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

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

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

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100

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102 advisory board for Principia Biopharma; and is on an advisory board for Immune Pharmaceuticals and Lilly. Dr.
103 Joly is a consultant for Roche, Principia Biopharma, Lilly and Biogen. Dr. Payne is a consultant for Syntimmune
104 and TG Therapeutics and receives grants Sanofi. Dr. Eming is an investigator for both Biotest AG and Fresenius
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121

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123

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125 **Abstract**

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

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

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

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

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

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

142

143 **Introduction**

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

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

156 In an attempt to garner greater international consensus, the International Bullous Diseases Consensus
157 Group, convened by Dr. Dedee Murrell and Dr. Victoria Werth, met in March 2016 at the annual
158 American Academy of Dermatology (AAD) conference in Washington D.C. with the goal of developing
159 international consensus guidelines for the diagnosis and management of pemphigus vulgaris and
160 pemphigus foliaceus. Prior to the meeting, members of the group, comprised of blistering disease
161 experts, completed a Delphi survey based on the EDF/EADV guidelines. Some of the tests and
162 treatments mentioned may not be available or officially registered in all countries and have been
163 assessed based on their scientific usefulness rather than regulation status. The Delphi technique is a
164 consensus-building process in which questionnaires are given to a group of experts in a series of rounds
165 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.

ACCEPTED MANUSCRIPT

167 **Methods**

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

176

177 **Initial Clinical Presentation of Pemphigus**

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

180 Major Objectives

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

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

198 Specialists Involved

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

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

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

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

- 212 • The referring dermatologist

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

224 Diagnosis

225 The diagnosis of pemphigus is based on the following criteria:

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

234 Clinical Evaluation

235 Medical History

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

247 Physical examination

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

254

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

256 The laboratory work up is delineated in Table 1.

257 **Therapeutic Management**

258 Objectives

- 259 • To promote healing of blisters and erosions
- 260 • To improve functional status
- 261 • To prevent/strictly limit development of new blisters and erosions
- 262 • To improve the quality of life
- 263 • To limit common side-effects usually associated with long-term immunosuppressive or
- 264 corticosteroid treatment

265 First-Line Treatment

266 The dosing of specific medications is delineated in Table 2.

- 267 • Corticosteroids
- 268 • Anti-CD20 monoclonal antibodies

269 Corticosteroid-Sparing Agents

270 First-Line Corticosteroid-Sparing Agents

- 271 • Azathioprine
- 272 • Mycophenolate mofetil or mycophenolic acid

273 Other Corticosteroid-Sparing Agents

- 274 • Intravenous immunoglobulins (IVIG)
- 275 • Immunoabsorption
- 276 • Cyclophosphamide

277 Supportive treatment that may be recommended:

- 278 • Proper dental care
- 279 • Intralesional injections of corticosteroids (triamcinolone acetonide) for isolated lesions.

- 280 • Topical treatment with potent corticosteroids (clobetasol propionate) or calcineurin inhibitors
- 281 applied directly to the lesions, and oral topical corticosteroids (such as triamcinolone acetonide
- 282 gel) directly to oropharyngeal erosions for use in combination with systemic therapy
- 283 • Antiseptic baths
- 284 • Covering erosive lesions, if present, using low adhesive wound dressings or local emollients, and
- 285 compresses.
- 286 • Analgesics (over the counter analgesics and opioids)
- 287 • Gels containing local anesthetics for application at the mucosal surfaces.
- 288 • Nutritional management with the help of a dietician or a nutritionist if malnutrition is related to
- 289 oral involvement or systemic corticosteroid therapy

290 Prophylaxis against Side Effects in Prolonged Corticosteroid Therapy

- 291 • Osteoporosis baseline screening and prophylaxis
- 292 • Ophthalmologic evaluation
- 293 • Vitamin D and calcium supplementation at initiation of corticosteroids treatment
- 294 • Treatment with bisphosphonates (i.e. alendronate, risedronate) in patients at risk (post-menopausal
- 295 women and men >50 years who will be on corticosteroid treatment > 3 months) of developing
- 296 osteoporosis
- 297 • Systemic antifungals, antiviral and antibiotic treatment should be used when clinically indicated
- 298 • H2-blockers or proton pump inhibitor use should be individualized to the patients given lack of
- 299 sufficient evidence.
- 300 • Anti-thrombotic prophylaxis in case of high risk of thrombosis
- 301 • Psychological support if required
- 302 • Physiotherapy if prolonged corticosteroid therapy is required

303 Vaccinations

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

309 **Monitoring**

310 Objectives

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

314 Definitions for Disease Outcome Parameters (12)

- 315 • Control of disease activity: The time at which new lesions cease to form and established lesions
316 begin to heal
- 317 • End of consolidation phase: The time at which no new lesions have developed for a minimum of 2
318 weeks and approximately 80% of lesions have healed. This is when most clinicians start to taper
319 steroids."
- 320 • Complete remission on therapy: The absence of new or established lesions while the patient is
321 receiving minimal therapy
- 322 • Complete remission off therapy: The absence of new and/or established lesions while the patient
323 is off all systemic therapy for at least 2 months

- 324 • Relapse/flare: Appearance of ≥ 3 new lesions/month that do not heal spontaneously within 1 week,
325 or by the extension of established lesions, in a patient who has achieved disease control
- 326 • Minimal therapy: Prednisolone (or the equivalent) at ≤ 10 mg/day and/or minimal adjuvant therapy
327 for at least 2 months

328 Approach to Be Maintained After Consolidation Phase

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

345 Scheduling and Content of Consultations

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

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

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

356 Clinical Evaluation

357 The clinical follow-up should seek to clarify:

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

365 Serological Monitoring Of Disease Activity

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

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

- 370 • Overall, serum concentrations of IgG autoantibodies against Dsg1 and Dsg3 correlate with the
371 clinical activity of pemphigus and may thus help in therapeutic decision making
- 372 • The persistence of high levels of anti-Dsg1 by ELISA has a positive predictive value for skin
373 relapses, whereas the persistence of anti-Dsg3 IgG does not necessarily indicate a mucosal relapse

374 Discontinuation of Treatment

- 375 • Discontinuation of treatment is primarily based on the clinical symptoms but may be also
376 supported by the findings of Dsg ELISA, IIF and/or negative DIF microscopy of a skin biopsy.
- 377 • Discontinuation of systemic corticosteroids may be proposed in patients in complete remission on
378 minimal therapy (prednisolone or equivalent at ≤ 10 mg/day). The adjuvants may be stopped 6–12
379 months after achieving complete remission on minimal therapy with adjuvants only.

380 Possible Sequelae

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

385

386 **Information for patients and their families**

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

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

396 **Areas for Future Studies**

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

401 **Intravenous CD20 inhibitors**

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

- 416 ▪ What is the ideal threshold in patients on systemic corticosteroids or immunosuppressants to
417 begin CD20 inhibitor therapy?
- 418 ▪ What is the optimal dose, frequency, total number of maintenance infusions to use?
- 419 ▪ Are these drugs indicated in patients with negative anti-DSG antibodies?
- 420 ▪ In cases of relapse, is a single dose of 1000mg/infusion of rituximab (or 375 mg/m² in
421 lymphoma protocol) enough to achieve remission instead of a full dose cycle of rituximab (2
422 x 1000 mg 2 weeks apart or 4 x 375 m²/week)?
- 423 • Long term side effects
- 424 ▪ Will more side effects occur when more patients are treated with multiple maintenance
425 infusions of CD20 inhibitors?

426 **Other treatment options**

- 427 • What role do other treatment options, like plasmapheresis, play in the treatment of pemphigus?
428

429 **Conclusion**

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

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- 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

Immune serological tests**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

Work-Up before Corticosteroid or Immunosuppressive Therapy

- 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 TPMT activity levels are more common
- Chest X-ray if Quantiferon gold or PPD is abnormal
- β 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

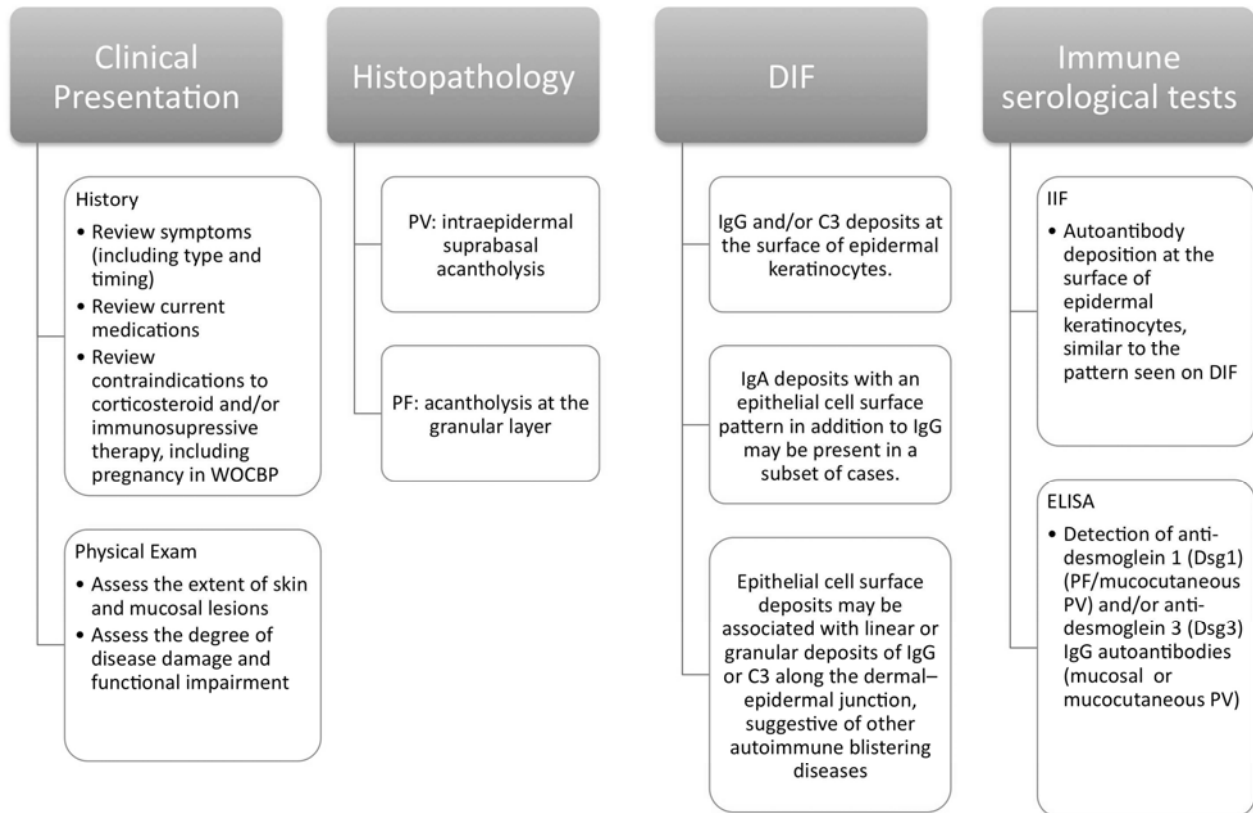
- Azathioprine (1–3 mg/kg/day).
 - Start first week 50 mg/day to detect idiosyncratic reactions such as sudden onset fevers, oral ulcers, elevated liver function tests and/or DRESS (and in case stop immediately), and then raise to desired dose. Although not predictive for idiosyncratic reactions, TPMT 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.
- Immunoabsorption
 - 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 immunoabsorption 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

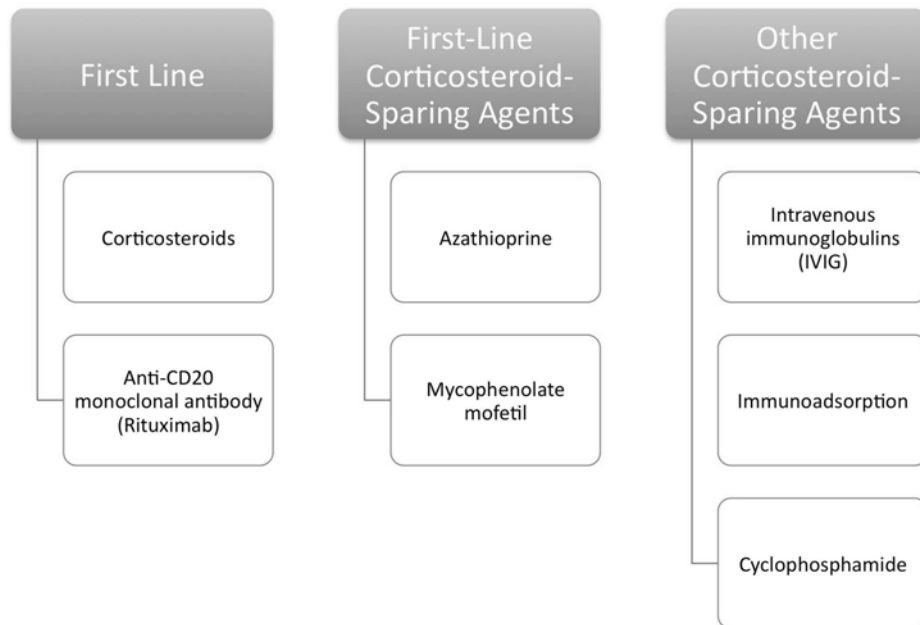
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486 **Figure 1: Diagnosis of Pemphigus**487 **Diagnosis requires clinical presentation and histopathology that are consistent with pemphigus**488 **and either a positive DIF or serological detection of autoantibodies against epithelial cell surface**489 **antigens.**



490

491 **Figure 2: Treatment Options**

492 The principal objective is to promote the healing of blisters and erosions, prevent development of new

493 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.

1 **Capsule summary**

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