies (e.g., rituximab *** 1 g given on day 0 and on day 14–21) in combination with 1.0 mg/kg/day of prednisolone equivalent *or* ▸ 1.0–1.5 mg/kg/day of prednisolone equivalent in combination with – Azathioprine (2.0–2.5 mg/kg/day; normal TPMT levels required) – Mycophenolate mofetil** (2 g/day) – Mycophenolic acid** (1,440 mg/day)	↑↑	Strong consensus (100 %) *Abstention:* patient representative
A combination of anti-CD20 antibodies and up to 1.0 mg/kg/day of prednisolone equivalent in combination with azathioprine (2.0–2.5 mg/kg/day; normal TPMT levels required), mycophenolate mofetil** (2 g/day), or mycophenolic acid** (1,440 mg/day) may be considered.	0	Strong consensus (100 %) *Abstention:* patient representative
As an alternative to daily oral administration of corticosteroids, IV pulse therapy is recommended (usually dexamethasone 100 mg [or 500–1,000 mg/day of prednisolone equivalent] on three consecutive days), initially at 3–4-week intervals, subsequently every 6–8 weeks.	↑↑	Strong consensus (100 %) *Abstention:* patient representative
If the initial dose proves to be inadequate to control disease activity* after 1–2 weeks, a higher corticosteroid dose (usually up to 2 mg/kg/day of prednisolone equivalent) may be recommended.	↑	Strong consensus (100 %) *Abstention:* patient representative
Subsequently, it is recommended to gradually taper the initial corticosteroid dose based on clinical presentation (see maintenance therapy).	↑↑	Strong consensus (100 %) *Abstention:* patient representative
*Control of disease activity is defined as absence of new lesions concurrent with improvement of existing lesions; **off-label use; ***off-label for pemphigus foliaceus.		

Treatment alternatives

Recommendation	Strength	Agreement
The following alternative may also be considered: ▸ Combination of systemic corticosteroids (1.0–2.0 mg/kg/day) + cyclophosphamide (1–2 mg/kg/day)	0	Consensus (77 %) *Abstention:* patient representative
The following alternative may also be considered: ▸ Combination of systemic corticosteroids (1.0–2.0 mg/kg/day) + dapsone* (up to 1.5 mg/kg/day; normal levels of glucose-6-phosphate dehydrogenase required)	0	Majority consensus (62 %) *Abstention:* patient representative

The following alternative may also be considered: ▸ Combination of systemic corticosteroids (1.0–2.0 mg/kg/day) + MTX** (10–25 mg once a week PO or SQ; for children 10–20 mg/m² body surface area per week PO or SQ)	o	Strong consensus (100 %) *Abstention:* patient representative
The following therapies may be recommended for treatment-resistant and particularly severe disease: ▸ Immunoapheresis (2–3 times the plasma volume per treatment on 3–4 consecutive days [corresponds to one cycle], every 3–4 weeks)The following therapy may be recommended for treatment-resistant disease: ▸ Intravenous immunoglobulins** (2 g/kg per cycle) at 4–6-week intervals.	↑	Strong consensus (100 %) *Abstention:* patient representative
▸ As immunoapheresis is more specific and does not require plasma protein replacement, it shall be preferred to plasmapheresis.	↑↑	Strong consensus (100 %) *Abstention:* patient representative

*for patients with pemphigus foliaceus in particular; **off-label use.

The intensity of treatment for pemphigus vulgaris/foliaceus is generally guided by disease severity and acuity and on treatment-relevant comorbidities. The objective of induction therapy is control of disease activity, defined as the absence of new lesions concurrent with improvement of existing lesions. Switching to maintenance therapy requires that no new lesions appear within a two-week consolidation phase and that approximately 80 % of initial lesions have healed.

Rituximab, a monoclonal anti-CD20 antibody, causes depletion of CD20-positive B cells from the peripheral blood; the effect lasts for approximately 6–12 months. In 2001, rituximab was introduced in the treatment of paraneoplastic pemphigus. Only a short time thereafter, the agent was first employed in the treatment of patients with recalcitrant pemphigus vulgaris/foliaceus [9–11]. Subsequently, various case series using different treatment protocols and adjuvant therapies reported on the clinical effectiveness of rituximab in patients with severe pemphigus [12–18]. In two meta-analyses of more than 500 pemphigus patients treated with rituximab, complete remission was achieved in 80–90 % of patients [19, 20].

A recent controlled prospective trial of 90 patients with new-onset pemphigus vulgaris/foliaceus provided conclusive evidence for the superiority of rituximab (two initial doses of 1 g, followed by 0.5 g after 12 and 18 months) in combination with short-term use of prednisolone (0.5–1.0 mg/kg/day for 3–6 months) over treatment with prednisolone alone (1.0–1.5 mg/kg/day for 12–18 months) [21]. After two years, 89 % of patients in the rituximab group were in complete remission with no further treatment required, compared to only 34 % in the prednisolone group ($p < 0.0001$). Moreover, the cumulative prednisolone dose was three times lower and the number of severe adverse events twice lower in the rituximab arm than in the prednisolone arm ($p < 0.0001$ and $p = 0.0084$, respectively) [21].

Severe adverse events, primarily infections, were observed in 4–10 % of patients treated with rituximab. The mortality rate was between 1.3 % and 1.9 % [14, 17, 19, 20, 22]. In nearly all cases, rituximab was combined with systemic corticosteroids and/or other immunosuppressive agents. To date, there has been no reported case of progressive multifocal leukoencephalopathy in pemphigus patients; this condition is known to be associated with rituximab therapy, particularly in individuals with lymphoproliferative disorders [23]. Using data from approximately 350,000 patients with rheumatoid arthritis, it has been calculated that the risk of developing progressive multifocal leukoencephalopathy following rituximab therapy is 2.5/100,000 cases [24].

Based on the data published by Joly et al. [21], rituximab was approved for the treatment of moderate-to-severe pemphigus vulgaris by the FDA in 2018 and by the EMA in 2019. A number of international experts have recommended the use of rituximab as first-line treatment for patients with moderate-to-severe pemphigus [25, 26].

Clinical studies have shown that immunosuppressive agents such as azathioprine, mycophenolate mofetil, mycophenolic acid, methotrexate, and cyclophosphamide have a steroid-sparing effect in the treatment of patients with pemphigus vulgaris/foliaceus [27–35].

A recent retrospective analysis revealed that the initial prednisolone dose (≤ 0.5 mg/kg or ≥ 1.0 mg/kg per day) had no effect on the rate of complete clinical remission off therapy. The median follow-up period in this study was 77 ± 64 months [36].

In a controlled prospective trial from Japan that investigated the use of high-dose intravenous immunoglobulins (IVIGs) in 61 pemphigus patients, a dose of 2 g/kg was superior to 1 g/kg IVIGs and to placebo [37]. In an unusual study design, clinical efficacy was evaluated based on the period of time during which patients were able to "escape" the treatment protocol.

While there are still no controlled prospective trials on the effects and efficacy of immunoapheresis in patients with

pemphigus, there is some evidence from monocenter studies that adjuvant immunoadsorption therapy may result in a rapid decrease in circulating anti-Dsg antibodies and may thus be effective in severe and/or recalcitrant cases [38–41].

There is no trial data on the use of topical corticosteroids in the treatment of pemphigus vulgaris/foliaceus; calcineurin inhibitors may be considered for topical treatment of oral/genital erosions (tacrolimus 0.1 %). In order to avoid bacterial superinfection, antibacterial/antiseptic treatment is recommended (including fusidic acid, triclosan 1 %, octenidine).

All published randomized controlled trials on the treatment of pemhigus have been summarized in a recent review [42].

Supportive measures

Recommendation	Strength	Agreement
Supportive measures are recommended, including stage-adjusted wound management, antiseptic treatment, atraumatic wound dressings, analgesic mouthwash (in case of oral involvement), adequate analgesia, dietary supplementation (in case of painful erosions of the oral cavity and/or hypopharynx) and regular dental check-ups.	↑↑	Strong consensus (100 %)*

*No new vote, as this recommendation was adopted from the previous guideline version.

Systemic maintenance therapy

Systemic maintenance therapy for pemphigus vulgaris/foliaceus without anti-CD20 antibodies

Recommendation	Strength	Agreement
As soon as control of disease activity* is achieved, it is recommended to taper the systemic corticosteroid dose by approximately 25 % every 7–14 days. Below 20 mg/day of prednisolone equivalent, it is recommended to slow the taper (dose reduction every 2–4 weeks). For long-term treatment, a corticosteroid dose below physiological levels (7.5 mg/day of prednisolone equivalent) is recommended. Subsequently, an even slower taper is recommended, depending on disease activity.	↑↑	Strong consensus (100 %)***
In case of relapse**, it may be recommended to return to the systemic corticosteroid dose given two reduction intervals prior, and to resume the taper after 14 days of disease control.	↑	Strong consensus (100 %)***
If there is no control of disease activity, it may be recommended to return to the initial systemic corticosteroid dose. If required, switching of the adjuvant immunosuppressive agent hitherto used may be recommended.	↑	Strong consensus (100 %)***
Following discontinuation of systemic corticosteroid treatment, it may be recommended to reduce the adjuvant immunosuppressive agent until reaching the required maintenance dose. After long-term complete remission, it is recommended to completely discontinue the adjuvant immunosuppressive agent.	↑	Strong consensus (100 %)***

*Control of disease activity is defined as the absence of new lesions concurrent with improvement of existing lesions; **relapse: > 3 new lesions (blisters or erosions) per month that do not heal spontaneously within one week; or progression of existing lesions in patients who previously achieved control of disease activity; ***no new vote, as this recommendation was adopted from the previous guideline version.

Systemic maintenance therapy for pemphigus vulgaris/foliaceus with anti-CD20 antibodies

Recommendation	Strength	Agreement
In case of complete remission after 6 months, it is recommended to taper and discontinue the corticosteroid in the following weeks.	↑↑	Strong consensus (100 %)
In case of relapse* after complete remission, reintroduction of anti-CD20 antibody therapy (e.g., rituximab 1 g), possibly in combination with systemic corticosteroids, is recommended.	↑↑	Strong consensus (100 %)

If there is a treatment response** but no complete remission after 6 months, reintroduction of anti-CD20 antibody therapy (e.g., rituximab 1 g) is recommended.	↑↑	Consensus (92 %) *Abstention:* 1 expert
Maintenance therapy with anti-CD20 antibodies (500–1,000 mg) after 6 and 12 months may be considered.	0	Consensus (92 %) *Abstention:* 1 expert

*Relapse: > 3 new lesions (blisters or erosions) per month that do not heal spontaneously within one week; or progression of existing lesions in patients who previously achieved control of disease activity; **treatment response: reduction of initial PDAI score by > 50 %.

In the aforementioned controlled prospective trial of 90 patients with new-onset PV and PF, all patients again received rituximab (500 mg) after 12 and 18 months, following an initial dose of 1 g given twice. The 500 mg dose was chosen because the sponsor of the trial only provided a total of 3 g of rituximab per patient, and two doses were scheduled to be administered after the initial dose [21]. Smaller studies and case series have shown that a rituximab dose of 500 mg is likewise clinically effective [43, 44]. Thus, it is currently impossible to issue a clear recommendation as to the rituximab dose to be administered for repeat treatment. In the controlled prospective trial conducted by Joly et al., eight of eleven relapses in the rituximab group occurred between months 6 and 12 [21]. It is therefore recommended that patients undergo maintenance therapy after 6 and 12 months. Given the lack of consensus in the literature, it remains up to each individual center/physician whether to initiate hydrocortisone replacement therapy or perform an ACTH stimulation test (Synacthen test) prior to complete discontinuation of long-term systemic corticosteroid treatment (the decision should likely be made in cooperation with endocrinologists).

Patient information

Patient information

Recommendation	Strength	Agreement
It is recommended to inform patients about their disease, both orally and in writing.*	↑↑	Strong consensus (100 %)
It is recommended to make patients aware of support groups, e.g., *Pemphigus und Pemphigoid Selbsthilfe e.V.* (www.pemphigus-pemphigoid-selbsthilfe.de) and/or *International Pemphigus and Pemphigoid Foundation* (www.pemphigus.org).	↑↑	Strong consensus (100 %)

*A patient information about bullous pemphigoid and pemphigus vulgaris/foliaceus can be found in the appendix of the long guideline version (see AWMF guideline registry).

Treatment of bullous pemphigoid (BP)

Severity-based treatment

Severity-based treatment of bullous pemphigoid

Recommendation	Strength	Agreement
For *mild bullous pemphigoid,* topical treatment with clobetasol propionate is recommended.	↑↑	Strong consensus (100 %)*
For *moderate bullous pemphigoid,* topical treatment with clobetasol propionate is recommended; combination with systemic treatment may be recommended, if required.	↑↑/↑	Consensus (89 %)*
For *severe bullous pemphigoid,* topical treatment with clobetasol propionate is recommended, usually in combination with systemic treatment.	↑↑	Strong consensus (100 %)*

*No new vote, as this recommendation was adopted from the previous guideline version.

There is no generally accepted classification of disease severity for bullous pemphigoid; the classification presented herein (mild, moderate, and severe disease) reflects the consensus of the guideline group (Table 2).

Studies have shown topical treatment with clobetasol at a daily dose of 40 g [45] as well as of 10–30 g to be equally effective as systemic prednisolone in the treatment of localized

Table 2 Classification of disease severity.

mild	< 10 % affected body surface area
moderate	10–30 % affected body surface area
severe	> 30 % affected body surface area

and moderate bullous pemphigoid, while causing fewer systemic adverse effects.

A substantial limitation to topical treatment is its practicability; in older bullous pemphigoid patients, twice-daily topical application on large areas of skin is usually not feasible.

With respect to topical tacrolimus as a substitute for topical corticosteroids, there have only been individual case reports, which presently do not warrant a treatment recommendation.

In order to avoid bacterial superinfection of erosions, topical antiseptic treatment is recommended, including chlorhexidine, triclosan 1 % and octenidine; atraumatic wound dressings should be used for large wounds. It is recommended to puncture large or otherwise bothersome blisters in a sterile manner. Leaving the blister roof intact provides additional protection from infection.

Systemic induction therapy

Induction therapy in patients with bullous pemphigoid

Recommendation	Strength	Agreement
For systemic treatment, it is recommended to start patients on a dose of 0.5 mg/kg/day of prednisolone equivalent (possibly lower), potentially in combination with adjuvant immunosuppressive/immunomodulatory therapy.	↑↑	Strong consensus (100 %)*
Alternatively, the following drugs may be recommended either as monotherapy or as adjuvant treatment in combination with corticosteroids: (strictly alphabetical order): ▸ Azathioprine: 2–2.5 mg/kg/day PO (normal TPMT activity required) (only as adjuvant therapy) ▸ Dapsone: up to 1.5 mg/kg/day PO (as adjuvant or systemic monotherapy) ▸ Doxycycline**: 200 mg/day PO as monotherapy or in combination with nicotinamide** (up to 2 g/day) PO (as adjuvant or sole systemic therapy) ▸ Methotrexate**: (up to 20 mg every week; in children 10–20 mg/m² every week) PO or SQ (as adjuvant or systemic monotherapy) ▸ Mycophenolate mofetil**: (2 g/day; in children 15–30 mg/kg/day; maximum daily dose: 2 g) or mycophenolic acid**: (1.44 g/day) PO (only as adjuvant therapy)	↑	Strong consensus on the choice of therapeutic options (100 %) Majority consensus regarding alphabetic order (54 %) (the other participants advocated for giving preference to dapsone and doxycycline or abstained from voting) *Abstentions:* 3 experts
For patients who do not achieve clinical remission while on the recommended induction therapies, the following therapeutic options a) May be recommended: ▸ High-dose intravenous immunoglobulins** (2 g/kg per cycle; 4–6 weeks intervals) ▸ Immunoadsorption/plasmapheresis ▸ Anti-CD20 antibodies (e.g., rituximab 1 g given twice, on day 0 and on day 14–21)	↑	Strong consensus (100 %)*
b) May be considered: ▸ Cyclophosphamide (2 mg/kg/day PO or 15–20 mg/kg IV at 4-week intervals) ▸ Anti-IgE monoclonal antibodies**.	0	Strong consensus (100 %)*

*No new vote, as this recommendation was adopted from the previous guideline version; **off-label use.

Unlike pemphigus, initial doses of > 1.0 mg/kg/day of prednisolone equivalent show little additional benefit for patients with bullous pemphigoid.

There is only limited evidence for the effectiveness of the various therapies used in the treatment of bullous pemphigoid. In the Cochrane review by Kirtschig et al., there was no difference in terms of disease control between azathioprine in combination with prednisone and prednisone alone (one study), between prednisolone in combination with azathioprine and prednisolone in combination with plasmapheresis (one study), between prednisolone in combination with mycophenolate mofetil or in combination with azathioprine (one study), and between tetracycline in combination with nicotinamide and prednisolone (one study) [46]. One study that was published after the aforementioned Cochrane review showed non-inferiority of doxycycline to prednisolone after 6 weeks (end point: number of patients with fewer than three blisters). However, the acceptable predefined margin of non-inferiority was very large (37 %). With respect to severe adverse events after 52 weeks, doxycycline showed a relevant benefit over prednisolone [47]. Another study that compared dapsone (1.5 mg/kg/day) versus azathioprine (1.5–2.5 mg/kg/day), each in combination with methylprednisolone (0.5 mg/kg/day), defined the time until complete tapering of methylprednisolone as primary end point and the overall methylprednisolone dose required as secondary end point [48]. The primary end point was not reached, as only very few patients (5 on azathioprine and 3 on dapsone) achieved this goal. The cumulative dose of methylprednisolone was lower in the dapsone group than in the azathioprine group ($p = 0.06$). There was no significant difference in the number of adverse events (18 in the azathioprine arm and 13 in the dapsone arm) including fatalities (3 in the azathioprine group and 1 in the dapsone group) [48].

Systemic maintenance therapy

Systemic maintenance therapy for bullous pemphigoid

Recommendation	Strength	Agreement
For patients on systemic corticosteroids who achieve disease control*, it is recommended to taper the systemic corticosteroid dose by approximately 25 % every 7–14 days. Below 20 mg/day of prednisolone equivalent, it is recommended to slow the taper (dose reduction every 2–4 weeks). For long-term treatment, a corticosteroid dose below physiological levels (7.5 mg/day of prednisolone equivalent) is recommended. Subsequently, an even slower taper is recommended, depending on disease activity.	↑↑	Strong consensus (100 %)***
In case of relapse**, it may be recommended to return to the systemic corticosteroid dose given two reduction intervals prior, and to resume the taper after 14 days of disease control.	↑	Strong consensus (100 %)***
If there is no control of disease activity during the systemic corticosteroid taper, return to the initial systemic corticosteroid dose may be recommended.	↑	Strong consensus (100 %)***
Alternatively, it may be recommended to add an adjuvant agent, or to switch the adjuvant agent hitherto used.	↑	Strong consensus (100 %)***
Systemic maintenance therapy for BP with anti-CD20 antibodies (rituximab): in case of complete remission after 3–6 months, it may be recommended to taper and discontinue the corticosteroid in the following weeks. In case of relapse after complete remission, reintroduction of anti-CD20 antibody therapy (e.g., rituximab 1 g), possibly in combination with systemic corticosteroids, may be recommended.	↑	Consensus (92 %) *Abstention:* 1 expert
If there is a treatment response**** but no complete remission after 6 months, reintroduction of anti-CD20 antibody therapy (e.g., rituximab 1 g) may be recommended.	↑	Consensus (92 %) *Abstention:* 1 expert

*Control of disease activity is defined as absence of new lesions concurrent with improvement of existing lesions; **relapse: > 3 new lesions per month (blisters, erosions, eczematous lesions, or urticarial papules/plaques) or one large (> 10 cm) lesion (eczematous lesion, urticarial papule/plaque) that do/does not heal spontaneously within one week; or progression of existing lesions or daily pruritus in patients who previously achieved control of disease activity; ***no new vote, as this recommendation was adopted from the previous guideline version; ****treatment response: reduction of the inital BPDAI >50 %.

Bullous pemphigoid frequently runs a chronic course. Patients should be clinically examined on a regular basis (initially at 14-day intervals and subsequently every 3–6 months, depending on clinical activity) until they achieve complete clinical remission or until treatment is discontinued.

The goals of maintenance therapy include control of disease activity, tapering of systemic corticosteroids and, if applicable, of adjuvant immunosuppressive agents as quickly as possible while avoiding relapses, as well as regular monitoring for treatment-related adverse effects (clinical presentation, lab tests).

Follow-up intervals should be guided by disease activity; initially every 14 days, followed by every 3–6 months for patients with low disease activity or remission.

Patient information

Patient information

Recommendation	Strength	Agreement
It is recommended to inform patients about their disease, both orally and in writing.*	↑↑	Strong consensus (100 %)
It is recommended to make patients aware of support groups, e.g., *Pemphigus und Pemphigoid Selbsthilfe e.V.* (www.pemphigus-pemphigoid-selbsthilfe.de) and/or *International Pemphigus and Pemphigoid Foundation* (www.pemphigus.org).	↑↑	Strong consensus (100 %)

*A patient information about bullous pemphigoid and pemphigus vulgaris/foliaceus can be found in the appendix of the long guideline version (see AWMF guideline registry).

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References

1 Eming R, Sticherling M, Hofmann SC et al. S2k guidelines for the treatment of pemphigus vulgaris/foliaceus and bullous pemphigoid. J Dtsch Dermatol Ges 2015; 13: 833–44.
2 Schmidt E, Goebeler M, Hertl M et al. S2k guideline for the diagnosis of pemphigus vulgaris/foliaceus and bullous pemphigoid. J Dtsch Dermatol Ges 2015; 13: 713–27.
3 Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF) – Ständige Komission Leitlinien. AWMF-Regelwerk „Leitlinien“. Available from http://www.awmf.org/leitlinien/awmf-regelwerk.html [Last accessed November 11, 2019].
4 Boulard C, Duvert Lehembre S, Picard-Dahan C et al. Calculation of cut-off values based on the Autoimmune Bullous Skin Disorder Intensity Score (ABSIS) and Pemphigus Disease Area Index (PDAI) pemphigus scoring systems for defining moderate, significant and extensive types of pemphigus. Br J Dermatol 2016; 175: 142–9.
5 Garcia-Melendez ME, Eichelmann K, Salas-Alanis JC et al. Pemphigus foliaceus in an 11-year-old mexican girl with response to oral dapsone. Case Rep Pediatr 2013; 2013: 291256.
6 Chatterjee M, Meru S, Vasudevan B et al. Pemphigus foliaceus masquerading as IgA pemphigus and responding to dapsone. Indian J Dermatol 2012; 57: 495–7.
7 Gurcan HM, Ahmed AR. Efficacy of dapsone in the treatment of pemphigus and pemphigoid: analysis of current data. Am J Clin Dermatol 2009; 10: 383–96.
8 Basset N, Guillot B, Michel B et al. Dapsone as initial treatment in superficial pemphigus. Report of nine cases. Arch Dermatol 1987; 123: 783–5.
9 Goebeler M, Herzog S, Brocker EB, Zillikens D. Rapid response of treatment-resistant pemphigus foliaceus to the anti-CD20 antibody rituximab. Br J Dermatol 2003; 149: 899–901.
10 Heizmann M, Itin P, Wernli M et al. Successful treatment of paraneoplastic pemphigus in follicular NHL with rituximab: report of a case and review of treatment for paraneoplastic pemphigus in NHL and CLL. Am J Hematol 2001; 66: 142–4.
11 Salopek TG, Logsetty S, Tredget EE. Anti-CD20 chimeric monoclonal antibody (rituximab) for the treatment of recalcitrant, life-threatening pemphigus vulgaris with implications in the pathogenesis of the disorder. J Am Acad Dermatol 2002; 47: 785–8.
12 Ahmed AR, Kaveri S, Spigelman Z. Long-term remissions in recalcitrant pemphigus vulgaris. N Engl J Med 2015; 373: 2693–4.
13 Ahmed AR, Spigelman Z, Cavacini LA, Posner MR. Treatment of pemphigus vulgaris with rituximab and intravenous immune globulin. N Engl J Med 2006; 355: 1772–9.
14 Colliou N, Picard D, Caillot F et al. Long-term remissions of severe pemphigus after rituximab therapy are associated with prolonged failure of desmoglein B cell response. Sci Transl Med 2013; 5: 175ra30.
15 Joly P, Mouquet H, Roujeau JC et al. A single cycle of rituximab for the treatment of severe pemphigus. N Engl J Med 2007; 357: 545–52.
16 Kasperkiewicz M, Shimanovich I, Ludwig RJ et al. Rituximab for treatment-refractory pemphigus and pemphigoid: a case series of 17 patients. J Am Acad Dermatol 2011; 65: 552–8.
17 Schmidt E, Goebeler M, Zillikens D. Rituximab in severe pemphigus. Ann N Y Acad Sci 2009; 1173: 683–91.
18 Schmidt E, Seitz CS, Benoit S et al. Rituximab in autoimmune bullous diseases: mixed responses and adverse effects. Br J Dermatol 2007; 156: 352–6.
19 Ahmed AR, Shetty S. A comprehensive analysis of treatment outcomes in patients with pemphigus vulgaris treated with rituximab. Autoimmunity Reviews 2015; 14: 323–31.

20 Wang HH, Liu CW, Li YC, Huang YC. Efficacy of rituximab for pemphigus: a systematic review and meta-analysis of different regimens. Acta Derm Venereol 2015; 95: 928–32.
21 Joly P, Maho-Vaillant M, Prost-Squarcioni C et al. First-line rituximab combined with short-term prednisone versus prednisone alone for the treatment of pemphigus (Ritux 3): a prospective, multicentre, parallel-group, open-label randomised trial. Lancet 2017; 389: 2031–40.
22 Kasperkiewicz M, Ellebrecht CT, Takahashi H et al. Pemphigus. Nat Rev Dis Primers 2017; 3: 17026.
23 Carson KR, Evens AM, Richey EA et al. Progressive multifocal leukoencephalopathy after rituximab therapy in HIV-negative patients: a report of 57 cases from the Research on Adverse Drug Events and Reports project. Blood 2009; 113: 4834–40.
24 Berger JR, Malik V, Lacey S et al. Progressive multifocal leukoencephalopathy in rituximab-treated rheumatic diseases: a rare event. J Neurovirol 2018; 24: 323–31.
25 Murrell DF, Pena S, Joly P et al. Diagnosis and management of pemphigus: Recommendations of an international panel of experts. J Am Acad Dermatol 2020; 82: 575–85 e1.
26 Schmidt E. Rituximab as first-line treatment of pemphigus. Lancet 2017; 389: 1956–8.
27 Beissert S, Werfel T, Frieling U et al. A comparison of oral methylprednisolone plus azathioprine or mycophenolate mofetil for the treatment of pemphigus. Arch Dermatol 2006; 142: 1447–54.
28 Chams-Davatchi C, Esmaili N, Daneshpazhooh M et al. Randomized controlled open-label trial of four treatment regimens for pemphigus vulgaris. J Am Acad Dermatol 2007; 57: 622–8.
29 Beissert S, Mimouni D, Kanwar AJ et al. Treating pemphigus vulgaris with prednisone and mycophenolate mofetil: a multicenter, randomized, placebo-controlled trial. J Invest Dermatol 2010; 130: 2041–8.
30 Ioannides D, Apalla Z, Lazaridou E, Rigopoulos D. Evaluation of mycophenolate mofetil as a steroid-sparing agent in pemphigus: a randomized, prospective study. J Eur Acad Dermatol Venereol 2012; 26: 855–60.
31 Vyas N, Patel NS, Cohen GF. Mycophenolate mofetil as a first-line steroid-sparing agent in the treatment of pemphigus vulgaris. J Drugs Dermatol 2013; 12: 210–6.
32 Baskan EB, Yilmaz M, Tunali S, Saricaoglu H. Efficacy and safety of long-term mycophenolate sodium therapy in pemphigus vulgaris. J Eur Acad Dermatol Venereol 2009; 23: 1432–4.
33 Baum S, Greenberger S, Samuelov L et al. Methotrexate is an effective and safe adjuvant therapy for pemphigus vulgaris. Eur J Dermatol 2012; 22: 83–7.
34 De Simone C, Caldarola G, Perino F et al. Enteric-coated mycophenolate sodium as a steroid-sparing agent in pemphigus treatment: a retrospective study. Dermatol Ther 2012; 25: 219–22.
35 Tran KD, Wolverton JE, Soter NA. Methotrexate in the treatment of pemphigus vulgaris: experience in 23 patients. Br J Dermatol 2013; 169: 916–21.
36 Almugairen N, Hospital V, Bedane C et al. Assessment of the rate of long-term complete remission off therapy in patients with pemphigus treated with different regimens including medium- and high-dose corticosteroids. J Am Acad Dermatol 2013; 69: 583–8.
37 Amagai M, Ikeda S, Shimizu H et al. A randomized double-blind trial of intravenous immunoglobulin for pemphigus. J Am Acad Dermatol 2009; 60: 595–603.
38 Behzad M, Mobs C, Kneisel A et al. Combined treatment with immunoadsorption and rituximab leads to fast and prolonged clinical remission in difficult-to-treat pemphigus vulgaris. Br J Dermatol 2012; 166: 844–52.
39 Kasperkiewicz M, Shimanovich I, Meier M et al. Treatment of severe pemphigus with a combination of immunoadsorption, rituximab, pulsed dexamethasone and azathioprine/mycophenolate mofetil: a pilot study of 23 patients. Br J Dermatol 2012; 166: 154–60.
40 Schmidt E, Klinker E, Opitz A et al. Protein A immunoadsorption: a novel and effective adjuvant treatment of severe pemphigus. Br J Dermatol 2003; 148: 1222–9.
41 Shimanovich I, Herzog S, Schmidt E et al. Improved protocol for treatment of pemphigus vulgaris with protein A immunoadsorption. Clin Exp Dermatol 2006; 31: 768–74.
42 Schmidt E, Kasperkiewicz M, Joly P. Lancet 2019; 394: 882–94.
43 Horvath B, Huizinga J, Pas HH et al. Low-dose rituximab is effective in pemphigus. Br J Dermatol 2011; 166: 405–12.
44 Kanwar AJ, Vinay K, Sawatkar GU et al. Clinical and immunological outcomes of high- and low-dose rituximab treatments in patients with pemphigus: a randomized, comparative, observer-blinded study. Br J Dermatol 2014; 170: 1341–9.
45 Joly P, Roujeau JC, Benichou J et al. A comparison of oral and topical corticosteroids in patients with bullous pemphigoid. N Engl J Med 2002; 346: 321–7.
46 Kirtschig G, Murrell D, Wojnarowska F, Khumalo N. Interventions for mucous membrane pemphigoid and epidermolysis bullosa acquisita. Cochrane Database Syst Rev 2003: Cd004056.
47 Williams HC, Wojnarowska F, Kirtschig G et al. Doxycycline versus prednisolone as an initial treatment strategy for bullous pemphigoid: a pragmatic, non-inferiority, randomised controlled trial. Lancet 2017; 389: 1630–8.
48 Sticherling M, Franke A, Aberer E et al. An open, multicentre, randomized clinical study in patients with bullous pemphigoid comparing methylprednisolone and azathioprine with methylprednisolone and dapsone. Br J Dermatol 2017; 177: 1299–305.

