Accepted Manuscript

Diagnosis and Management of Pemphigus: recommendations by an International Panel of Experts

Dedee F. Murrell, MA, BMBCh, MD, FACD, Sandra Peña, MD, Pascal Joly, MD, PhD, Branka Marinovic, MD, PhD, Takashi Hashimoto, MD, PhD, Luis A. Diaz, MD, Animesh A. Sinha, MD, PhD, Aimee S. Payne, MD, PhD, Maryam Daneshpazhooh, MD, Rüdiger Eming, MD, Marcel F. Jonkman, MD, PhD, Daniel Mimouni, MD, Luca Borradori, MD, Soo-Chan Kim, MD, PhD, Jun Yamagami, MD, PhD, Julia S. Lehman, MD, Marwah Adly Saleh, MD, PhD, Donna A. Culton, MD, PhD, Annette Czernik, MD, John J. Zone, MD, David Fivenson, MD, Hideyuki Ujiie, MD, PhD, Katarzyna Wozniak, MD, PhD, Ayşe Akman-Karakaş, MD, Philippe Bernard, MD, PhD, Neil J. Korman, MD, PhD, Frédéric Caux, MD, PhD, Kossara Drenovska, MD, PhD, Catherine Prost-Squarcioni, MD, PhD, Snejina Vassileva, MD, PhD, Ron J. Feldman, MD, PhD, Adela Rambi Cardones, MD, Johann Bauer, MD, Dimitrios Ioannides, MD, PhD, Hana Jedlickova, MD, PhD, Francis Palisson, MD, Aikaterini Patsatsi, MD, PhD, Soner Uzun, MD, Savas Yayli, MD, Detlef Zillikens, MD, Masayuki Amagai, MD, PhD, Michael Hertl, MD, Enno Schmidt, MD, PhD, Valeria Aoki, MD, PhD, Sergei A. Grando, MD, PhD, DSc, Hiroshi Shimizu, MD, PhD, Sharon Baum, MD, Guiseppe Cianchini, MD, Claudio Feliciani, MD, Pilar Iranzo, MD, Jose M. Mascaró, Jr., MD, Cezary Kowalewski, MD, Russell Hall, MD, Richard Groves, MD, Karen E. Harman, MB, BChir, DM, FRCP, M. Peter Marinkovich, MD, Emanual Maverakis, MD, Victoria P. Werth, MD

PII: S0190-9622(18)30207-X

DOI: 10.1016/j.jaad.2018.02.021

Reference: YMJD 12328

To appear in: *Journal of the American Academy of Dermatology*

Received Date: 23 March 2017

Revised Date: 18 January 2018

Accepted Date: 3 February 2018

Please cite this article as: Murrell DF, Peña S, Joly P, Marinovic B, Hashimoto T, Diaz LA, Sinha AA, Payne AS, Daneshpazhooh M, Eming R, Jonkman MF, Mimouni D, Borradori L, Kim S-C, Yamagami J, Lehman JS, Saleh MA, Culton DA, Czernik A, Zone JJ, Fivenson D, Ujiie H, Wozniak K, Akman-

Karakaş A, Bernard P, Korman NJ, Caux F, Drenovska K, Prost-Squarcioni C, Vassileva S, Feldman RJ, Cardones AR, Bauer J, Ioannides D, Jedlickova H, Palisson F, Patsatsi A, Uzun S, Yayli S, Zillikens D, Amagai M, Hertl M, Schmidt E, Aoki V, Grando SA, Shimizu H, Baum S, Cianchini G, Feliciani C, Iranzo P, Mascaró Jr. JM, Kowalewski C, Hall R, Groves R, Harman KE, Marinkovich MP, Maverakis E, Werth VP, Diagnosis and Management of Pemphigus: recommendations by an International Panel of Experts, *Journal of the American Academy of Dermatology* (2018), doi: 10.1016/j.jaad.2018.02.021.

Diagnosis and Management of Pemphigus: recommendations by an International Panel of Experts.

Dedee F. Murrell[1], MA, BMBCh, MD, FACD, Sandra Peña[2,3], MD, Pascal Joly[4], MD, PhD, Branka Marinovic[5], MD, PhD, Takashi Hashimoto[6], MD, PhD, Luis A. Diaz[7], MD, Animesh A. Sinha[8] , MD, PhD, Aimee S.Payne[3], MD, PhD, Maryam Daneshpazhooh[9], MD, Rüdiger Eming[10], MD, Marcel F. Jonkman[11], MD, PhD, Daniel Mimouni[12], MD, Luca Borradori[13], MD, Soo-Chan Kim[14], MD, PhD, Jun Yamagami[15], MD, PhD, Julia S. Lehman[16], MD, Marwah Adly Saleh[17], MD, PhD, Donna A. Culton[7], MD, PhD, Annette Czernik[18], MD, John J. Zone[19], MD, David Fivenson[20], MD, Hideyuki Ujiie[21], MD, PhD, Katarzyna Wozniak[22], MD, PhD, Ayşe Akman-Karakaş[23], MD, Philippe Bernard[24], MD, PhD, Neil J. Korman[25], MD, PhD, Frédéric Caux[26], MD, PhD, Kossara Drenovska[27], MD, PhD, Catherine Prost-Squarcioni[28], MD, PhD, Snejina Vassileva[27], MD, PhD, Ron J. Feldman[29], MD, PhD, Adela Rambi Cardones[30], MD, Johann Bauer[31], MD, Dimitrios Ioannides[32], MD, PhD, Hana Jedlickova[33], MD, PhD, Francis Palisson[34], MD, Aikaterini Patsatsi[35], MD, PhD, Soner Uzun[23], MD, Savas Yayli[36], MD, Detlef Zillikens[37], MD, Masayuki Amagai[15], MD, PhD, Michael Hertl[38], MD, Enno Schmidt[37], MD, PhD, Valeria Aoki[39], MD, PhD, Sergei A. Grando[40], MD, PhD, DSc, Hiroshi Shimizu[21], MD, PhD, Sharon Baum[41], MD, Guiseppe Cianchini[42], MD, Claudio Feliciani[43], MD, Pilar Iranzo[44], MD, Jose M. Mascaró Jr.[44], MD, Cezary Kowalewski[22], MD, Russell Hall[30], MD, Richard Groves[45], MD, Karen E. Harman[45], MB, BChir, DM, FRCP, M. Peter Marinkovich[46], MD, Emanual Maverakis[47], MD and Victoria P. Werth[2,3], MD

[1] Department of Dermatology at St George Hospital, University of New South Wales, Sydney, Australia.

[2] Corporal Michael J. Crescenz Veterans Affairs Medical Center, Philadelphia, PA, USA.

[3] Department of Dermatology at the Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA.

[4] Department of Dermatology, Rouen University Hospital, Rouen, France

[5] Department of Dermatology and Venereology, Zagreb University Hospital Center and School of Medicine, Zagreb, Croatia.

[6] Kurume University Institute of Cutaneous Cell Biology, Kurume, Japan

[7] Department of Dermatology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

[8] Department of Dermatology, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, Buffalo, NY, USA.

[9] Department of Dermatology, Autoimmune Bullous Diseases Research Center, Tehran University of Medical Sciences, Tehran, Iran.

[10] Department of Dermatology and Allergology, University Hospital, Philipps-Universität Marburg, Marburg, Germany.

[11] University Medical Center Groningen, University of Groningen, Groningen, The Netherlands.

[12] Department of Dermatology, Rabin Medical Center, Beilinson Campus,, Petach Tikva, Israel; Sackler School of Medicine, Tel Aviv University, Tel Aviv. Israel

[13] Department of Dermatology, University Hospital of Bern, Bern, Switzerland.

[14] Department of Dermatology, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea

[15] Department of Dermatology, Keio University School of Medicine, Tokyo, Japan.

[16] Department of Dermatology, Mayo Clinic College of Medicine, Rochester, MN, USA.

[17] Department of Dermatology, Faculty of Medicine, Cairo University, Egypt.

[18] Department of Dermatology, Icahn School of Medicine at Mount Sinai, New York, NY, USA.

[19] Department of Dermatology, School of Medicine, University of Utah, Salt Lake City, Utah, USA.

[20] St Joseph Mercy Health System, Department of Dermatology, Ann Arbor, Michigan, USA.

[21] Department of Dermatology, Hokkaido University Graduate School of Medicine, Japan

[22] Department of Dermatology and Immunodermatology, Medical University of Warsaw, Warsaw, Poland.

[23] Department of Dermatology and Venereology, Faculty of Medicine, Akdeniz University, Antalya, Turkey.

[24] Department of Dermatology, Reims University Hospital, University of Champagne-Ardenne, Reims, France.

[25] Department of Dermatology and the Murdough Family Center for Psoriasis, University Hospitals Case Medical Center, Cleveland, Ohio, USA.

[26] Department of Dermatology, Avicenne Hospital, University Paris 13, Bobigny, France.

[27] Department of Dermatology and Venereology, Medical Faculty, University of Medicine, Sofia, Bulgaria

[28] Department of Dermatology, Department of Histology, Reference Center for Autoimmune Bullous Diseases, Avicenne Hospital, University Paris 13, Bobigny, France.

[29] Department of Dermatology, Emory University School of Medicine, Atlanta, Georgia, USA.

[30] Dermatology, Duke University Medical Center, Durham, NC, USA.

[31] Division of Molecular Dermatology, Department of Dermatology, Paracelsus Medical University Salzburg, Salzburg, Austria.

[32] First Department of Dermatology, Aristotle University, Thessaloniki, Greece.

[33] Department of Dermatovenereology, St. Anna University Hospital, Masaryk University, Brno, Czech Republic.

[34] Facultad de Medicina, Clínica Alemana, Santiago, Chile.

[35] Second Dermatology Department, Aristotle University School of Medicine, Papageorgiou General Hospital, Thessaloniki, Greece.

[36] Dermatology Department, School of Medicine, Karadeniz Technical University , Trabzon , Turkey.

[37] Department of Dermatology, University of Lubeck, Lubeck, Germany.

[38] Department of Dermatology, University Hospital, Marburg, Germany.

[39] Departamento de Dermatologia, Universidade de Sao Paulo, Sao Paulo 04038, Brazil

[40] Department of Dermatology, University of California, Irvine, California; Department of Biological Chemistry Cancer Center, University of California, Irvine, California; Research Institute, Institute for Immunology, University of California, Irvine, California.

[41] Sheba Medical Center, Dermatology Department, Tel-Hashomer, Ramat-Gan, Israel.

[42] Department of Immunodermatology, Istituto Dermopatico dell'Immacolata, IRCCS, Rome, Italy; Laboratory of Molecular and Cell Biology, Istituto Dermopatico dell'Immacolata, IRCCS, Rome, Italy.

[43] Clinica Dermatologica, Universita' Di Parma, Italy

[44] Department of Dermatology, Hospital Clínic, Universitat de Barcelona, Barcelona, Spain.

[45] University Hospitals Leicester, Leicester Royal Infirmary, Infirmary Square, Leicester. LE1 5WW. United Kingdom.

[46] Department of Dermatology, Stanford University School of Medicine, Stanford, California; Center for Clinical Sciences Research, and Division of Dermatology, Department of Veterans Affairs Palo Alto Healthcare System, Palo Alto, California.

[47] Department of Dermatology, School of Medicine, University of California, Davis, USA.

Address correspondence to:

Dedee F. Murrell, MA, BMBCh, MD, FACD

Department of Dermatology

St George Hospital

Gray Street, Kogarah, Sydney, NSW 2217,Australia

E-Mail d.murrell @ unsw.edu.au

Victoria P. Werth, MD

Professor of Dermatology and Medicine, Department of Dermatology

University of Pennsylvania, Philadelphia, Pennsylvania.

Tel.: 215-615-2940, Fax: 866-755-0625, Email: werth@mail.med.upenn.edu.

Funding: This work is partially supported by the Department of Veterans Affairs (Veterans Health Administration, Office of Research and Development, Biomedical Laboratory Research and Development) (VPW). Dr. Pena's clinical research is funded by an NIH training grant.

No human subjects were used in the study and therefore IRB approval was not necessary.

Conflict of Interest: Dr.Murrell is an investigator and speaker for Roche. She is an investigator and on an advisory board for Principia Biopharma; and is on an advisory board for Immune Pharmaceuticals and Lilly. Dr. Joly is a consultant for Roche, Principia Biopharma , Lilly and Biogen. Dr. Payne is a consultant for Syntimmune and TG Therapeutics and receives grants Sanofi. Dr. Eming is an investigator for both Biotest AG and Fresenius Medical Care and is a speaker for Biotest AG and Novartis. Dr. Jonkman is a monitor for Roche. Dr. Prost is an investigator for Roche. Dr. Yayli is an investigator for Roche. Dr. Zillikens is on the advisory board for Roche and a consultant for Euroimmun,UCB, Fresenius, Almirall, and oGEN-x. Dr. Zillikens has received grants and is a speaker for Euroimmun, Miltenyi/Biogen, Fresenius/Roche, Biotest AG, Almirall, and Dompe/Janssen. Dr. Amagai receives speaker honoraria and grants from Nihon Pharmaceutical Co., Ltd, and reseach support from Medical & Biological Laboratories Co., Ltd. Dr. Hertl is on an advisory board for Roche, Biogen, and Novartis and has received grants from Biotest and Fresenius; and is a speaker for Janssen. Dr. Schmidt has received grants from Euroimmun and Fresenius; and is a speaker for Biotest and Fresenius. Dr. Hall is a consultant for Stieffel at GSK Company, Eli Lilly, Syntimmune, and Immune Sciences and is on the DSM board for Roche and has received grants from Immune Sciences. Dr. Peña, Dr. Marinovic, Dr. Hashimoto, Dr. Diaz, Dr. Sinha, Dr. Daneshpazhooh, Dr. Mimouni, Dr. Borradori, Dr. Kim, Dr. Yamagami, Dr. Lehman, Dr. Saleh, Dr. Culton, Dr. Czernik, Dr. Zone, Dr. Fivenson, Dr. Ujiie, Dr. Wozniak, Dr. Akman-Karakaş, Dr. Bernard, Dr. Korman, Dr. Caux, Dr. Drenovska, Dr. Vassileva, Dr. Feldman, Dr. Cardones, Dr. Bauer, Dr. Ioannides, Dr. Jedlickova, Dr. Palisson, Dr. Patsatsi, Dr. Uzun, Dr. Aoki, Dr. Grando, Dr. Shimizu, Dr. Baum, Dr. Cianchini, Dr. Feliciani, Dr. Iranzo, Dr. Mascaró Jr., Dr. Kowalewski, Dr. Groves, Dr. Harman, Dr. Marinkovich, Dr. Maverakis, and Dr. Werth have no conflict of interest to declare.

Keywords: pemphigus vulgaris, pemphigus foliaceus, treatment, guidelines, consensus, CD20 inhibitor

Word Count: Abstract: 208, Text: 2780**, References:** 12, **Figures**: 2, **Tables:** 2

Abstract

Background: Several European countries recently developed international diagnostic and management guidelines for pemphigus, which have been instrumental in the standardization of pemphigus management,

Objective: We now present results from a subsequent Delphi consensus to broaden the generalizability of recommendations.

Methods: A preliminary survey, based on the European Dermatology Forum (EDF) and the European Academy of Dermatology and Venereology (EADV) guidelines, was sent to a panel of international experts to determine the level of consensus. The results were discussed at the International Bullous Diseases Consensus Group in March 2016 during the annual American Academy of Dermatology (AAD) conference. A second survey was sent following the meeting to more experts to achieve greater international consensus.

Results: The 39 experts participated in the first round of the Delphi-survey while 54 from 21 countries completed the second round. The number of statements in the survey was reduced from 175 topics in Delphi I to 24 topics in Delphi II based on Delphi results and meeting discussion.

Limitations: Each recommendation represents the majority opinion and therefore may not reflect all possible treatment options available.

Conclusions: We present here the recommendations resulting from this Delphi process. This international consensus includes intravenous CD20 inhibitors as a first line therapy option for moderate to severe pemphigus.

Introduction

Pemphigus encompasses a spectrum of rare mucocutaneous bullous diseases that are autoimmune in origin. Due to the rarity of these diseases, it can take patients months before being diagnosed with pemphigus, during which time many are treated for other blistering diseases (1, 2). Even once the diagnosis is made, treatment regimens can vary greatly as there is no defined standard of care due to the paucity of large-scale clinical trials evaluating their efficacy (1).

There have been recent national attempts to standardize the diagnosis and management of pemphigus from individual countries, including the UK, France, Japan, and Germany (3- 6). However, it was the European Dermatology Forum (EDF) and the European Academy of Dermatology and Venereology (EADV), which passed the first international guidelines for the management of pemphigus (7). While these efforts have been instrumental in the standardization of pemphigus management, the lack of involvement from countries outside of Europe may render these guidelines non-generalizable to other countries.

In an attempt to garner greater international consensus, the International Bullous Diseases Consensus Group, convened by Dr. Dedee Murrell and Dr. Victoria Werth, met in March 2016 at the annual American Academy of Dermatology (AAD) conference in Washington D.C. with the goal of developing international consensus guidelines for the diagnosis and management of pemphigus vulgaris and pemphigus foliaceus. Prior to the meeting, members of the group, comprised of blistering disease experts, completed a Delphi survey based on the EDF/EADV guidelines. Some of the tests and treatments mentioned may not be available or officially registered in all countries and have been assessed based on their scientific usefulness rather than regulation status. The Delphi technique is a consensus-building process in which questionnaires are given to a group of experts in a series of rounds to ultimately achieve opinion convergence (8). The results of the questionnaire were discussed in the

166 meeting and a follow-up survey was sent out to further consensus.

Methods

The first round of surveys was delivered via email in February 2016 and completed by 39 expert participants. The results of the survey were tallied and delivered to the group. A median score of 70 percent or greater per question was used as the consensus threshold for agreement, while a median score of 30 or lower was established as the consensus threshold for disagreement. Statements that achieved median scores between 30 and 70 were determined as having reached no consensus among participants and discussed during the meeting. Afterwards, these statements were revised according to the opinion of the participants and sent out and completed by 54 individuals in the subsequent round. The survey was designed and distributed using RedCAP software.

Initial Clinical Presentation of Pemphigus

The initial evaluation of suspected pemphigus should seek to determine the signs or symptoms present that would corroborate the diagnosis of pemphigus, as well as to screen for possible comorbidities.

Major Objectives

- To verify the diagnosis of pemphigus
- To evaluate possible risk factors, severity factors and comorbidities
- To specify the type of initial involvement (skin, mucosa) and its extent
- To evaluate the prognosis depending on the age of the patient and general condition (Karnovsky score, optional)
- There are two clinical scores, Pemphigus Disease and Area Index (PDAI) and/or Autoimmune Bullous Skin Intensity and Severity Score (ABSIS), which are currently being used as clinical outcome parameters and in clinical trials for the evaluation of the extent and activity of pemphigus. Presently, there are no agreed upon cutoff values to define mild, moderate, or severe disease for

either the PDAI or the ABSIS; however, there have been two studies which have attempted to define these values. In one multicenter study based in Japan, researchers evaluated both newly diagnosed as well as relapsing pemphigus patients and determined PDAI cutoff values of 0-8 for mild, 9-24 for moderate, and ≥25 for severe disease (9). Another multicenter study, conducted internationally, assessed only patients with newly diagnosed pemphigus and determined cut-off values of 15 and 45 for PDAI and 17 and 53 for ABSIS, to distinguish between mild, moderate and severe (significant and extensive) forms of pemphigus (10). While these studies greatly add to our understanding of disease activity scoring, it is premature to definitively state cutoff values presently.

Specialists Involved

The management of patients with pemphigus is the responsibility of dermatologists with experience in treating bullous diseases. If extensive, the initial management of the disease usually requires hospitalization until clinical control of the bullous eruption is achieved. In limited forms of pemphigus, additional diagnostic examinations and clinical monitoring can be done in either an inpatient or outpatient setting.

The overall disease management is coordinated by the dermatologist with the cooperation of the referring dermatologist/family practitioner, the general physician and other medical specialists and hospital doctors from the center of reference and/or geographical area (if a reference center exists in the particular country).

Rarely, the disease can occur during childhood, and children should be managed by a multidisciplinary team, jointly by a reference center, a pediatric dermatology department or a pediatrician.

Other health professionals who may serve as supportive adjuncts are as follows:

- The referring dermatologist

- The patient's primary care provider to manage comorbidities and monitor for treatment side-effects
- Other specialists whose expertise is necessary, based on comorbidities and/or mucosal locations of pemphigus, such as internists, cardiologists, stomatologists, ophthalmologists, otorhinolaryngologists, gastroenterologists, gynecologists, urologists, proctologists, rheumatologists, oncologists, dieticians, physiotherapists and psychologists
- Home health nurses, where available, in selected cases in which home care is required and applicable, e.g. elderly or disabled patients with residual mucosal or skin lesions following hospitalization
- Nurse specialist/practitioner to aid in the management of stable patients, making phone calls, or changing wound dressings.

Diagnosis

The diagnosis of pemphigus is based on the following criteria:

- Clinical presentation
- Histopathology
- Direct immunofluorescence microscopy (DIF) of perilesional skin
- Serological detection of serum autoantibodies against epithelial cell surface by indirect immunofluorescence microscopy (IIF) and/or enzyme-linked immunosorbent assay (ELISA)
- Diagnosis requires clinical presentation and histopathology that are consistent with pemphigus and either a positive DIF or serological detection of autoantibodies against epithelial cell surface antigens.

Clinical Evaluation

Medical History

- Timing of symptoms
- Functional symptoms, i.e. pain, pruritus, intensity of dysphagia, ocular and ENT symptoms, dysuria, anogenital problems and weight loss
- Contraindications of systemic corticosteroid treatment and developing complications of immunosuppressive treatments
- Contraception and plans for pregnancy in women of child bearing potential
- Medication history with special attention to causes of drug-induced pemphigus, including D-penicillamine, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and cephalosporins,
- Psychological tolerance of possible side-effects due to treatment, especially corticosteroids
- Quality of life impact due to disease burden

Physical examination

- Extent of skin and mucosal lesions and the degree of disease damage
- Patient's overall state of health and comorbidities:
  - General condition (Karnovsky index)
  - Weight
  - Vital signs, including blood pressure and temperature
  - Comorbidities (neoplastic, cardiovascular, musculoskeletal, etc.)

The changes from the European guidelines are summarized in the supplementary material.

The laboratory work up is delineated in Table 1.

Therapeutic Management

Objectives

- To promotehealing of blisters and erosions
- To improve functional status
- To prevent/strictly limit development of new blisters and erosions
- To improve the quality of life
- To limit common side-effects usually associated with long-term immunosuppressive or corticosteroid treatment

First-Line Treatment

The dosing of specific medications is delineated in Table 2.

- Corticosteroids
- Anti-CD20 monoclonal antibodies

Corticosteroid-Sparing Agents

First-Line Corticosteroid-Sparing Agents

- Azathioprine
- Mycophenolate mofetil or mycophenolic acid

Other Corticosteroid-Sparing Agents

- Intravenous immunoglobulins (IVIG)
- Immunoadsorption
- Cyclophosphamide

Supportive treatment that may be recommended:

- 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) 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 corticosteroids treatment
- Treatment with bisphosphonates (i.e. alendronate, risedronate) in patients at risk (post-menopausal women and men >50 years who will be on corticosteroid treatment > 3 months) of developing osteoporosis
- Systemic antifungals, antiviral and antibiotic treatment should be used when clinically indicated
- H2-blockers or proton pump inhibitor use should be individualized to the patients given lack of sufficient evidence.
- Anti-thrombotic prophylaxis in case of high risk of thrombosis
- Psychological support if required
- Physiotherapy if prolonged corticosteroid therapy is required

Vaccinations

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

Monitoring

Objectives

- To evaluate the efficacy and safety of treatment
- To plan the gradual reduction of immunosuppressive treatment, and the duration of maintenance therapy or its discontinuation

Definitions for Disease Outcome Parameters (12)

- 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. This is when most clinicians start to taper steroids."
- Complete remission on 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 is off all systemic therapy for at least 2 months

- Relapse/flare: Appearance of ≥3 new lesions/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 ≤10 mg/day and/or minimal adjuvant therapy for at least 2 months

Approach to Be Maintained After Consolidation Phase

- Expect slow clinical improvement, often requiring a period of 1–3 months for complete healing of lesions
- Start tapering steroids as soon as disease control is reached or up to the end of consolidation phase
- Decrease predniso(lo)ne by 25% every two weeks, until 20 mg per day. Once at 20 mg per day, decrease predniso(lo)ne by 2.5 mg a week; and then at 10 mg/day, decrease dose by 1 mg per day after that.
- Go back to last dose if >3 lesions reappear during the tapering of oral corticosteroid therapy
- If relapse occurs (i.e the appearance of ≥3 new lesions/month that do not heal spontaneously within 1 week, or there is extension of established lesions), increase the oral corticosteroid dose by going back to the second to last dose until control of the lesions is achieved within 2 weeks, then resume taper.
- If disease control is still not reached despite this, go back to initial dose.
    - If oral corticosteroids are given alone: add an immunosuppressant (especially in case of early-stage relapse occurring despite continued high-dose corticosteroid treatment)
    - If oral corticosteroids are already combined with an immunosuppressant, consider a change in immunosuppressant

Scheduling and Content of Consultations

The frequency of consultations (physical exam, additional exams) depends on:

- The patient's clinical condition including comorbidities
- The severity and disease course specific to the patient's pemphigus during treatment
- The therapeutics used (monitoring, tolerance, side-effects)
- The level of disease activity measure by the ABSIS and/or PDAI, (optional)

Initially, follow-up visits should be offered every two weeks until clinical disease control is achieved. In the consolidation phase, patients should be seen every 1-2 weeks in order to determine how soon patients could be started on a steroid taper. Then, during tapering phase, for the next 3 months, monthly clinical follow-ups are recommended. Once in partial or complete remission on minimal therapy, visits can be less frequent, such as every 3 months.

Clinical Evaluation

The clinical follow-up should seek to clarify:

- Level of disease control
- Presence of adverse effects due to treatment including:
  - Diabetes, high blood pressure, cardiac insufficiency, myopathy, osteoporosis, avascular bone necrosis, glaucoma, cataract due to corticosteroids
  - Infections, notably respiratory, hepatitis, or hematological abnormalities (leucopenia) as a result of immunosuppression
  - Mental disorders

Serological Monitoring Of Disease Activity

Determination of serum autoantibodies at the initiation of treatment, after 3 months and every 3–6 months based on the evolution, or in case of relapse by:

- ELISA: anti-Dsg1 and/or Dsg3 IgG
- If ELISA is not available: IIF microscopy utilizing monkey esophagus

- Overall, serum concentrations of IgG autoantibodies against Dsg1 and Dsg3 correlate with the clinical activity of pemphigus and may thus help in therapeutic decision making
- The 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 is primarily based on the clinical symptoms but may be also supported by the findings of Dsg ELISA, IIF and/or negative DIF microscopy of a skin biopsy.
- Discontinuation of systemic corticosteroids may be proposed in patients in complete remission on minimal therapy (prednisolone or equivalent at ≤10 mg/day). The adjuvants may be stopped 6–12 months after achieving complete remission on minimal therapy with adjuvants only.

Possible Sequelae

- Pemphigus may cause permanent sequelae not only due to the involvement of skin and mucosa but also due to treatment side effects, justifying request for recognition or help from departmental disability centers where available. The extent of immunosuppressive therapy increases the risk of side-effects.

Information for patients and their families

- Education about the disease, its clinical course and prognosis, treatment, relapse signs, and possible side-effects of treatment.
- Awareness of self-support groups, which may help disseminate information regarding the disease, provide comfort and share the experience of patients regarding daily life. Additionally, it may contribute to a better overall management of the disease by promoting cooperation between patients, patient associations and health professionals.

- Information about referral centers
- Education about triggers such as drugs, operations, radiation and physical trauma
- Counseling on dietary restrictions not necessary due to insufficient evidence

Areas for Future Studies

These recommendations are a working document whose purpose is to provide clinicians the most up-to-date consensus on the diagnosis and management of pemphigus. Further studies are needed to clarify optimal therapeutic regimens and describe their safety and efficacy in the treatment of pemphigus. Some areas identified by the authors include:

Intravenous CD20 inhibitors

- Although a recent clinical trial has demonstrated superior efficacy and safety of the intravenous CD20 inhibitor, rituximab, with short term lower doses of corticosteroids than standard dose systemic corticosteroids initially with slow tapering (9), several questions remain about how best to use it:
  - How should other medications be combined with intravenous CD20 inhibitors?
  - Should corticosteroids be used in combination with intravenous CD20 inhibitors from the start to gain disease control and reduce unnecessary iatrogenic morbidity for patients?
  - In some patients with comorbidities or mild disease, can CD20 inhibitors be used alone or with a topical corticosteroid?
  - What is the role of other immunosuppressives, IVIG, immunoadsorption, etc., along with CD20 inhibitors?
- Dosing of CD20 inhibitors
  - Is there a specific disease activity level in which patients can be treated with only oral steroids and not necessarily CD20 inhibitors?

- What is the ideal threshold in patients on systemic corticosteroids or immunosuppressants to begin CD20 inhibitor therapy?
- What is the optimal dose, frequency, total number of maintenance infusions to use?
- Are these drugs indicated in patients with negative anti-DSG antibodies?
- In cases of relapse, is a single dose of 1000mg/infusion of rituximab (or 375 mg/m2 in lymphoma protocol) enough to achieve remission instead of a full dose cycle of rituximab (2 x 1000 mg 2 weeks apart or 4 x 375 m^2/week)?

- Long term side effects
  - Will more side effects occur when more patients are treated with multiple maintenance infusions of CD20 inhibitors?

Other treatment options

- What role do other treatment options, like plasmapheresis, play in the treatment of pemphigus?

Conclusion

In summary, we present here the recommendations arising from a Delphi process involving 39 pemphigus experts. We make recommendations for evaluation and treatment of pemphigus, including initial evaluation, diagnosis, and management, as well as strategies for maintenance therapy and tapering of medications in remission.

References

1. Mimouni D, Nousari C, Cummins D, Kouba D, David M, Anhalt G. Differences and similarities among expert opinions on the diagnosis and treatment of pemphigus vulgaris. Journal of the American Academy of Dermatology. 2003;49(6):1059-1062. doi:10.1016/s0190-9622(03)02738-5.
2. Venugopal S Murrell D. Diagnosis and Clinical Features of Pemphigus Vulgaris. Immunology and Allergy Clinics of North America. 2012;32(2):233-243. doi:10.1016/j.iac.2012.04.003.
3. Joly P, Bernard P, Bedane C, Prost C, Ingen-Housz-Oro S. Pemphigus. Guidelines for the diagnosis and treatment. Centres de reference des maladies bulleuses auto-immunes. Societe Francaise de Dermatologie. Ann Dermatol Venereol 2011; 138: 252–258.
4. Committee for Guidelines for the Management of Pemphigus Disease, Amagai, M., Tanikawa, A., Shimizu, T., Hashimoto, T., Ikeda, S., Kurosawa, M., Niizeki, H., Aoyama, Y., Iwatsuki, K. and Kitajima, Y. (2014), Japanese guidelines for the management of pemphigus. The Journal of Dermatology, 41: 471–486. doi: 10.1111/1346-8138.12486
5. Eming, R., Sticherling, M., Hofmann, S. C., Hunzelmann, N., Kern, J. S., Kramer, H., Pfeiffer, C., Schuster, V., Zillikens, D., Goebeler, M., Hertl, M., Nast, A., Orzechowski, H.-D., Sárdy, M., Schmidt, E., Sitaru, C., Sporbeck, B. and Worm, M. (2015), S2k guidelines for the treatment of pemphigus vulgaris/foliaceus and bullous pemphigoid. Journal der Deutschen Dermatologischen Gesellschaft, 13: 833–844. doi: 10.1111/ddg.12606
6. Harman, K.E., Albert, S. and Black, M.M. (2003), Guidelines for the management of pemphigus vulgaris. British Journal of Dermatology, 149: 926–937. doi:10.1111/j.1365-2133.2003.05665.x
7. Hertl M, Jedlickova H, Karpati S et al. Pemphigus. S2 Guideline for diagnosis and treatment - guided by the European Dermatology Forum (EDF) in cooperation with the European Academy

457 of Dermatology and Venereology (EADV). Journal of the European Academy of Dermatology
458 and Venereology. 2014;29(3):405-414. doi:10.1111/jdv.12772.
459 8. Hsu C, Sandford B. The Delphi Technique: Making Sense Of Consensus. Practical Assessment,
460 Research & Evaluation. 2007;12(10). Available at: http://pareonline.net/getvn.asp?v=12&n=4.
461 9. Shimizu, T., Takebayashi, T., Sato, Y., Niizeki, H., Aoyama, Y., Kitajima, Y., Iwatsuki, K.,
462 Hashimoto, T., Yamagami, J., Werth, V. P., Amagai, M. and Tanikawa, A. (2014), Grading
463 criteria for disease severity by pemphigus disease area index. J Dermatol, 41: 969–973.
464 doi:10.1111/1346-8138.12649
465 10. Boulard, C., Duvert Lehembre, S., Picard-Dahan, C., Kern, J.S., Zambruno, G., Feliciani, C.,
466 Marinovic, B., Vabres, P., Borradori, L., Prost-Squarcioni, C., Labeille, B., Richard, M.A.,
467 Ingen-Housz-Oro, S., Houivet, E., Werth, V.P., Murrell, D.F., Hertl, M., Benichou, J., Joly, P.
468 and the International Pemphigus Study Group (2016), Calculation of cut-off values based on the
469 Autoimmune Bullous Skin Disorder Intensity Score (ABSIS) and Pemphigus Disease Area Index
470 (PDAI) pemphigus scoring systems for defining moderate, significant and extensive types of
471 pemphigus. Br J Dermatol, 175: 142–149. doi:10.1111/bjd.14405
472 11. Joly P, Maho-Vaillant M, Prost-Squarcioni C, et al. (in press). First-line use of Rituximab
473 combined with short-term-prednisone versus corticosteroid alone in the treatment of patients
474 with Pemphigus: a prospective multicenter randomized trial. The Lancet.
475 12. Murrell DF, Daniel BS, Joly P, et al. Definitions and outcome measures for bullous pemphigoid:
476 Recommendations by an international panel of experts. Journal of the American Academy of
477 Dermatology. 2012;66(3):10.1016/j.jaad.2011.06.032. doi:10.1016/j.jaad.2011.06.032.
478

479 **Table 1: Laboratory Work-up**

Histopathology

- A biopsy should be taken of a recent (<24 h) small vesicle or 1/3 of the peripheral portion of a blister and 2/3 perilesional skin (placed in 4% formalin solution) for routine histopathological analysis: intraepidermal suprabasal acantholysis in PV or acantholysis at the granular layer in PF.

Direct immunofluorescence microscopy (DIF)

- Skin biopsy of perilesional skin (up to 1 cm from a recent lesion), put into a cryotube for transportation in saline (delivery <36 h) in a cylinder of liquid nitrogen or Michel's fixative for DIF analysis:
  - DIF: IgG and/or C3 deposits at the surface of epidermal keratinocytes. The smooth and reticular staining pattern is also referred to as 'chicken wire', 'honeycomb' or 'fishnet-like'.
  - IgA deposits with an epithelial cell surface pattern in addition to IgG may be present in a subset of cases.
  - Epithelial cell surface deposits may be associated with linear or granular deposits of IgG or C3 along the dermal–epidermal junction, suggestive of other autoimmune blistering diseases including paraneoplastic pemphigus or pemphigus erythematosus, or the coexistence of pemphigus and pemphigoid

<u>Immune serological tests</u>

Indirect immunofluorescence microscopy (IIF)

- IIF test on monkey esophagus or human skin to search for autoantibodies against surface proteins of epidermal keratinocytes, similar to the pattern seen on DIF.

- In case of atypical presentation or the suspicion of another autoimmune bullous disorder, additional immunopathological tests may be performed, such as IIF on rat bladder and immunoblot/immunoprecipitation
- IIF on human cells with recombinant expression of desmoglein 1, desmoglein 3 or envoplakin (Euroimmun) is an alternative where desmoglein- or envoplakin-specific ELISA cannot be used

ELISA

- Detection of anti-desmoglein 1 (Dsg1) (PF/mucocutaneous PV) and/or anti-desmoglein 3 (Dsg3) IgG autoantibodies (mucosal or mucocutaneous PV) by ELISA (MBL, Euroimmun)
- The detection of IgG autoantibodies by ELISA is positive in more than 90% of cases
- In general, the ELISA index correlates with the extent and/or activity of disease (see remark above) and prognostic value for relapse, helping to guide treatment. Large prospective cohort studies are, however, missing in this context to provide reliable data about predictive value

<u>Work-Up before Corticosteroid or Immunosuppressive Therapy</u>

- Complete blood count
- Creatinine, blood electrolytes
- Transaminases, gamma GT, alkaline phosphatase
- Total serum protein, albumin
- Fasting serum glucose
- Hepatitis B, C and HIV

- Quantiferon gold or PPD is recommended

Recommended, on indication or optional:

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

480

481

482 Table 2: Medication Dosing

First-Line Treatment

Corticosteroids

- Systemic corticosteroid therapy (predniso(lo)ne at 0.5 mg to 1.5 mg/kg/day)
  - Systemic corticosteroids (oral or intravenous pulses) can be combined with an immunosuppressive adjuvant at the onset of therapy, especially in cases of increased risk of corticosteroid therapy, complications due to expected prolonged use (>4 months) or dose dependency above minimal therapy (>10 mg/day). However, there is limited evidence that the addition of adjuvants is superior to treatment with corticosteroids alone.
  - While limited, studies have not shown IV corticosteroid pulses to have an additional benefit on top of conventional first-line treatment with oral predniso(lo)ne and immunosuppressive adjuvants. While more evidence is needed, 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

Currently there are two intravenous CD20 inhibitors available, rituximab and ofatumumab. All the published trials so far have used rituximab.

- 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 (11). Allows for more rapid tapering of corticosteroid doses and a major corticosteroid sparing effect.
- A course of intravenous rituximab consists of 2 x 1000 mg (2 weeks apart) or 4 x 375

mg/m2 (1 week apart).

- Treatment can be repeated in case 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.
- The incidence of unforeseen fatal infections such as progressive multifocal leukoencephalopathy (PML) cannot be estimated due to the rarity of pemphigus.

Corticosteroid-Sparing Agents

First-Line Corticosteroid-Sparing Agents

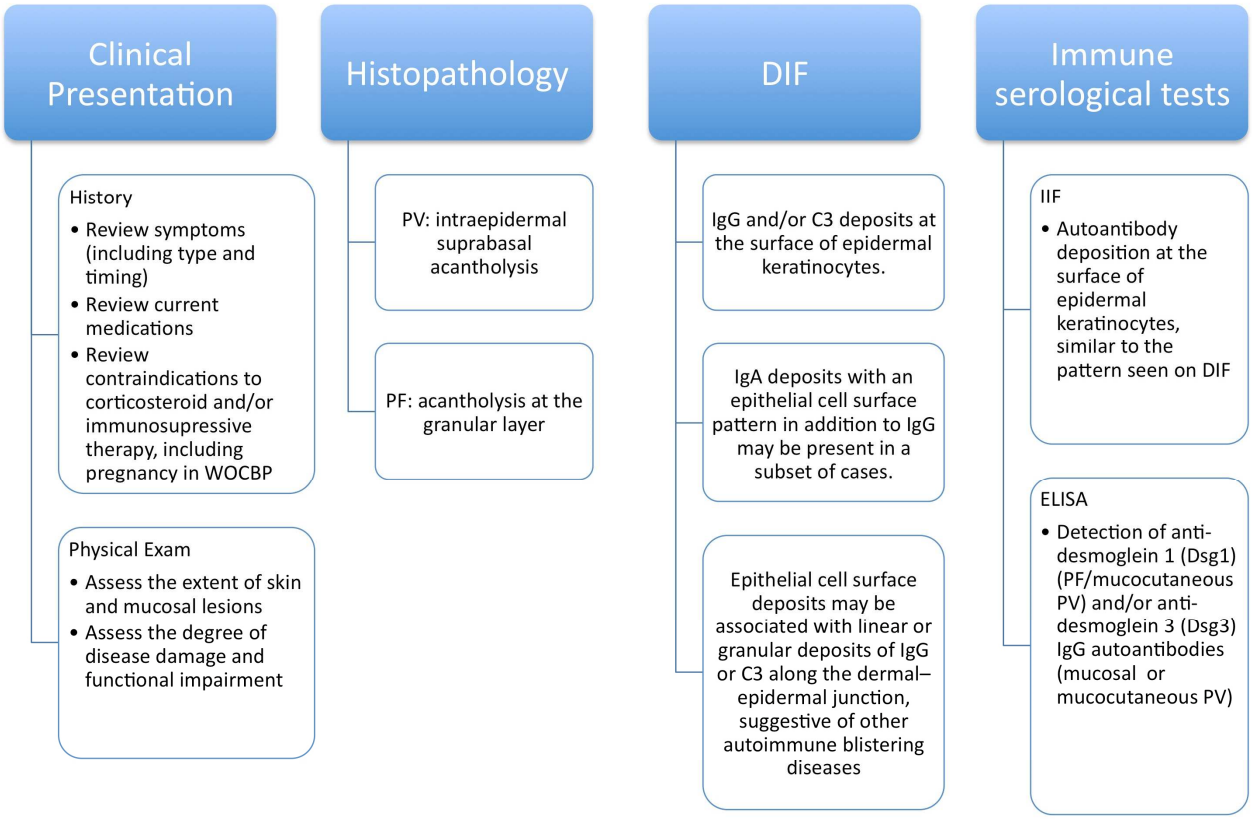
- Azathioprine (1–3 mg/kg/day).
  - Start first week 50 mg/day to detect idiosyncratic reactions such as sudden onset fevers, oral ulcers, elevated liver function tests and/or DRESS (and in case stop immediately), and then raise to desired dose. Although not predictive for idiosyncratic reactions, TPMT activity should be evaluated in countries/ethnicities where there is a higher incidence of polymorphisms before commencing therapy because recommended azathioprine doses vary based upon TPMT activity. In general, adults with pemphigus and high TPMT activity are treated with normal doses of azathioprine (up to 2.5 mg/kg/day). Patients with intermediate or low TPMT activity should receive a lower maintenance dose (up to 0.5 to 1.5 mg/kg/day) depending on level of enzyme activity. Patients that lack TPMT activity should avoid treatment with azathioprine.
- Mycophenolate mofetil (30 mg/kg-45 mg/kg/day) or mycophenolic acid (1440 mg/day).

Other Corticosteroid-Sparing Agents

- Intravenous immunoglobulins (IVIG) (2g/kg over 2-5 days per month)
    - Treatment is generally combined with systemic corticosteroids (initially) and immunosuppressive adjuvants
    - Treatment should be performed over several days to avoid side-effects
    - Aseptic meningitis is a rare but important side-effect of IVIG treatment which needs to be kept in mind in patients who commonly experience episodes of migraine
    - Although uncommon, patients with IgA deficiency should receive IgA-depleted IVIG treatment.
- Immunoadsorption
    - First-line treatment option in emergency situations where available
    - Second-line corticosteroid sparing agent where available
    - Contraindications include severe systemic infections, severe cardiovascular diseases, hypersensitivity against components of the immunoadsorption column, treatment with angiotensin-converting enzyme inhibitors and extensive hemorrhagic diathesis
- Cyclophosphamide
    - Use in cases of limited resources or in severe cases that have not responded to other treatments
    - Use as a drug of last resort due to long-term side effects

483

484



485

486 **Figure 1: Diagnosis of Pemphigus**

487 **Diagnosis requires clinical presentation and histopathology that are consistent with pemphigus**

488 **and either a positive DIF or serological detection of autoantibodies against epithelial cell surface**

489 **antigens.**

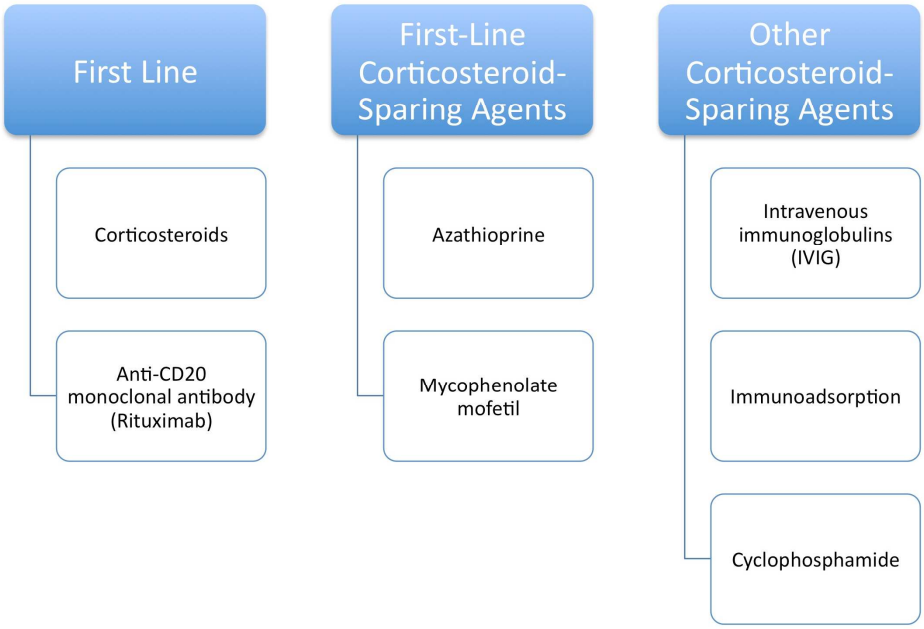


Figure 2: Treatment Options

The principal objective is to promote the healing of blisters and erosions, prevent development of new lesions, and minimize serious side effects of treatment.

Table 1:Summary of the changes made to previous guidelines

The following is a summary of the differences with the EDF/EADV guidelines.

- The following set of guidelines was revised to include diagnostic and management interventions for pemphigus vulgaris (PV) and pemphigus foliaceus (PF) only.
- The roles of general practitioners, nurse practitioners, and home care health nurses were defined.
- The titles “first-line” and “second-line” adjuvants were changed to “first-line corticosteroid sparing agents” and “other corticosteroid sparing agents”.
- Intravenous CD20 inhibitors were added as a first-line treatment recommendation for moderate to severe pemphigus
- The following qualifying statement was added to the recommendation regarding analysis of thiopurine methyltransferase (TPMT) activity when azathioprine is considered: “in countries where genetic polymorphisms for decreased TMPT activity levels are more common.”
- “In case of elevated risk” was removed as a qualifying statement with regards to checking a Quantiferon or purified protein derivative (PPD) skin test to rule out tuberculosis prior to initiating treatment.
- Statements of facts as opposed to recommendations were removed.

Capsule summary

- The European Dermatology Forum and the European Academy of Dermatology and Venereology (EDF/EADV) passed management guidelines for pemphigus.
- We present the recommendations of international experts, which have resulted from a Delphi consensus gathering exercise based on the EDF/EADV guidelines.
- This international consensus includes intravenous CD20 inhibitors as a first line therapy option for moderate to severe pemphigus.