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How do experts treat patients with bullous pemphigoid around the world? An international survey.

Marine Guignant, Billal Tebirt, Dedee F. Murrell, Masayuki Amagai, Valeria Aoki, Johannes Bauer, Giuseppe Ciancinni, Donna Culton, Maryam Daneshpazhooh, Dipankar De, Janet Fairley, Russell Hall, Soo-Chan Kim, Neil J. Korman, Cezary Kowalewski, Daniel Mimouni, Aikaterini Patsatsi, Vivien Hebert, Marwah Adly Mohamed Saleh, Enno Schmidt, Eli Sprecher, Soner Uzun, Vanessa Venning, Victoria P. Werth, Detlef Zillikens, Pascal Joly

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Title

How do experts treat patients with bullous pemphigoid around the world? An international survey.

Authors

Marine Guignant [(1)], Billal Tebirt[(1)], Dedee F Murrell [(2)], Masayuki Amagai [(3)], Valeria Aoki [(4)], Johannes Bauer [(5)], Giuseppe Ciancinni [(6)], Donna Culton [(7)], Maryam Daneshpazhooh [(8)], Dipankar De [(9)], Janet Fairley [(10)], Russell Hall [(11)], Soo-Chan Kim [(12)], Neil J. Korman [(13)], Cezary Kowalewski [(14)], Daniel Mimouni [(15)], Aikaterini Patsatsi [(16)], Vivien Hebert [(1)], Marwah Adly Mohamed Saleh [(17)], Enno Schmidt [(18,19)], Eli Sprecher [(20)], Soner Uzun [(21)], Vanessa Venning [(22)], Victoria P. Werth [(23)], Detlef Zillikens[(18)], Pascal Joly [(1)].

(1) Department of Dermatology, Rouen University Hospital and INSERM U1234, Centre de référence des maladies bulleuses autoimmunes, Normandie University, Rouen.

(2) Department of Dermatology, St George Hospital, University of New South Wales, Sydney, Australia.

(3) Department of Dermatology, Keio University School of Medicine, Tokyo, Japan; Laboratory for Skin Homeostasis, RIKEN Center for Integrative Medical Sciences, Kanagawa, Japan.

(4) Department of Dermatology, University of Sao Paulo, Sao Paulo, Brazil.

(5) Department of Dermatology, University Hospital of the Paracelsus Medical University, Salzburg, Austria.

(6) Department of Dermatology Ospedale Classificato Cristo RE, Rome, Italy.

(7) Department of Dermatology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA.

(8) Bullous Diseases Research Center, Department of Dermatology, Razi Hospital, Tehran University of Medical Sciences, Tehran, Iran.

(9) Department of Department of Dermatology, Venereology, and Leprology, Postgraduate Institute of Medical Education and Research, Chandigarh, India.

(10) Department of Dermatology, University of Iowa, Iowa City, Iowa; Department of Veterans Affairs Medical Center, Iowa City, Iowa.

(11) Department of Dermatology, Duke University School of Medicine , Durham, North Carolina, USA.

(12) Department of Dermatology, Gangnam Severance Hospital, Seoul, Korea.

(13) Department of Dermatology, University Hospitals Cleveland Medical Center, Cleveland, Ohio, USA.

(14) Department of Dermatology and Immunodermatology, Medical University of Warsaw, Warsaw, Poland.

(15) Department of Dermatology, Rabin Medical Center, Beilinson Hospital, Petah Tikva, Israel; Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel.

(16) Department of Dermatology, Medical School, Aristotle University of Thessaloniki "Papageorgiou" General Hospital, Thessaloniki, Greece.

(17) Department of Dermatology, Cairo University, Cairo, Egypt.

(18) Department of Dermatology, University of Lübeck, Lübeck, Germany.

(19) Lübeck Institute of Experimental Dermatology (LIED), University of Lübeck, Lübeck, Germany

(20) Department of Dermatology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel.

(21) Department of Dermatology and Venereology, Faculty of Medicine, Akdeniz University, Antalya, Turkey.

(22) Department of Dermatology, Churchill Hospital, Oxford, United Kingdom.

(23) Department of Dermatology, University of Pennsylvania, Philadelphia, Pennsylvania, USA.

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Corresponding author: Dr Billal Tedbirt

Clinique Dermatologique

Rouen University Hospital

1 rue de Germont

76031 Rouen, France

Telephone: +33 2 32 88 68 41

Fax: +33 2 32 88 80 55

Email: bilal.tedbirt@chu-rouen.fr

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Authors' ORCIDS :

- Marine Guignant : 0000-0002-1891-528X
- Billal Tedbirt : 0000-0001-7404-010X
- Murell Dedee F : 0000-0003-2971-0199
- Amagai Masayuki : 0000-0003-3314-7052
- Aoki Valeria : 0000-0003-4256-4413
- Bauer Johannes : 0000-0002-5624-2055
- Cianchini Giuseppe : 0000-0002-7605-4780
- Culton Donna Aline : 0000-0002-7692-6446
- Daneshpazhooh Maryam : 0000-0003-1020-8895
- De Dipankar : 0000-0001-8682-2598
- Fairley Janet A : 0000-0002-8203-0486
- Russell Hall : 0000-0001-7621-4935
- Kim Soo-Chan : 0000-0002-2327-4755
- Neil Korman : 0000-0002-9785-3442
- Kowalewski Cezary : 0000-0002-6608-9066
- Mimouni Daniel : 0000-0001-7158-2085
- Patsatsi Aikaterini : 0000-0001-9616-2001
- Hébert Vivien : 0000-0001-9071-2033
- Saleh Marwah Adly : 0000-0002-9487-8708
- Schmidt Enno : 0000-0002-1206-8913
- Eli Sprecher : 0000-0002-4093-1032
- Uzun Soner : 0000-0001-7059-5474
- Venning Vanessa : 0000-0001-6880-0678
- Werth Victoria P : 0000-0003-3030-5369
- Zillikens Detlef : 0000-0002-5668-307X
- Joly Pascal : 0000-0002-5734-0255

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ACRONYM LIST

AAD: American Academy of Dermatology

BP: bullous pemphigoid

CS: corticosteroid

EADV: European Academy of Dermatology and Venereology

EDF: European Dermatology Forum

RCT: randomized controlled trial

USA: United States of America

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Abstract

Many treatments are currently proposed to treat bullous pemphigoid (BP) patients. We assessed treatment modalities of BP depending on the different countries, BP extent and patients' comorbidities. We surveyed worldwide experts about how they treat BP patients. Sixty-one experts from 27 countries completed the survey. Severe and moderate BP were treated with oral prednisone (61.4% and 53.7%), or superpotent topical corticosteroids (CS) (38.6% and 46.3% respectively). Conventional immunosuppressants were more frequently combined with oral prednisone (74.5%), than with super-potent topical CS (37.5%) in severe BP. Topical CS were mainly used in Europe in mild (81.1%), moderate (55.3%) and severe BP (54.3%). In the USA and Asia, systemic CS were mainly proposed to treat severe (77.8% and 100%), moderate (70% and 77.8%), but also mild BP (47.1% and 33.3% respectively). Most experts reduced the initial dose of oral CS in patients with diabetes mellitus (48.1%) or cardiac insufficiency (40.2%), but rarely changed BP treatment in patients with neurological disorder or neoplasia. This survey showed major differences in the way that BP patients are treated between AmeriPac countries (USA, Latin America and Australia) and Asia on the one hand, and Europe and the Middle East on the other hand.

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Introduction

Treatment of bullous pemphigoid (BP) remains challenging, since elderly BP patients have a poor tolerance for many treatments (Joly et al, 2002; Bernard et al, 1995; Jung et al, 1995; Langan et al, 2008; Korman, 1998). The main deleterious prognostic factors of BP include older age, poor general condition, comorbidities, in particular debilitating neurological disorders, and the use of high doses of systemic corticosteroids (CS) (Joly et al, 2002; Rzany et al, 2002; Joly et al, 2012; Cortés et al, 2011; Joly et al, 2005). A wide range of treatments are available, the use of which is highly variable and largely depends on dermatologists' experience. High doses of oral CS are still considered the mainstay of treatment for BP patients in some countries, whereas they are no longer recommended in other countries, due to the frequency and severity of their side effects (Korman, 1998; Fine, 1995; Westerhof, 1989). Medium doses of oral prednisone have recently been proposed by a panel of experts in the EADV/ EDF guidelines, without clear evidence from the literature (Cozzani et al, 2018). Superpotent topical CS have been demonstrated to be safer and more effective than high doses of oral prednisone in patients with extensive BP, but their use is limited by the poor practicability of this treatment (Joly et al, 2002; Joly et al; 2012; Sobocinski et al, 2016; Terra et al, 2014). The usefulness of immunosuppressants as first line therapies and CS-sparing agents remains debatable because no randomized controlled trial (RCT) has demonstrated a benefit of this combined treatment over CS alone (Beissert et al, 2007; Guillaume et al, 1993; Kirtschig et al, 2010). Finally, the use of immunomodulants such as tetracycline, dapsone or fumarate seems extremely heterogeneous among countries (Williams et al, 2017; Bouscarat et al, 1996; Feliciani et al, 2015). These latter treatment options are mentioned in the European and Japanese guidelines (Ujiie et al, 2019), despite conflicting results from the literature. Tetracyclines have been claimed to be non-inferior to medium doses of prednisone in a RCT (Williams et al, 2017),

while in the real life, 72% of the patients who were started with tetracyclines alone required additional oral prednisolone, and only 12% of patients were able to continue doxycycline alone throughout the study (Micallef et al, 2021). Similarly a CS-sparing effect of dapsone is often claimed, while in a RCT comparing dapsone and azathioprine, only 11% of patients treated with dapsone were able to completely taper CS (Sticherling et al, 2017). The purpose of this worldwide survey was to assess treatment modalities of BP patients depending on the different countries, BP extent and patients comorbidities.

Results

Experts

A survey was sent to 78 experts identified by their publications in the field of BP. They were practicing in 27 countries in Europe, USA, Asia, Middle East, Australia and South America. Sixty-one surveys (78.2%) were completed. Fifty-four percent of the responses came from Europe, 19.7% from the United States of America (USA), 11.5% from Middle Eastern countries, 11.5% from Asia, 1.6% from Australia and 1.6% from South America (Brazil).

Most treatments were available in the different countries except fumarate, which is only available in Germany. Additionally, superpotent topical CS, rituximab, mycophenolate mofetil (MMF) and intravenous immunoglobulins were either not reimbursed and / or only available to a small number of BP patients in some European countries (Hungary, Croatia), as well as in Singapore, Australia, Iran, andTurkey..

Management of patients with bullous Pemphigoid depending on disease severity.

The respective frequencies of the various treatments used depending on the clinical severity of BP are shown in Table 1.

Treatment of severe types of BP. Severe BP was treated with oral prednisone or super potent topical CS in 51/83 (61.4%) and 32/83 (38.6%) of cases, respectively. The most frequently used initial dose of prednisone was 0.75mg/kg/day (51.0% of responses which indicated the use of prednisone), whereas the initial doses of clobetasol propionate were quite variable, ranging from 20mg/d (50.0% of responses) to 30 mg/day (34.4%) and 40 mg/day (34.4%).

Conventional immunosuppressants (MMF, methotrexate and azathioprine) were more frequently associated with oral prednisone, 38/51 (74.5% of responses), than with super potent topical CS, 12/32 (37.5%). Interestingly, among the 50 responses mentioning the use of an immunosuppressant, azathioprine, 17/38 (44.7%) and MMF, 13/38 (34.2%) were the main immunosuppressants associated with oral CS, whereas methotrexate was mainly associated with topical CS, 6/12 (50.0%). Doxycycline and dapsone were associated with (oral or topical) CS in 18/83 (21.6%) and 11/83 (13.3%) of responses, respectively.

Treatment of moderate types of BP. Oral prednisone and topical CS were used in 43/80 (53.7%) and 37/80 (46.3%) of cases, respectively. Immunosuppressants were less frequently associated with oral CS than in severe types of BP, 21/43 (48.8%) versus 38/51 (74.5%) of responses (p=0.02). The most frequently used initial doses of oral prednisone was 0.5mg/kg/day in 65.1% of cases, and that of clobetasol propionate was between 20g/day, 23/37 (62.2%) and 30g/day, 11/37 (29.7%). Immunomodulators were associated with oral or topical CS in proportions quite similar to those proposed in severe BP, doxycycline in 19/80 cases (23.8%) and dapsone in 6/80 cases (7.5%). Doxycycline and dapsone were associated with oral or topical CS in 19/80 cases (23.8%) and 6/80 cases (7.5%), respectively.

Treatment of mild types of BP. Topical CS were proposed in 50/70 (71.4%) of cases to treat mild types of BP, mainly at an initial dose of 20g/day, 16/50 (32.0% of responses), whereas oral prednisone was proposed in 20/70 cases (28.6%), mainly at an initial-dose of 0.5mg/kg/day,

14/20 (70.0%). Tetracyclines were more frequently used to treat these mild types of BP, 24/70 (34.3%), than conventional immunosuppressants, 9/70 (12.9%), (P=0.005).

Treatment of localized types of BP. Topical CS were used in 63/65 cases (96.9 %), mainly at an initial dose of 20g/day in 24/63 (39.3%) of responses. Doxycycline was associated with topical CS in 9/61 (14.8%) of cases.

During the consolidation phase, patients with a favorable course were usually treated with the same treatments as those used during the initial phase of treatment. Oral and / or topical CS doses were first tapered in between 71.7% and 87.8% of cases, and then stopped before reducing immunosuppressants.

Management of patients with bullous pemphigoid by experts from different geographic areas.

We then analyzed experts' responses according to the geographic areas, i.e. USA, South America, Europe, Middle East, Asia, and Australia. Since treatment modalities of BP were quite similar in USA, Australia, and South America (AmeriPac group), we pooled their responses in the analysis. The main treatments used by experts from Europe, USA/Australia/South America, Asia and Middle East, depending on the clinical severity of BP, are shown in Table 2.

Severe BP. Oral CS (usually at an initial dose of 0.5 to 0.75 mg/kg/day) were mostly used in the AmeriPac group, 14/18 (77.8%), Asia, 7/7 (100%) and Middle East, 7/10 (70%), whereas both oral CS, 21/46 (45.7%) and topical CS, 25/46 (54.3%) were used in Europe. Conventional immunosuppressants (MMF, methotrexate and azathioprine) were almost systematically associated with CS in the AmeriPac group, 17/18 (94.4%) and Asia, 6/7 (85.7%) and less frequently in Europe, 24/46 (52.1%) and Middle East, 3/10 (30%). Immunosuppressants which

were most commonly associated with CS in Europe were methotrexate, 10/24, (41.7%) of responses mentioning the use of an immunosuppressant and azathioprine, 12/24 (50.0%), whereas MMF and azathioprine were preferentially used in the AmeriPac group , 10/17 (58.8%) and 5/17 (29.4%) respectively, and in Asia , 2/6 (33.3%) and 4/6 (66.7%), respectively.

Moderate BP. As in severe BP, oral CS (alone or associated with immunosuppressants or immunomodulants) were mainly used in the AmeriPac group and Asia, 14/20 (70.0%) and 7/9 (77.8%) of responses respectively, whereas both oral and topical CS were used in Europe and the Middle East: oral CS, 17/38 (44.7%) and 4/8 (50%) respectively, topical CS, 21/38 (55.3%) and 4/8 (50.0%), respectively.

Mild BP. Topical CS were most frequently used in Europe, 30/37 (81.1%) of responses, and the Middle East, 6/7 (85.7%), whereas in the AmeriPac group and Asia, both topical, 9/17 (52.9%) and 2/6 (33.3%) respectively, and oral CS, 8/17 (47.1%) and 4/6 (66.7%) were used. Conventional immunosuppressants were very rarely used in Europe in mild types of BP, 3/37 (8.1%), and a little bit more frequently, 5/17 (29.4%) by the AmeriPac dermatologists. Doxycycline (associated with oral or topical CS) was mostly used in AmeriPac group 11/17 (64.7%) and Asia, 3/6 (50%) and less frequently in Europe, 8/37 (21.6%) and the Middle East, 2/7 (28.6%). Dapsone was used almost exclusively in Europe in association with topical corticosteroids, 6/30 (20%).

Localized BP. Topical CS were almost exclusively used in these localized types of BP worldwide, 60/62 (96.8% of responses), most often alone, 55/62 (81.6%), or rarely associated with doxycycline, 7/62 (11.3%).

Management of patients with severe associated medical conditions.

Treatment modifications according to comorbidities are shown in Table 3. Experts reduced the initial doses of oral CS or, if possible, did not use any oral CS in patients with severe diabetes mellitus (48.1%) or cardiac insufficiency (40.2%). This was particularly true in patients with severe types of BP, usually treated with the highest doses of prednisone. Most experts did not modify the treatment of BP patients with severe neurological conditions, regardless of the BP severity (45.6%, 60.6% and 85.7% of responses in patients with severe, moderate and mild BP respectively). Similarly, most experts did not modify the treatment in BP patients who had an associated neoplasia in particular in those with severe BP (57.9%). They indicated not using immunosuppressants in patients with neoplasia in only 22.8% of cases. Experts avoided methotrexate or any other immunosuppressant in patients with renal insufficiency in only 21.1% and in 23.0% of cases.

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Discussion

This survey showed that the two main treatments proposed for BP patients were oral prednisone and superpotent topical CS. High doses of oral CS have been considered the mainstay of treatment for BP patients for many years (Korman, 1998; Westerhof, 1989). The poor tolerance of high doses of oral CS in elderly BP patients has been suspected in many open studies in the literature (Rzany et al, 2002; Joly et al, 2005; Roujeau et al, 1998), and has been definitely demonstrated in a RCT, which showed that superpotent topical CS were safer and more effective than 1mg/kg/day of oral prednisone (Joly et al, 2002). Accordingly, a 1.0 mg/kg/d dose of oral prednisone was rarely proposed by experts (17.5%), even in patients with severe BP. The most frequently proposed starting dose of prednisone was 0.5 to 0.75 mg/day (Morel and Guillaume, 1984). A starting dose of 0.5 mg//kg/day of prednisone has been

recommended in the European Guidelines on BP (Feliciani et al, 2015), despite the lack of evidence showing the efficacy of this medium dose in patients with extensive BP (Kirtschig et al, 2010; Singh et al, 2011; Daniel et al, 2011). An initial dose of 0.5mg/kg/day was frequently proposed by experts in patients with mild and moderate BP, which is in accordance with the RCT by Joly et al. which showed a 91% rate of disease control with this dosage in patients with mild/ moderate BP (Joly et al, 2002).

Clobetasol propionate cream was used at an initial dose of between 20 and 30g/day, as was done in 3 large clinical trials, that showed a 74% to 100% rate of clinical remission in both types of BP (Joly et al, 2002; Terra et al, 2014; Joly et al, 2009).

Despite the fact that no RCT could demonstrate any benefit from the association of conventional immunosuppressants and CS over CS alone (Kirtschig et al, 2010; Daniel et al, 2011), immunosuppressants were widely proposed by experts mainly in association with systemic CS in the treatment of severe BP. In fact, while several open label studies evaluating methotrexate, MMF and azathioprine have suggested their efficacy either alone (Paul et al, 1994; Greaves et al, 1971; Grundmann-Kollmann et al, 1999) or in association with systemic or topical corticosteroids (Beissert et al, 2007; Guillaume et al, 1993; Du Thanh et al, 2011), the only RCT which assessed the safety and efficacy of azathioprine in addition to oral CS showed no benefit and an increased risk of treatment side effects, in particular severe infections in patients with the combined treatment relative to those who received oral prednisone alone (Guillaume et al, 1993). In our survey, methotrexate was most commonly proposed in association with topical corticosteroids (mainly in European countries), whereas azathioprine and MMF were preferentially associated with oral prednisone (Beissert et al, 2007).

Dapsone was rarely proposed (from 4.7% up to 15.7%) regardless of BP severity. Its efficacy has been suggested in small retrospective case series and a recent RCT (Bouscarat et al, 1996;

Schmidt et al, 2005; Gürcan et al, 2009). Doxycycline was proposed in a minority of patients with mild and moderate types of BP (23.9% and 34.3% respectively), while a recent RCT suggested that a regimen associating doxycycline and topical CS would be non-inferior to a medium dose of oral prednisolone (Williams et al, 2017).

Interestingly, the way experts treat the different types of BP was quite different between the AmeriPac countries (USA, Latin America and Australia) and Asia on the one hand, and Europe and the Middle East on the other hand. Topical CS were mainly used by experts from Europe and the Middle East to treat mild (around 80%), moderate BP (around 50%), and severe types of BP (54.3%). These findings are in accordance with the European guidelines, which recommended the use of topical CS as first-line treatment for both mild, moderate, and severe types of BP (20). Conversely, systemic CS were mainly proposed by AmeriPac and Asian dermatologists, not only in moderate (70% and 77.8% respectively) and severe types of BP (77.8% and 100%), but also quite frequently in mild types of BP (47.1 and 33.3% respectively). This finding might be explained by the different Health Care systems and the very high price of clobetasol propionate cream in the US, Australia, and some Asian countries. Moreover, the absence of dermatology-specific in-patient hospitalization units in the US and Australia makes application of topical CS over large body surface areas difficult.

As expected, many experts suggested not to use oral CS, or at least to reduce the dose of CS in BP patients with diabetes mellitus or cardiac insufficiency, and to avoid the use of methotrexate in patients with renal insufficiency. Surprisingly, only 22.8% of experts avoided immunosuppressants in BP patients with an associated cancer.

A limitation of our study is the presence of only one expert from Africa and nine Asian experts. This is related to the fact that the 78 experts who participated in this publication were first identified by their publications in the field of BP, and agreed to complete the survey, and

participated in the international meeting on autoimmune bullous diseases during which the relevance of questions in the survey were discussed. However, we aimed to only survey renowned international experts who have published in the field of autoimmune bullous diseases. Since there could be more than one answer to a given question in the survey, the number of responses was higher than the number of experts. This could have led to an over-representation of the responses of experts who completed several responses.

Overall, this study showed a wide heterogeneity of treatments used in patients with bullous pemphigoid, which appears to be at least as much related to physicians' habits and characteristics of the different health care systems as to evidence-based medicine.

Material and methods

A preliminary survey was sent by e-mail to a panel of international experts in the field of autoimmune bullous diseases in March 2017. Survey questions were related to the different options used for the initial and the consolidation phases of treatment of BP patients, depending on severity and patients' associated disorders.

Disease severity was classified as severe (more than 30 new blisters per day or more than 30 intact recent blisters), moderate (10 to 30 new blisters per day or 10 to 30 intact recent blisters), mild (less than 10 new blisters per day or less than 10 intact recent blisters) and localized BP. The different comorbidities considered were the presence of a severe or debilitating neurological condition (severe dementia, stroke, severe Parkinson’s disease, bed-ridden patients), severe diabetes, cardiac insufficiency or severe cardiovascular conditions, renal insufficiency and associated cancer.

The relevance of questions in the survey and the different ways of treating BP patients were discussed by the International Bullous Diseases Consensus Group (IBDCG) during an international meeting on autoimmune bullous diseases in Lübeck (Germany) in June 2017. Based on the comments and discussions, the initial survey was modified and sent to a larger number of international experts in order to ensure the widest possible representation. The final results were discussed by the IBDCG in March 2018 during the annual meeting of the American Academy of Dermatology (AAD) in San Diego (USA).

Responses are expressed in numbers and percentages. Since participants were allowed to tick several responses, the percentages were calculated using the number of responses instead of the number of authors. The frequencies were compared using Fisher's exact test. A value of $p < 0.05$ was considered as statistically significant.

Data availability statement

No datasets were generated or analyzed during this study.

CONFLICT OF INTEREST

- Dedee F Murrell is consultant for Roche, Principia-bio, Lilly, GSK, Novartis, Sanofi, Regeneron, ArgenX. Coinventor of BPDAI. Inventor, ABQOL & TABQOL.
- Masayuki Amagai has received research grants from Maruho, Kose, and JSR.
- Valeria Aoki conducted clinical trial for Roche
- Johannes Bauer is consultant for Castle Creek Pharma, KBHB, TWI
- Donna Culton is consultant for Principia Biopharma, Afyx Therapeutics and Cabaletta Bio.
- Russell Hall is consultant and/or clinical trial investigator for Cabelleta, Argenx, Principia, Regeneron, Akari , Alexion. Editor, *JID Innovations*.
- Neil J. Korman has served as a consultant, principal investigator, advisory board member, or speaker for AbbVie, Amgen, Celgene, Chemocentryx, Dermira, Eli Lilly, Genentech, GlaxoSmithKline, Immune, Janssen, Kyowa Hakko Kirin Pharma, Leo Pharma, Menlo Therapeutics, Novartis, Pfizer, Principia, Prothena,

Regeneron, Rhizen, Sun Pharma, Syntimmune, Trevi, UCB, Valeant and XBiotech.

- Aikaterini Patsatsi is consultant for Principia Biopharma, Jannsen, Leo, Novartis, Abbvie, Lilly, UCB, Genesis Pharma - Greece
- Enno Schmidt is consultant for UCB, Incyte, ArgenX, Roche, Genetech, AstraZeneca, Admirx, Synthon, Imevax, and Thermo Fisher. In addition, he received honoraria form Novartis, Biotest, and Fresenius. He has research grants with UCB, Incyte, ArgenX, Admirx, Synthon, Biotest,
- Eli Sprecher is consultant for Solgel, Pierre Fabre, Kamari, BIOMX, Bayer
- Soner Uzun is consultant for Roche
- Victoria P. Werth is consultant for for Genentech, Janssen, Lilly, Principia,AstraZeneca, Astra-Zeneca, Argenx, Regeneron; **Grants:** Genentech, Syntimmune, Regeneron
- Detlef Zillikens has obtained support for research and development work, lecturing and consulting from Abbvie, ArgenX, Biotest, Euroimmun , Fresenius, Janssen, and UCB Pharma within the last 3 years. Speakers´Honoraria/ Travel Support: Biotest, Fresenius, Miltenyi, Roche, Biogen, Abbvie, UCB, Janssen, Novartis.
- Pascal Joly is consultant for Roche, Amgen, Principia Biopharma, Argenx, Astra Zeneca and Thermofisher, Sanofi, Akari, Janssen, Novartis, Servier, Chugai, Kezar Life Science, Regeneron, UCB, Lilly, Abbvie.

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International experts who completed the survey:

Alexandre Marina. Dermatology Department, APHP, Avicenne Hospital, Bobigny, France.
Akman-Karakaş Ayşe. Department of Dermatology and Venerology, Faculty of Medicine, Akdeniz University, Antalya, Turkey.
Amagai Masayuki. Department of Dermatology, Keio University School of Medicine, Tokyo, Japan, PC160-8582.

Aoki Valeria. Department of Dermatology, University of Sao Paulo, Sao Paulo, Brazil.
Bauer Johannes. Division of Molecular Dermatology, Department of Dermatology, Paracelsus Medical University Salzburg, Salzburg, Austria.
Bedane Christophe. Department of Dermatology, University Hospital Dupuytren, Limoges, France.
Bernard Philippe. Department of Dermatology, Reims University Hospital, University of Champagne-Ardenne, Reims, France.
Caproni Marzia. Department of Surgery and Translational Medicine, Section of Dermatology, University of Florence, Florence, Italy.
Caux Frédéric. Department of Dermatology, Avicenne Hospital, University Paris 13, Bobigny, France.
Ciancinni Giuseppe. Department of Immunodermatology, Istituto Dermopatico dell'Immacolata, IRCCS, Rome, Italy; Laboratory of Molecular and Cell Biology, Istituto Dermopatico dell'Immacolata, IRCCS, Rome, Italy.
Culton Donna. Department of Dermatology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA.
Daneshpazhooh Maryam. Bullous Diseases Research Center, Department of Dermatology, Razi Hospital, Tehran University of Medical Sciences, Tehran, Iran.
De Dipankar. Department of Department of Dermatology, Venereology, and Leprology, Postgraduate Institute of Medical Education and Research, Chandigarh, India.
Dmochowski Marian. Cutaneous Histopathology and Immunopathology Section, Department of Dermatology, Poznan University of Medical Sciences, Poznan, Poland.
Drenovska Kossara. Department of Dermatology and Venereology, Medical Faculty, Medical University-Sofia, Sofia, Bulgaria.
Eming Rüdiger. Department of Dermatology and Allergology, University Hospital, Philipps-Universität Marburg, Marburg, Germany.
Fairley Janet. Department of Dermatology, University of Iowa, Iowa City, Iowa; Department of Veterans Affairs Medical Center, Iowa City, Iowa.
Feldman Ron. Department of Dermatology, Emory University, Atlanta, Georgia, USA.
Feliciani Claudio. Section of Dermatology, Department of Clinical and Experimental Medicine, University of Parma, 43100 Parma, Italy
Fivenson David. St Joseph Mercy Health System, Department of Dermatology, Ann Arbor, Michigan, USA.
Goebeler Matthias. Department of Dermatology, Venereology, and Allergology, University Hospital Wuerzburg, Wuerzburg, Germany.
Grando Sergei A. 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.
Hall Russell. Division of Dermatology, Duke Medical Center, Durham, North Carolina, USA.
Hashimoto Takashi. Kurume University School of Medicine, Kurume, Japan.
Hertl Michael. Department of Dermatology, University Hospital, Marburg, Germany.
Hofmann Silke. Helios Hospital Wuppertal, Department of Dermatology, Allergology and Dermatosurgery, Wuppertal, Germany.
Ioannides Dimitrios. First Dermatology Department, Aristotle University of Thessaloniki, Delfon 124, 54643, Thessaloniki, Greece..
Jedlickova Hana. First Department of Dermatovenereology, Masaryk University, St. Anna Faculty Hospital, 656 91, Brno, Czech Republic

Joly Pascal. Clinique Dermatologique, Institut National de la Sante et de la Recherche Medicale (INSERM), INSERM U905, Rouen University Hospital, University of Rouen, Rouen, France; Dermatology Department, Rouen University Hospital, University of Rouen, Rouen, France.
Jonkman Marcel. University Medical Center Groningen, University of Groningen, Groningen, The Netherlands.
Kim Soo-Chan. Department of Dermatology, Gangnam Severance Hospital, Seoul, Korea.
Korman Neil. Department of Dermatology, University Hospitals Cleveland Medical Center, Cleveland, Ohio, USA.
Kowalewski Cezary. Department of Dermatology and Immunodermatology, Medical University of Warsaw, Warsaw, Poland.
Lehman Julia. Department of Dermatology, Mayo Clinic, Rochester, Minnesota, USA
Lim Yen Loo. Department of Dermatology, National Skin Centre, Singapore.
Marinovic Branka. Department of Dermatology and Venereology, Zagreb University Hospital Center and School of Medicine, Zagreb, Croatia.
Marzano Angelo. Unità Operativa di Dermatologia, IRCCS Fondazione Cá Granda, Ospedale Maggiore Policlinico, Dipartimento di Fisiopatologia Medico-Chirurgica e dei Trapianti, Università degli Studi di Milano, Milan, Italy.
Mascaro Jose Manuel Jr. Department of Dermatology, Hospital Clínic, Universitat de Barcelona, Barcelona, Spain.
Meng-Sui Lee. Department of Dermatology, Taipei City Hospital, Taiwan.
Mimouni Daniel. Department of Dermatology, Rabin Medical Center, Beilinson Hospital, Petah Tikva, Israel; Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
Murrell Dedee. Department of Dermatology at St George Hospital, University of New South Wales, Sydney, Australia
Musette Philippe. Department of Dermatology, Rouen University Hospital, University of Rouen, Rouen, France.
Parajuli Niraj. Department of Dermatology and Venereology, National Academy of Medical Sciences, Bir Hospital, Kathmandu, Nepal
Patsatsi Aikaterini. Department of Dermatology, Medical School, Aristotle University of Thessaloniki "Papageorgiou" General Hospital, Thessaloniki, Greece.
Payne Aimee. Department of Dermatology, University of Pennsylvania, Philadelphia, PA 19104, USA.
Prost Catherine. Department of Dermatology, Department of Histology, Reference Center for Autoimmune Bullous Diseases, Avicenne Hospital, University Paris 13, Bobigny, France.
Rubenstein David. Department of Dermatology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA.
Saleh Marwah Adly. Department of Dermatology, Cairo University, Cairo, Egypt.
Sárdy Miklós. Department of Dermatology and Allergology, Ludwig -Maximilian University, Munich, Germany
Schmidt Enno. Department of Dermatology, University of Lübeck, Lübeck, Germany.
Seta Vannina. Department of Dermatology, APHP, Avicenne Hospital, Bobigny, France.
Setterfield Jane. St John's Institute of Dermatology (GKT), St Thomas' Hospital, London, UK.
Sprecher Eli. Department of Dermatology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel.
Uzun Soner. Department of Dermatology and Venereology, Faculty of Medicine, Akdeniz University, Antalya, Turkey.
Van Beek Nina. Department of Dermatology, University of Lübeck, Lübeck, Germany.
Vassileva Snejina. Department of Dermatology and Venereology, Medical Faculty, Medical University-Sofia, 1 Georgi Sofiiski Boulevard, 1431 Sofia, Bulgaria.

Venning vanessa. Department of Dermatology, Churchill Hospital, Oxford, United Kingdom
Werth Victoria. Corporal Michael J. Crescenz Veterans Affairs Medical Center, University of Pennsylvania, Philadelphia, Pennsylvania; Department of Dermatology, University of Pennsylvania, Philadelphia, Pennsylvania, USA.
Wozniak Katarzyna. Department of Dermatology and Immunodermatology, Medical University of Warsaw, Warsaw, Poland.
Yayli Savas. Department of Dermatology, School of Medicine, Karadeniz Technical University, Trabzon, Turkey.
Zillikens Detlef. Department of Dermatology, University of Lübeck, Lübeck, Germany.
Zone John. Department of Dermatology, School of Medicine, University of Utah, Salt Lake City, Utah, USA.

AUTHOR CONTRIBUTIONS:

Conceptualization : PJ

Formal analysis : MG, BT, PJ

Supervision : PJ

Validation : PJ

Visualization : MG, BT

Writing – original draft : MG, BT, PJ

Writing – review and editing : MG, BT, DM, MA, VA, JB, GC, ADC, MD, DD, JF, RH, SCK, NJK, CK, DM, AP, VH, MAS, ES, ES, SU, VV, VPW, DZ, PJ

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Table 1. Treatment modalities of patients with bullous pemphigoid depending on disease severity.

	SEVERE/EXTENSIVE n (%)	**MODERATE** n (%)	**MILD** n (%)	**LOCALIZED** n (%)
INITIAL TREATMENT	n=83*	n= 80*	n= 70*	n= 65*
Prednisone +/- immunosuppressant	**51 (61.4)**	**43 (53.7)**	**20 (28.6)**	**2 (3.1)**
Dose of prednisone	n=51	n = 43	n = 20	n = 2
1.0mg/kg/d	9 (17.6)	5 (11.6)	1 (5.0)	0 (0.0)
0.75mg/kg/d	26 (51.0)	4 (9.3)	1 (5.0)	0 (0.0)
0.5mg/kg/d	15 (29.4)	28 (65.1)	14 (70.0)	2 (100)
0.1-0,3mg/kg/d	0 (0.0)	0 (0.0)	2 (10.0)	0 (0.0)
Immunosuppressant / immunomodulant when associated to prednisone	n=51	n = 43	n = 20	n = 2
Mycophenolate mofetil	13 (25.5)	9 (20.9)	1 (5.0)	0 (0)
Methotrexate	8 (15.6)	3 (7.0)	2 (10.0)	0 (0)
Azathioprine	17 (33.3)	9 (20.9)	2 (10.0)	0 (0)
Doxycylin +/- Nicotinamide +/- potent topical corticosteroids	15 (29.4)	10 (23.3)	8 (40.0)	1 (50.0)
Dapsone +/- potent topical corticosteroids	8 (15.7)	2 (4.7)	3 (15.0)	0 (0)
Rituximab	5 (9.8)	0 (0)	0 (0)	0 (0)
Intravenous immunoglobulin	6 (11.7)	1 (2.3)	1 (5.0)	0 (0)
Topical corticosteroid +/- immunosuppressant	**32 (38.6)**	**37 (46.3)**	**50 (71.4)**	**63 (96.9)**
Dose of topical corticosteroid	n= 32	n = 37	n= 50	n=63
40g/d	11 (34.4)	6 (16.2)	2 (4.0)	0 (0)

30g/d	11 (34.4)	11 (29.7)	6 (12.0)	6 (9.8)
10g/d	0 (0)	0 (0)	0 (0)	2 (3.3)
Immunosuppressant / immunomodulant when associated to topical corticosteroid	n=32	n = 37	n= 50	n=63
Mycophenolate mofetil	2 (6.3)	4 (10.8)	1 (2.0)	0 (0)
Methotrexate	6 (18.8)	4 (10.8)	1 (2.0)	0 (0)
Azathioprine	4 (12.5)	5 (13.5)	2 (4.0)	2 (3.3)
Doxycyclin +/- nicotinamide	3 (9.4)	9 (24.3)	16 (32.0)	9 (14.8)
Dapsone	3 (9.4)	4 (10.8)	6 (12.0)	1 (1.6)
Rituximab	1 (3.1)	0 (0)	0 (0)	0 (0)
Intravenous immunoglobulin	1 (3.1)	1 (2.7)	1 (2.0)	0 (0)
CONSOLIDATION PHASE	n = 76	n = 75	n = 65	n = 62
Prednisone +/- immunosuppressant	42 (55.3)	32 (42.7)	15 (23.1)	2 (3.2)
Topical corticosteroid +/- immunosuppressant	27 (35.5)	31 (41.3)	46 (70.8)	57 (91.9)
Immunosuppressant alone	7 (9.2)	12 (16.0)	4 (6.2)	3 (4.8)
Tapering of treatment:	n = 41	n = 35	n = 28	n = 11
Reduction and finally omitting the corticosteroid before reducing the immunosuppressant	36 (87.8)	28 (80.0)	20 (71.4)	9 (81.8)
Reduction of the corticosteroid in parallel with reduction of the immunosuppressant and omitting the corticosteroid first	3 (7.3)	4 (11.4)	2 (7.1)	1 (9.1)
Reduction of the corticosteroid in parallel with reduction of the IS and omitting the immunosuppressant first	2 (4.9)	3 (8.6)	6 (21.4)	1 (9.1)

*data are expressed as number of responses

Table 2. Treatment modalities of patients with bullous pemphigoid in Europe, USA/Australia/South America, Middle East and Asia depending on disease severity.

	Europe n (%)	**USA/Australia/ South America** n (%)	**Asia** n (%)	**Middle East** n (%)
SEVERE	n= 46	n=18	n=7	n=10
Prednisone alone or + immunosuppressant	21 (45.7)	14 (77.8) [0.03]	7 (100.0) [0.01]	7 (70.0)[0.3]
Topical corticosteroid alone or + immunosuppressant	25 (54.3)	4 (22.2) [0.03]	0 (0) [0.01]	3 (30.0)[0.3]
MODERATE	n=38	n=20	n=9	n=8
Prednisone alone or + immunosuppressant	17 (44.7)	14 (70.0) [0.1]	7 (77.8) [0.1]	4 (50.0) [1]
Topical corticosteroid alone or + immunosuppressant	21 (55.3)	6 (30.0) [0.1]	2 (22.2) [0.1]	4 (50.0) [1]
MILD	n=37	n=17	n=6	n=7
Prednisone alone or + immunosuppressant	7 (18.9)	8 (47.1) [0.05]	4 (66.7) [0.03]	1 (14.3) [1]
Topical corticosteroid alone or + immunosuppressant	30 (81.1)	9 (52.9) [0.05]	2 (33.3) [0.03]	6 (85.7) [1]
LOCALIZED	n=33	n=15	n=7	n=7

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Prednisone alone	0 (0)	1 (6.7) [0.3]	1 (14.3) [0.2]	0 (0.0) [1]
Topical corticosteroid alone or + immunosuppressant	33 (100)	14 (93.3) [0.3]	6 (85.7) [0.2]	7 (100.0) [1]

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Data are expressed in number of responses. Comparison are calculated by exact Fischer test, versus European group
Severe, > 30 new blisters per day or >30 intact recent blisters
Moderate, 10 to 30 new blisters per day or 10 to 30 intact recent blisters
Mild, <10 new blisters per day or <10 intact recent blisters

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Table 3. Management of patients with bullous pemphigoid according to associated disorders

n (%)	Severe / debilitating neurological condition (Severe dementia, stroke, severe Parkinson's disease, bed ridden patients…)			Severe Diabetes mellitus			Cardiac insufficiency / severe cardiovascular associated condition			Renal insufficiency (creatinine clearance<40 ml/min)			Associated cancer		
Nb of responses	**SEVERE** 79	**MODERATE** 71	**MILD** 63	**SEVERE** 79	**MODERATE** 69	**MILD** 62	**SEVERE** 77	**MODERATE** 73	**MILD** 66	**SEVERE** 74	**MODERATE** 72	**MILD** 65	**SEVERE** 57	**MODERATE** 55	**MILD** (51)
No change	36 (45.6)	43 (60.6)	54 (85.7)	19 (24.1)	34 (49.3)	48 (77.4)	26 (33.8)	38 (52.1)	49 (74.2)	32 (43.2)	40 (55.6)	53 (81.5)	33 (57.9)	40 (72.7)	47 (92.1)
No or lower dose of corticosteroids	22 (27.8)	16 (22.5)	3 (4.8)	38 (48.1)	24 (34.8)	8 (12.9)	31 (40.2)	20 (27.4)	5 (7.6)	16 (21.6)	10 (13.9)	5 (7.7)	4 (7.0)	2 (3.6)	1 (2.0)
No some / any immunosuppressant	7 (8.9)	4 (5.6)	1 (1.6)	1 (1.3)	0 (0.0)	0 (0.0)	7 (9.1)	4 (5.5)	6 (9.1)	17 (23.0)	12 (16.7)	3 (4.6)	13 (22.8)	9 (16.3)	2 (3.9)
Complete change of regimen and use other drugs	14 (17.7)	8 (11.3)	5 (7.9)	21 (26.6)	11 (15.9)	6 (9.7)	13 (16.9)	11 (15.1)	6 (9.1)	9 (12.2)	10 (13.9)	4 (6.2)	7 (12.3)	4 (7.3)	1 (2.0)

Extensive / Severe BP (> 30 new blisters /day or >30 intact recent blisters)
Moderate BP (10- 30 new blisters /day or 10-30 intact recent blisters)
Mild, but non localized BP (<10 new blisters /day or <10 intact recent blisters)

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