Acad Med J 2025;5(Suppl 1):S9-S16.
UDC: 616.527-085
https://www.doi.org/10.53582/AMJ255109mt
Guidelines

GUIDELINES FOR THE SYSTEMIC TREATMENT OF PATIENTS WITH PEMPHIGUS AT THE UNIVERSITY CLINIC FOR DERMATOLOGY – SKOPJE

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Abstract

Pemphigus encompasses a group of life-threatening autoimmune bullous diseases characterized by blisters and erosions on the mucous membranes and skin, requiring a standardized approach to diagnosis and treatment. According to current recommendations, the treatment of diseases in this group involves the use of systemic corticosteroids in combination with immunosuppressants (azathioprine and mycophenolate mofetil), as well as biological therapy with rituximab, which has already been approved as a first-line treatment for moderate to severe pemphigus vulgaris in Europe and the USA.

These guidelines were developed for the needs of the University Clinic of Dermatology – Skopje, which serves as a referral center for the diagnosis and treatment of pemphigus in the Republic of North Macedonia. They are based on the Updated S2K guidelines on the management of pemphigus vulgaris and foliaceus initiated by the European Academy of Dermatology and Venereology (EADV). The guidelines include general information about the disease, a system for grading disease severity, and recommendations for treatment and monitoring.

Objectives of the guidelines

These guidelines aim to optimize the treatment of adult patients with pemphigus, focusing on reducing disease-related complications and improving quality of life. They provide a comprehensive overview of available treatments and their effectiveness, update recommendations for biological therapies, and establish a treatment algorithm that integrates both biological and non-biological options. Additionally, the guidelines include clear recommendations for monitoring and managing patients throughout their treatment, ensuring the best possible care and outcomes.

Target group of users of the guidelines

The Guideline is primarily intended for dermatologists at the University Clinic for Dermatology in Skopje.

Methodology

The guidelines are based on the Updated S2K guidelines on the management of pemphigus vulgaris and foliaceus initiated by the European Academy of Dermatology and Venereology (EADV)[1].

Guideline development and consensus process

The chapters and recommendations were developed by a working group of specialist physicians at the Dermatology Clinic with extensive experience in clinical dermatology and the treatment of patients with Pemphigus, as well as resident physicians involved in the technical preparation of the text.

Each chapter and all recommendations were reviewed, discussed, and amended where necessary. The Expert Collegium and then the Management Board of the University Clinic for Dermatology in Skopje, reviewed and adopted the Guideline with the necessary consensus.

Treatment of pemphigus patients at the University Clinic for Dermatology – Skopje

The University Clinic for Dermatology in Skopje serves as the primary referral center for diagnosing and treating pemphigus in Macedonia. It offers comprehensive diagnostic services, including skin biopsies, light microscopy, and advanced methods like direct immunofluorescence (DIF) and testing for pemphigus autoantibodies (desmoglein 1 and 3 IgG). Treatment includes hospital care, ongoing outpatient monitoring, and a skilled medical team supported by trained nursing staff for local therapy. The clinic is the only public healthcare institution in Macedonia capable of diagnosing and treating pemphigus. It also collaborates with other dermatological institutions to ensure continuity in care.

Main characteristics and initial evaluation of pemphigus

Pemphigus encompasses a group of life-threatening autoimmune bullous diseases characterized by flaccid bullae and erosions of the skin and mucous membranes. The severity of the disease results from its progressive course, accompanied by increased catabolism, loss of body fluids and proteins, and secondary bacterial or viral infections, which may lead to sepsis and heart failure. Two main clinical variants are distinguished: pemphigus vulgaris (PV) and pemphigus foliaceus (PF), as well as rarer variants like pemphigus vegetans. The pathophysiological mechanism involves the binding of IgG autoantibodies to the desmosomal adhesion proteins, desmoglein 3 (Dsg3) and desmoglein 1 (Dsg1), on the surface of keratinocytes[1].

The initial evaluation of a pemphigus patient includes a thorough clinical exam, medical history, and investigation of potential drug triggers. Paraclinical assessments should screen for comorbidities and risks associated with corticosteroid or immunosuppressive treatments. Disease impact is measured using the Dermatology Life Quality Index (DLQI), and vaccination status is checked before starting therapy. Dermatological examination assesses mucocutaneous lesions, and the extent of disease is measured using the PDAI questionnaire[2,3].

Diagnosis is based on clinical presentation, histopathology, direct immunofluorescence (DIF), and serological tests for autoantibodies (e.g., Dsg1, Dsg3). Lesional biopsies, DIF analysis, and serology (IIF and ELISA) confirm the diagnosis.

In cases of atypical presentation, paraneoplastic pemphigus (PNP) should be considered, with specific histopathology and DIF findings. Immunoblot and immunoprecipitation may further help diagnose PNP.

Investigations before initiating corticosteroid or immunosuppressive therapy

Before starting corticosteroid or immunosuppressive therapy, several investigations are recommended, including blood tests (e.g., complete blood count, liver function tests), screening for infections (e.g., hepatitis B, C, HIV), and specific tests depending on the treatment (e.g., serum IgA for IVIG, G6PD activity for dapsone). Additional tests may include chest X-rays, tuberculosis screening, abdominal ultrasound, and pregnancy testing for women.

Therapeutic approach

The therapeutic approach aims to control lesions and minimize side effects, focusing on healing bullous/mucosal lesions, preventing relapses, and improving quality of life. Treatment also seeks to reduce long-term risks from immunosuppressive therapy. In cases of extensive disease, hospitalization in a dermatology department is advised, while limited cases may be managed outpatient. Children with the disease should be treated by a multidisciplinary team.

Treatment guidelines

For mild forms of Pemphigus Foliaceus (PF) and Pemphigus Vulgaris (PV) with body surface area (BSA) involvement < 5%, limited oral lesions that do not impair food intake, and a PDAI score ≤ 15, initial management may include:

- Topical corticosteroids or systemic corticosteroid therapy (prednisolone at 0.5–1.0 mg/kg/day).
- Dapsone (50–100 mg/day) in conjunction with either topical or systemic corticosteroids[24,25,26].
- Alternatively, rituximab (two infusions of 1 g, two weeks apart) either alone or combined with oral corticosteroids (prednisolone 0.5 mg/kg/day), with rapid tapering of corticosteroids aiming for discontinuation within 3–4 months [7,8].

For patients initially treated with dapsone and/or topical corticosteroids without oral corticosteroids or rituximab, and who still exhibit active lesions, positive anti-Dsg1 antibodies in serum, and significant quality of life impairment (as measured by DLQI), second-line therapies may include:

- Rituximab (two infusions of 1 g, two weeks apart), either alone or in combination with oral corticosteroids (prednisolone 0.5 mg/kg/day) and rapid tapering, aiming to discontinue corticosteroids within 3–4 months [9,10].
- If rituximab is contraindicated or unavailable, systemic corticosteroid therapy (prednisolone 0.5–1.0 mg/kg/day) with or without azathioprine (1–2.5 mg/kg/day), mycophenolate mofetil (2 g/day), or mycophenolate sodium (1,440 mg/day) may be considered [11,12].
- For patients who are already on corticosteroids but still have active lesions, the addition of rituximab may be indicated.

For mild forms of PV, the initial approach involves systemic corticosteroid therapy (prednisolone 0.5–1.0 mg/kg/day) with or without azathioprine (2.0 mg/kg/day), mycophenolate mofetil (2 g/day), mycophenolate sodium (1,440 mg/day), or rituximab (two infusions of 1 g, two weeks apart). If corticosteroids are used, a rapid tapering strategy should be implemented to discontinue corticosteroid therapy within 3–4 months [8,13,14].

For patients treated with prednisolone/prednisolone 0.5–1.0 mg/kg/day who experience persistent active lesions, or those with adverse effects or contraindications to standard immunosuppressive agents, and with positive anti-Dsg3 antibodies and significant quality of life impairment, rituximab (two infusions of 1 g, two weeks apart), either alone or in combination with oral corticosteroids (prednisolone 0.5 mg/kg/day) with a rapid taper, is recommended.

For patients who begin treatment with prednisolone/prednisolone 0.5–1.0 mg/kg/day plus rituximab and still have active lesions, an increase in prednisolone to 1 mg/kg/day is recommended.

For moderate and severe forms of Pemphigus with significant mucosal involvement (mouth, nasopharynx, conjunctiva, genitals) and/or extensive skin lesions (> 5% BSA), a first-line regimen includes rituximab (two infusions of 1 g, two weeks apart) combined with systemic corticosteroids (prednisolone 1 mg/kg/day), with progressive tapering of corticosteroids over 6 months. In patients with contraindications to corticosteroids, rituximab monotherapy or combination therapy with topical corticosteroids may be considered. If rituximab is contraindicated or unavailable, systemic corticosteroid therapy (prednisolone 1.0–1.5 mg/kg/day) with or without azathioprine, mycophenolate mofetil, or mycophenolate sodium may be indicated, particularly for patients at high risk of severe corticosteroid-related side effects[8,13,14].

For patients diagnosed with paraneoplastic pemphigus (PNP), consultation with an oncologist is advised prior to the administration of rituximab or other therapies, given the potential underlying malignancy.

Maintenance therapy after initial retuximab treatment

For patients in complete remission at six months, another rituximab infusion might be needed if anti-Dsg antibodies are still elevated. If remission is incomplete, two additional infusions of rituximab may be given. At 12 and 18 months, a single rituximab infusion is recommended for those in complete remission, especially if anti-Dsg antibodies are positive. There's no evidence supporting rituximab use beyond 18 months in complete remission. Anti-Dsg antibodies should be monitored every six months, and if levels rise after initially disappearing, additional rituximab infusions may be necessary. If disease control is not achieved three to four weeks after therapy, increasing prednisone or using intravenous corticosteroids is recommended. If only systemic corticosteroids were used, increasing prednisone and adding rituximab or immunosuppressants should be considered [10,15,16,17,18,19].

Lack of initial disease control

Lack of initial disease control (3–4 weeks post therapy) for patients initially treated with rituximab and prednisone, prednisone should be increased to 1.5 mg/kg/day or intravenous corticosteroids: methylprednisolone 0.5–1 g/day or dexamethasone 100 mg/day for three consecutive days at initial intervals of 3–4 weeks. For patients initially treated with systemic corticosteroids alone, prednisone should be increased 1.5 mg/kg/day and add rituximab (2 × 1g). If rituximab is unavailable, add an immunosuppressant (azathioprine 1–2.5 mg/kg/day, mycophenolate mofetil 2 g/day, or mycophenolate sodium 1,440 mg/day).

Refractory or severe cases of pemphigus

For treating severe or resistant cases of pemphigus, several treatment options are available:

Intravenous Immunoglobulins (IVIG) can be given over several days and are effective for some patients, though they should not be used in individuals with IgA deficiency [20].

Corticosteroid pulse therapy, using high doses of medications like methylprednisolone or dexamethasone, is often administered in cycles. Immunoadsorption is another option, where blood is filtered to remove antibodies, but it is not suitable for those with severe infections or certain heart conditions[19,21,22].

Conventional immunosuppressive therapies like azathioprine and mycophenolate mofetil help manage the condition, with doses being gradually increased to reduce side effects. Other medications, such as methotrexate and cyclosporine, are generally avoided, and cyclophosphamide may be considered for cases that don't respond to other treatments [23].

Supportive treatments for pemphigus include the use of intralesional corticosteroids for localized lesions and topical steroids for oral sores. Antiseptic baths with chlorhexidine are helpful for extensive skin lesions, while light dressings and emollients are used to care for wounds. Pain management, including analgesics and anesthetic gels, can help manage discomfort. Good oral hygiene and proper nutrition are also key, especially for patients with oral involvement or nutritional issues due to the disease or its treatment.

Measures during prolonged corticosteroid therapy

During prolonged corticosteroid therapy, it's important to start vitamin D and calcium supplements to prevent osteoporosis. Bisphosphonates are recommended for high-risk patients to prevent bone loss. Regular eye check-ups are necessary, as corticosteroids can cause eye issues. Antifungal, antiviral, and antibiotic treatments should be used as needed due to immune suppression. Medications like H2 blockers or proton pump inhibitors can help prevent gastric ulcers, especially if NSAIDs are also used. Psychological support should be offered to manage mood changes, and physiotherapy may be considered to address muscle weakness. For high-risk individuals, antithrombotic prophylaxis may be necessary to prevent thrombosis.

Monitoring

Pemphigus typically follows a chronic, relapsing course and requires ongoing monitoring to assess treatment efficacy and safety, as well as to plan for the gradual reduction of immunosuppressive therapy. The monitoring process includes evaluating clinical symptoms and potential side effects, often using a multidisciplinary approach.

After the consolidation phase, systemic corticosteroids should be tapered over 4–6 months, particularly if rituximab is part of the treatment. A tapering regimen is outlined for both mild and moderate/severe forms of the condition, with dosages gradually reduced each month. For the final month, there are different options for discontinuing corticosteroids, such as stopping treatment after an ACTH test, slow tapering, or maintaining a minimal dose, especially for patients with persistent anti-Dsg antibodies [24].

When corticosteroids are used without rituximab, tapering should be adjusted based on clinical response. While there's no consensus on the best tapering approach, one option involves reducing prednisone by 10–25% every 2–3 weeks until 15–25 mg/day, after which further tapering methods (either slower or faster) are debated. If anti-Dsg1 antibody levels are high, slower tapering may be recommended to reduce the risk of relapse, as high levels predict skin relapses. Anti-Dsg3 IgG levels are less predictive for mucosal relapses unless they are very high [24].

Treatment of relapses

For patients treated with rituximab and corticosteroids, relapses during tapering may require increased oral corticosteroids or an additional cycle of rituximab depending on the timing. If a relapse occurs after prednisone is stopped, expert evaluation is recommended due to limited evidence. For those not initially treated with rituximab, relapses during tapering

should be managed with rituximab or, if unavailable or contraindicated, with increased corticosteroids and other immunosuppressive medications until disease control is achieved.

Follow-up

Evaluation of treatment efficacy is primarily based on clinical symptoms. The frequency of follow-up (physical examinations, additional tests) must be tailored to the patient's clinical condition, disease severity, and course during treatment, using clinical outcomes (e.g., PDAI). Follow-ups every 2–4 weeks are recommended until disease control is achieved, followed by every 4–8 weeks during corticosteroid tapering, and later every 8–16 weeks until complete remission off therapy and normalization of anti-Dsg antibody levels. Serological monitoring should include measuring autoantibody levels at treatment start, after 3 months, and every 3–6 months or during relapses. ELISA for anti-Dsg1 and/or Dsg3 IgG is preferred, but IIF microscopy can be used if ELISA is unavailable. Autoantibody levels correlate with clinical activity and help guide treatment, but high titers of anti-Dsg3 are the most reliable indicators of relapse.

Discontinuation of treatment

Treatment discontinuation is based primarily on clinical symptoms, combined with Dsg ELISA and/or IIF microscopy findings. Systemic corticosteroids may be discontinued after performing an ACTH test in patients in complete remission on minimal therapy (prednisone or equivalent at $\leq$ 10 mg/day) with negative circulating anti-Dsg antibodies. Adjuvant corticosteroid-sparing agents are recommended to be discontinued 6–12 months after achieving complete remission on therapy.

Potential sequelae

Pemphigus may cause sequelae due to involvement of the skin, conjunctiva, oral, pharyngeal, laryngeal mucosa, esophagus, and anogenital mucosa, as well as treatment-related adverse effects. This warrants recognition or assistance from disability centers.

Patient information

Patients and their families should be informed about the clinical course and prognosis, treatment, signs of disease relapse, and possible treatment-related adverse effects. Patients should be warned about potential triggering factors, such as certain medications, surgeries, infections, radiation, and sun exposure. Currently, there are no specific recommendations for dietary restrictions.

Written information will be available on the Clinic's website.

Patient associations

The formation of patient support groups for pemphigus or other similar associations is recommended. These associations aim to promote disease awareness, facilitate patient experience-sharing regarding daily life, and disseminate information. Such efforts can contribute to better overall disease management and foster collaboration between patients and healthcare professionals.

Conflict of interest statement. None declared.

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