New concept of pemphigoid diagnosis

Professor Marcel Jonkman
Department of Dermatology, University of Groningen

UK
8 OCTOBER 2018

University

MARCEL JONKMAN DOESN'T HAVE LONG

A good death

Retirement

These days Jonkman focuses mainly on his family and his friends. ‘I don’t think we can influence the world as much as we think. Many things are left up to chance; they’re random. We shouldn’t kid ourselves. Some things you just can’t change.’

He is enjoying life in spite of his condition. Before, he was always working – but he realises now that he has suddenly been given time. ‘I’m finally retired.’

He recently decided at the last minute to sit for a portrait that will hang in the staff room at his faculty. He is also having a film made of his life for his children and potential grandchildren to enjoy. He reads books. He spends time with his wife and children. Friends and colleagues visit him from time to time. ‘I’ve opened up, and others have opened up with me’, he says. ‘Now that death is so close the only thing that’s left is love. I’m enjoying my retirement. It’s just a shame it’s so short.’

Cell, Vol. 88, 543–551, February 21, 1997, Copyright ©1997 by Cell Press

Revertant Mosaicism in Epidermolysis Bullosa Caused by Mitotic Gene Conversion

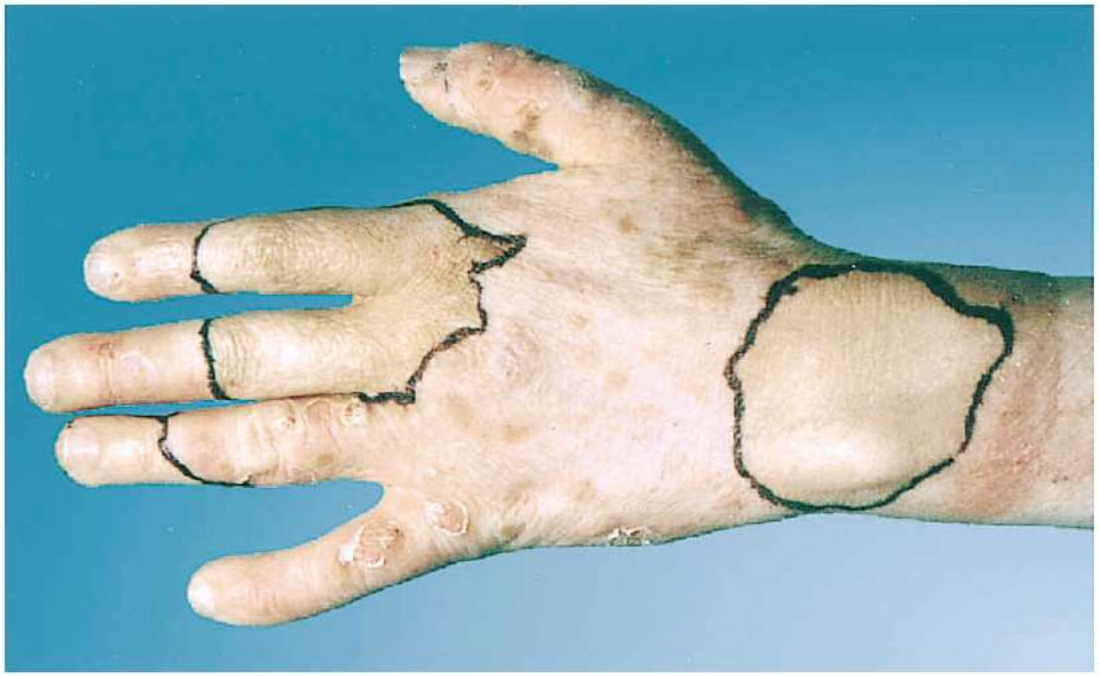
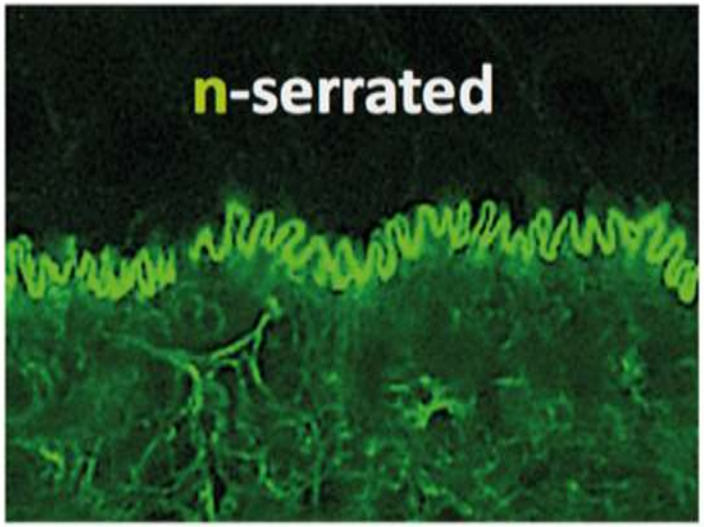


Figure 1. Clinically Unaffected Patches of Skin with Phylloid Pattern in the Mosaic Proband with Generalized Atrophic Benign Epidermolysis Bullosa

Patches of skin that never blister (outlined with a solid line) show normal pigmentation.

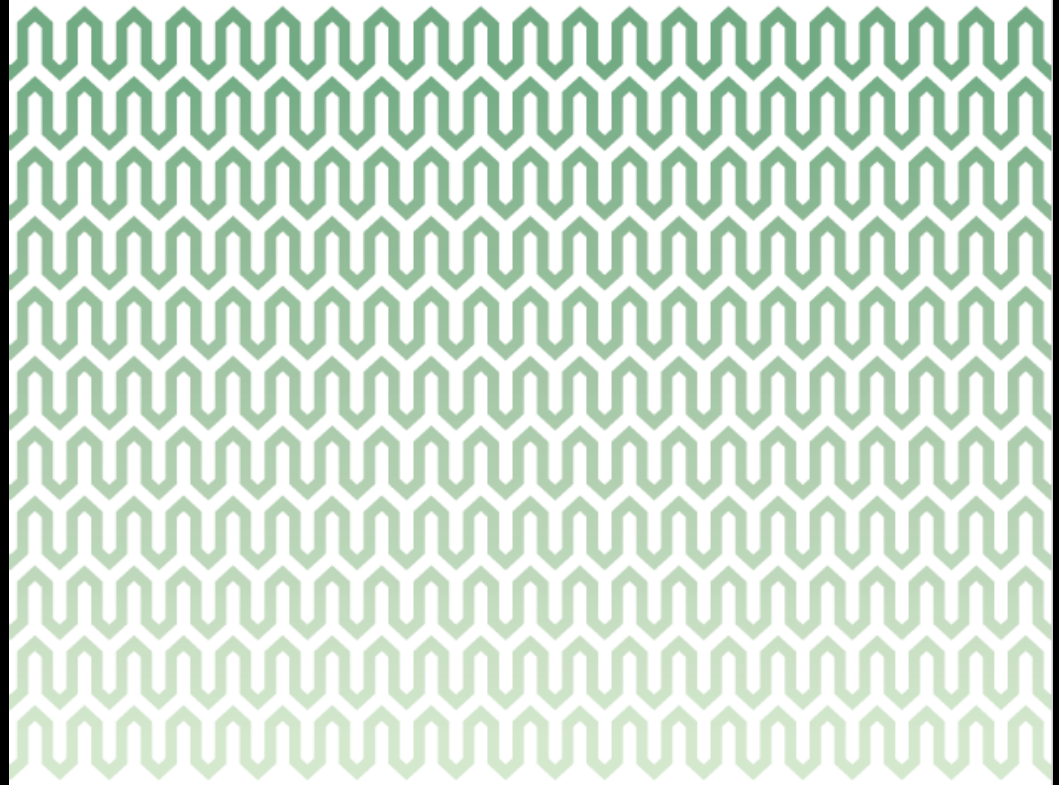
Serration pattern
www.nversusu.umcg.nl

DIF BMZ			
IIF salt-split	epidermal side	dermal side	dermal side
sAIBD	BP MMP CP LAD	p200 anti-LN-332	EBA bSLE

British Journal of Dermatology 2004; **151:** 112–118.

DIAGNOSIS OF

PEMPHIGOID DISEASES



JOOST M. MEIJER

CENTER FOR BLISTERING DISEASES
DEPARTMENT OF DERMATOLOGY
UNIVERSITY OF GRONINGEN
UNIVERSITY MEDICAL CENTER GRONINGEN
GRONINGEN, THE NETHERLANDS

Increasing incidence

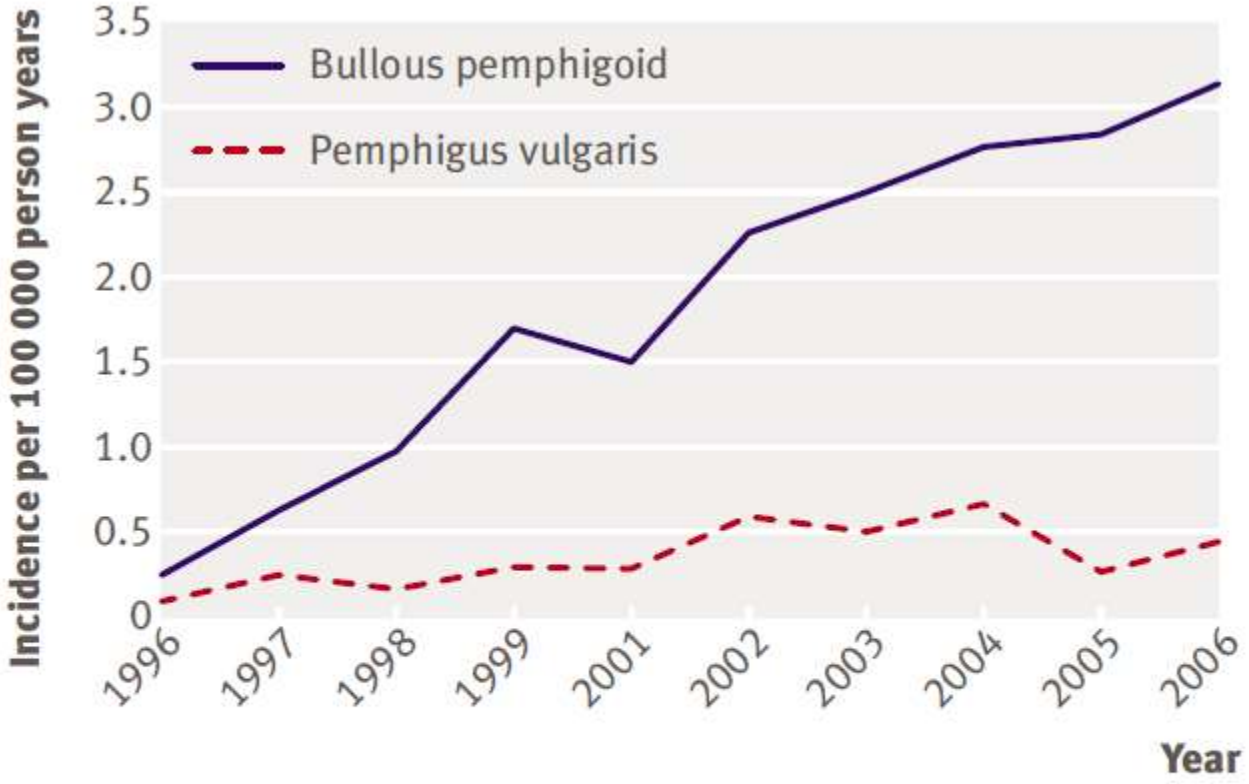


Fig 4 | Age adjusted rates of bullous pemphigoid and pemphigus vulgaris, with direct standardisation to European standard population

Langan BMJ 2008

High mortality

Acta Derm Venereol. 2018 Dec 27;99(1):72-77. doi: 10.2340/00015555-2930.

Mortality in Patients with Bullous Pemphigoid: A Retrospective Cohort Study, Systematic Review and Meta-analysis.

Kridin K[1], Shihade W, Bergman R.

Author information

Abstract

There is little consensus regarding mortality data in bullous pemphigoid (BP). The aim of this study was to evaluate mortality among a relatively large cohort of Israeli patients with BP and to perform a meta-analysis synthesizing existing data on 1-year mortality rates of patients with BP. This retrospective cohort study of 287 patients diagnosed with BP between 2000 and 2015 compared the mortality of patients with BP with age- and sex-matched control subjects in the general population. The results showed 1-, 5- and 10-year mortality rates of 26.9%, 56.9% and 69.5%, respectively, and a 3.4-fold higher risk of death. A systematic review and meta-analysis were then performed using a random effects model. Including the current study, 25 studies comprising 4,594 patients met the eligibility criteria. The pooled estimate of 1-year mortality rate was 23.5% (95% confidence interval 20.2-26.8; $I2=81\%$; $p < 0.001$). The pooled 1-year mortality rate of European cohorts was prominently higher relative to the pooled rates of cohorts from the USA and Asia.

Bullous Pemphigoid as Pruritus in the Elderly
A Common Presentation

Christiaan V. Bakker, MD; Jorrit B. Terra, MD; Hendri H. Pas, PhD; Marcel F. Jonkman, MD, PhD

IMPORTANCE In the literature, patients with bullous pemphigoid have been reported to have itch without blisters. Clinical observations in these patients have varied from eczematous or urticarial to papular or nodular skin lesions. Here we investigated the spectrum of clinical variants.

OBSERVATIONS Fifteen patients with itch without blisters had immunopathologic findings of bullous pemphigoid. Mean age at diagnosis was 81.7 years. No blistering occurred during the mean 2.2 years of follow-up. Mean delay of diagnosis was 2.8 years. Clinical symptoms were heterogeneous: pruritus sine materia (no primary skin lesions), eczematous, urticarial, papular, and/or nodular skin lesions were seen. Treatment with potent topical corticosteroids or methotrexate sodium led to remission in 11 patients.

CONCLUSIONS AND RELEVANCE Itch without skin lesions can be the only symptom of bullous pemphigoid. Therefore, it is important to include serologic and direct immunofluorescence in the diagnostic algorithm of itch. We propose the unifying term *pruritic nonbullous pemphigoid* for all patients with immunopathologic findings of bullous pemphigoid, itch, and no blisters.

JAMA Dermatol. 2013;149(8):950-953. doi:10.1001/jamadermatol.2013.756

Nonbullous pemphigoid: A systematic review

Aniek Lamberts, MD, Joost M. Meijer, MD, and Marcel F. Jonkman, MD, PhD
Groningen, The Netherlands

Background: Bullous pemphigoid is an autoimmune disease that typically presents with tense bullae and severe pruritus. However, bullae can be lacking, a subtype termed nonbullous pemphigoid.

Objective: To summarize the reported characteristics of nonbullous pemphigoid.

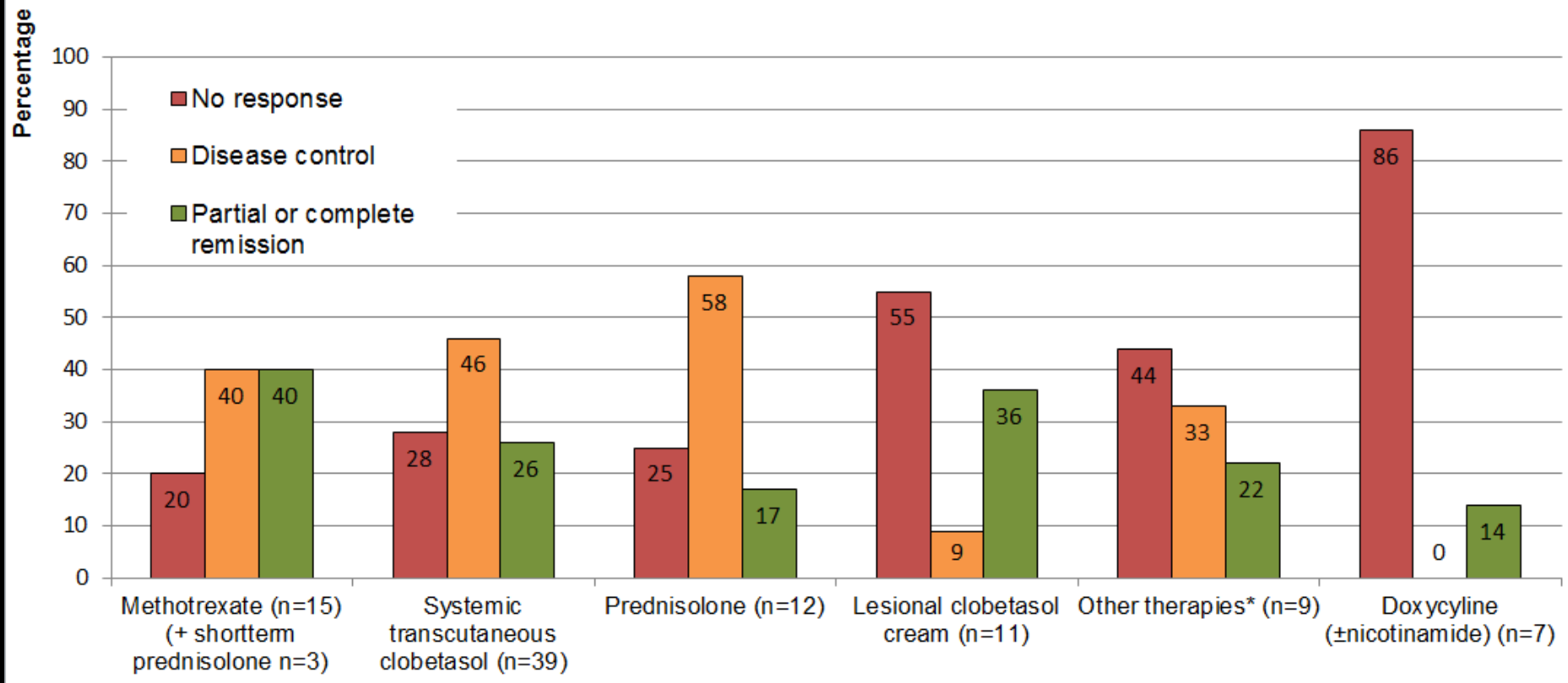
Methods: The EMBASE and MEDLINE databases were searched using "nonbullous pemphigoid" and various synonyms. Case reports and series describing nonbullous pemphigoid were included.

Results: The search identified 133 articles. After selection, 39 articles were included, presenting 132 cases. Erythematous, urticarial plaques (52.3%) and papules/nodules (20.5%) were the most reported clinical features. The mean age at presentation was 74.9 years. Histopathology was commonly nonspecific. Linear depositions of IgG and/or C3 along the basement membrane zone were found by direct immunofluorescence microscopy in 93.2%. Indirect immunofluorescence on salt-split skin was positive in 90.2%. The mean diagnostic delay was 22.6 months. A minority of patients (9.8%) developed bullae during the reported follow-up.

Limitations: Results are mainly based on case reports and small case series.

Conclusion: Nonbullous pemphigoid is an underdiagnosed variant of pemphigoid that most often does not evolve to bullous lesions and mimics other pruritic skin diseases. Greater awareness among physicians is needed to avoid delay in diagnosis. (J Am Acad Dermatol 2018;78:989-95.)

Response to therapy as 1e/2e line for nonbulleus pemphigoid



Relapses:	5 (33%)	12 (43%)	9 (100%)	1 (20%)	0 (0%)	0 (0%)

Lamberts … Jonkman, unpublished data

Pemphigoid subtype	Target antigens	Clinical symptoms	Immunofluorescence findings	
			DIF EBMZ	IIF SSS
Bullous pemphigoid	BP180 BP230	Pruritus, urticaria, tense blisters without predominant mucosal involvement	n-serrated IgG ± IgA, C3c	epidermal
Nonbullous pemphigoid	BP180 BP230	Pruritus, eczematous lesions, urticarial plaques, erythematous papules or nodules.	n-serrated IgG ± IgA, C3c	epidermal
Pemphigoid gestationis	BP180 BP230	In 2nd or 3rd trimester of pregnancy, intense pruritic urticarial rash and tense blisters starting around umbilicus and then spread over the body	n-serrated C3c ± IgG	epidermal
Linear IgA disease	BP180 LAD-1 LABD-97	Tense blisters and erosions in 'string of pearls', without predominant mucosal involvement	n-serrated IgA	epidermal
Epidermolysis bullosa acquisita	Type VII collagen	Mechanobullous variant: acral blistering that heal with scarring and milia. Inflammatory variant: widespread vesicles and blisters, without scarring or milia	u-serrated IgG ± IgA	dermal
Anti-p200 pemphigoid	p200	Pruritus, tense bullae, vesicles, urticarial plaques, predominantly on the extremities and trunk	n-serrated IgG ± C3c	dermal
Lichen planus pemphigoides	BP180 BP230	Tense blisters independent of the lichenoid plaques and papules of lichen planus	n-serrated IgG ± C3c	epidermal
Anti-plectin pemphigoid	Plectin	Pruritus, urticaria, tense blisters without predominant mucosal involvement	n-serrated IgG ± C3c	epidermal
Brunsting-Perry pemphigoid	BP180 LAD-1	Erosions and blisters confined to the head, face, neck and upper trunk leaving atrophic scars	n-serrated IgG ± C3c	epidermal
Mucous membrane pemphigoid	BP180 BP230	Erosions and blisters of the oral, nasal, eyes, pharyngeal, laryngeal, oesophagus and anogenital mucosa	n-serrated IgG ± IgA, C3c	epidermal
Ocular mucous membrane pemphigoid	BP180	Erosions and blisters of the oral, nasal, eyes, pharyngeal, laryngeal, oesophagus and anogenital mucosa	n-serrated IgG ± IgA	epidermal
Localized vulvar pemphigoid	BP180	Erosions and blisters of the oral, nasal, eyes, pharyngeal, laryngeal, oesophagus and anogenital mucosa	n-serrated IgG ± IgA, C3c	epidermal
Anti-laminin-332 mucous membrane pemphigoid	laminin-332	Erosions and blisters of the oral, nasal, eyes, pharyngeal, laryngeal, oesophagus and anogenital mucosa	n-serrated IgG ± C3c	dermal

JAMA Dermatology | Original Investigation

Assessment of Diagnostic Strategy for Early Recognition of Bullous and Nonbullous Variants of Pemphigoid

Joost M. Meijer, MD, PhD; Gilles F. H. Diercks, MD, PhD; Emma W. G. de Lang, MD; Hendri H. Pas, PhD; Marcel F. Jonkman, MD, PhD

IMPORTANCE A substantial number of patients with bullous pemphigoid do not develop skin blisters and may not have received the correct diagnosis. Diagnostic criteria and an optimal diagnostic strategy are needed for early recognition and trials.

OBJECTIVES To assess the minimal requirements for diagnosis of bullous and nonbullous forms of pemphigoid and to evaluate the optimal diagnostic strategy.

DESIGN, SETTING, AND PARTICIPANTS This paired, multivariable, diagnostic accuracy study analyzed data from 1125 consecutive patients with suspected pemphigoid who were referred to the Groningen Center for Blistering Diseases from secondary and tertiary care hospitals throughout the Netherlands. Eligible participants were patients with paired data on at least (1) a skin biopsy specimen for the direct immunofluorescence (DIF) microscopy test; (2) indirect immunofluorescence on a human salt-split skin substrate (IIF SSS) test; and (3) 1 or more routine immunoserologic tests administered between January 1, 2002, and May 1, 2015. Samples were taken from patients at the time of first diagnosis, before introduction of immunosuppressive therapy, and within an inclusion window of a maximum of 4 weeks. Data analysis was conducted from October 1, 2015, to December 1, 2017.

MAIN OUTCOMES AND MEASURES Pairwise DIF, IIF SSS, IIF on monkey esophagus, BP180 and BP230 enzyme-linked immunosorbent assays, and immunoblot for BP180 and BP230 tests were performed. The results were reported in accordance with 2015 version of the Standards for Reporting Diagnostic Accuracy.

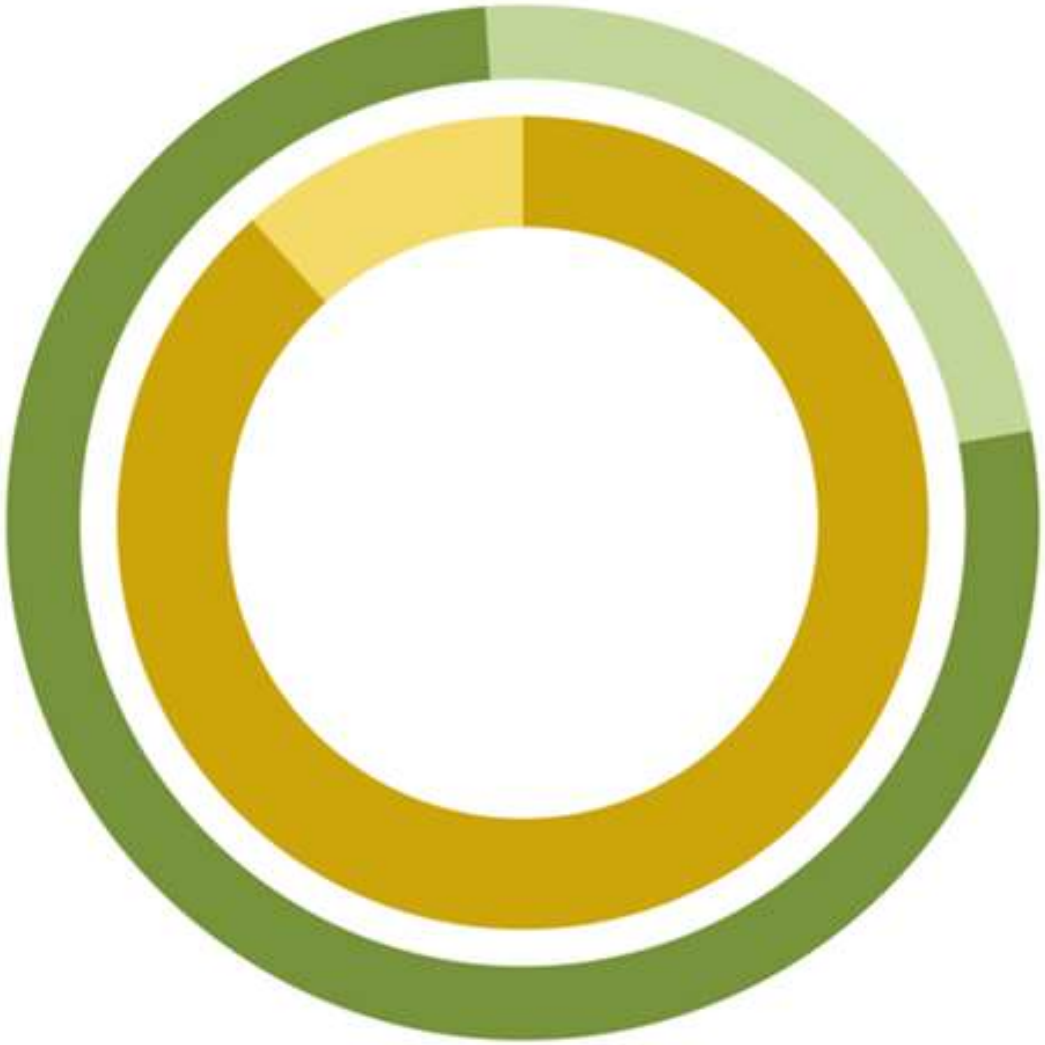
RESULTS Of the 1125 patients analyzed, 653 (58.0%) were women and 472 (42.0%) were men, with a mean (SD) age of 63.2 (19.9) years. In total, 343 participants received a pemphigoid diagnosis, with 782 controls. Of the 343 patients, 74 (21.6%, or 1 in 5) presented with nonbullous pemphigoid. The DIF microscopy was the most sensitive diagnostic test (88.3% [n = 303]; 95% CI, 84.5%-91.3%), whereas IIF SSS was less sensitive (77.0% [n = 263]; 95% CI, 72.2%-81.1%) but was highly specific (99.9%; 95% CI, 99.3%-100%) and complemented most cases with negative DIF findings. Results of the BP180 NC16A enzyme-linked immunosorbent assay did not add diagnostic value for initial diagnosis in multivariable logistic regression analysis of combined tests. These findings lead to the proposed minimal criteria for diagnosing pemphigoid: (1) pruritus and/or predominant cutaneous blisters, (2) linear IgG and/or C3c deposits (in an n-serrated pattern) by DIF on a skin biopsy specimen, and (3) positive epidermal side staining of IgG by IIF SSS on a serum sample; this proposal extends bullous pemphigoid with the unrecognized nonbullous form.

CONCLUSIONS AND RELEVANCE Both DIF and IIF SSS tests should be performed for diagnosis of the bullous and nonbullous variants of pemphigoid, and the BP180 NC16A enzyme-linked immunosorbent assay is recommended as an add-on test for disease activity monitoring.

Editorial

Supplemental content

Author Affiliations: Center for Blistering Diseases, Department of Dermatology, University of Groningen, University Medical Center Groningen, Groningen, the



Immunoreactivity in patients with pemphigoid n = 343

DIF

POSITIVE 88.3%

NEGATIVE 11.6%

IIF SSS

POSITIVE 77.0%

NEGATIVE 23.0%

Minimal diagnostic criteria

At least two positive out of three criteria:

1) pruritus and/or predominant cutaneous blisters
2) positive linear IgG and/or Complement C3 depositions (in n-serrated pattern) along the BMZ by DIF on a skin biopsy
3) positive epidermal side staining of IgG by IIF SS on serum.

PREVALENCE OF PRURITUS AND PEMPHIGOID IN NURSING HOME RESIDENTS (SSENIOR): A CROSS SECTIONAL STUDY OF AN UNDER-RECOGNIZED DISEASE

JOOST M. MEIJER*[a], ANIEK LAMBERTS*[a], HENDRIKA J. LUIJENDIJK[b], GILLES F.H. DIERCKS[a], HENDRI H. PAS[a], SYTSE U. ZUIDEMA[b], MARCEL F. JONKMAN[a], ON BEHALF OF THE SSENIOR STUDY GROUP

Recommended treatment for pemphigoid

Localized	Mild	Severe
Lesional clobetasol	Doxycycline 200 mg	
	Transcutaneous systemic clobetasol	Transcutaneous systemic clobetasol
	Prednisolon 0.5 mg/kg	Prednisolon 0.75-1 mg/kg
		+ Methotrexate 7.5 mg/wk
		Rituximab

GUIDELINES

BJD
British Journal of Dermatology

British Association of Dermatologists' guidelines for the management of bullous pemphigoid 2012

V.A. Venning,[1] K. Taghipour,[2] M.F. Mohd Mustapa,[3] A.S. Highet[4] and G. Kirtschig[5]

GUIDELINES

BJD
British Journal of Dermatology

Management of bullous pemphigoid: the European Dermatology Forum consensus in collaboration with the European Academy of Dermatology and Venereology

C. Feliciani,[1] P. Joly,[2] M.F. Jonkman,[3] G. Zambruno,[4] D. Zillikens,[5] D. Ioannides,[6] C. Kowalewski,[7] H. Jedlickova,[8] S. Kárpáti,[9] B. Marinovic,[10] D. Mimouni,[11] S. Uzun,[12] S. Yayli,[13] M. Hertl[14] and L. Borradori[15]

Am J Clin Dermatol (2017) 18:513–528
DOI 10.1007/s40257-017-0264-2

REVIEW ARTICLE

Bullous Pemphigoid: A Review of its Diagnosis, Associations and Treatment

Philippe Bernard[1] · Frank Antonicelli[2]

Table 3 Therapeutic options for the treatment of BP

Treatment	Level of evidence[a]	Mechanism of action in BP
Superpotent topical corticosteroids	1	Anti-inflammatory
Oral corticosteroids (prednisone 0.5–1 mg/kg/day)	1	Anti-inflammatory or immunosuppressive[b]
Azathioprine	1	Immunosuppressive
Mycophenolate mofetil	1	Immunosuppressive
Methotrexate	2	Anti-inflammatory or immunomodulatory
Chlorambucil	3	Immunosuppressive
Cyclophosphamide	3	Immunosuppressive
Tetracyclines + nicotinamide	2	Anti-inflammatory
Dapsone	3	Anti-inflammatory
Intravenous immunoglobulin	3	Immunomodulatory
Plasmapheresis[c]	1	Removal of autoantibodies
Immunoabsorption	3	Removal of autoantibodies
Rituximab	3	Removal of B lymphocytes
Omalizumab	3	Blockage of IgE autoantibodies

BP bullous pemphigoid, *IgE* immunoglobulin E

[a] Key to evidence-based support: (1) large, randomized prospective study; (2) small randomized study (prospective or retrospective) or large retrospective case series; (3) small case series or case reports

An open, multicentre, randomized clinical study in patients with bullous pemphigoid comparing methylprednisolone and azathioprine with methylprednisolone and dapsone

M. Sticherling,[1,2] A. Franke,[3] E. Aberer,[4] R. Gläser,[5] M. Hertl,[2,6] C. Pfeiffer,[7,8] B. Rzany,[9] S. Schneider,[10,11] I. Shimanovich,[12] T. Werfel,[13] A. Wilczek,[1] D. Zillikens[12,14] and E. Schmidt[12,14]

Objectives To study the corticosteroid-sparing potential of azathioprine and dapsone.

Methods This was a prospective, multicentre, randomized, nonblinded clinical trial that compared the efficacy and safety of two parallel groups of patients with BP treated with oral methylprednisolone 0·5 mg kg^{-1} per day in combination with either azathioprine 1·5–2·5 mg kg^{-1} per day or dapsone 1·5 mg kg^{-1} per day. Nine German and Austrian departments of dermatology included 54 patients based on clinical lesions, positive direct immunofluorescence (IF) microscopy and detection of serum autoantibodies by indirect IF microscopy, immunoblotting or enzyme-linked immunosorbent assay. The primary end point was the time until complete tapering of methylprednisolone, and the most important secondary end point was the cumulative corticosteroid dose.

Results In eight patients (five azathioprine, three dapsone), methylprednisolone could be discontinued after a median time of 251 days in the azathioprine group and 81 days in the dapsone group. The median cumulative corticosteroid dose was 2·65 g for azathioprine compared with 1·92 g for dapsone ($P = 0·06$). The median numbers of days when corticosteroids were applied were 148 and 51, respectively ($P = 0·24$). No significant difference in the number of adverse events was seen between the treatment arms. Four patients (8%) died within the observation period of 12 months.

Conclusions Due to the lower than intended number of patients, the results of the primary and secondary end points were not or only barely significant. Dapsone appeared to have a moderately higher corticosteroid-sparing potential than azathioprine. The combination regimen of either drug with oral methylprednisolone is associated with a relatively low 1-year mortality in this vulnerable patient population.

THERAPEUTICS

BJD
British Journal of Dermatology

Combined treatment with low-dose methotrexate and initial short-term superpotent topical steroids in bullous pemphigoid: an open, multicentre, retrospective study

A. Du-Thanh, S. Merlet, H. Maillard,* P. Bernard,† P. Joly,‡ E. Estève,§ M.A. Richard,¶ C. Pauwels,** S. Ingen-Housz-Oro,†† B. Guillot and O. Dereure

Background The interest of long-term superpotent topical steroids (STS) in bullous pemphigoid (BP) has been supported by randomized controlled trials. However, inadequate compliance, poor cutaneous tolerance and nursing difficulties are potential drawbacks. Open-label studies on limited series of patients suggested that low-dose methotrexate (MTX) may be useful, permitting long-term maintenance of a clinical remission obtained by initial, short-term STS.

Objectives Open, clinical records-based retrospective analysis of a multicentre series of patients receiving a combined regimen of initial, short-term STS and MTX followed by long-term MTX alone. The primary objective was evaluation of the clinical efficiency of this strategy based on initial clinical remission and subsequent clinical maintenance. The secondary objective was evaluation of the tolerance (type and rating of adverse events) of this combined regimen.

Methods Seventy patients with BP (mean age 82·7 years) were included. Treatment consisted of an initial combination of STS and MTX for a mean duration of 12·3 weeks followed by long-term MTX alone for a mean duration of 8·48 months with a mean and median MTX dosage of 10 mg per week.

Results One hundred per cent of the patients showed an initial, complete clinical remission after a mean time interval of 21·9 days. The overall rate of long-term disease control was 76%, whereas 24% of patients experienced at least one relapse during subsequent treatment with MTX alone. Drug-related adverse effects were mainly haematological and gastrointestinal and resulted in treatment discontinuation in 11 patients (16%). Six patients (9%) died during the follow-up period with one death (1%) most likely to be related to treatment.

Conclusions Long-term low-dose MTX combined with short-term STS may result in protracted control of BP in carefully selected patients. These results should prompt randomized controlled trials comparing this treatment with the more usual regimen of long-term STS alone.

Doxycycline versus prednisolone as an initial treatment strategy for bullous pemphigoid: a pragmatic, non-inferiority, randomised controlled trial

*Hywel C Williams, Fenella Wojnarowska, Gudula Kirtschig, James Mason, Thomas R Godec, Enno Schmidt, Joanne R Chalmers, Margaret Childs, Shernaz Walton, Karen Harman, Anna Chapman, Diane Whitham, Andrew J Nunn, on behalf of the UK Dermatology Clinical Trials Network BLISTER Study Group**

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This online publication has been corrected. The corrected version first appeared at thelancet.com on October 26, 2017

See Comment page 1586

*Listed at the end of the Article

Centre of Evidence Based Dermatology, University of Nottingham, Nottingham, UK (Prof H C Williams DSc, J R Chalmers PhD, G Kirtschig MD); Nuffield Department of Clinical Medicine, University of Oxford, Oxford, UK (Prof F Wojnarowska PhD); Institute of General Medicine and Interprofessional Care, University of Tübingen, Tübingen, Germany (G Kirtschig); Warwick Medical School, University of Warwick, Coventry, UK (Prof J Mason PhD); Medical Research Council Clinical Trials Unit at University College London, London, UK (T R Godec MSc, Prof A J Nunn MSc); Department

Summary

Background Bullous pemphigoid is a blistering skin disorder with increased mortality. We tested whether a strategy of starting treatment with doxycycline gives acceptable short-term blister control while conferring long-term safety advantages over starting treatment with oral corticosteroids.

Methods We did a pragmatic, multicentre, parallel-group randomised controlled trial of adults with bullous pemphigoid (three or more blisters at two or more sites and linear basement membrane IgG or C3). Participants were randomly assigned to doxycycline (200 mg per day) or prednisolone (0·5 mg/kg per day) using random permuted blocks of randomly varying size, and stratified by baseline severity (3–9, 10–30, and >30 blisters for mild, moderate, and severe disease, respectively). Localised adjuvant potent topical corticosteroids (<30 g per week) were permitted during weeks 1–3. The non-inferiority primary effectiveness outcome was the proportion of participants with three or fewer blisters at 6 weeks. We assumed that doxycycline would be 25% less effective than corticosteroids with a 37% acceptable margin of non-inferiority. The primary safety outcome was the proportion with severe, life-threatening, or fatal (grade 3–5) treatment-related adverse events by 52 weeks. Analysis (modified intention to treat [mITT] for the superiority safety analysis and mITT and per protocol for non-inferiority effectiveness analysis) used a regression model adjusting for baseline disease severity, age, and Karnofsky score, with missing data imputed. The trial is registered at ISRCTN, number ISRCTN13704604.

Findings Between March 1, 2009, and Oct 31, 2013, 132 patients were randomly assigned to doxycycline and 121 to prednisolone from 54 UK and seven German dermatology centres. Mean age was 77·7 years (SD 9·7) and 173 (68%) of 253 patients had moderate-to-severe baseline disease. For those starting doxycycline, 83 (74%) of 112 patients had three or fewer blisters at 6 weeks compared with 92 (91%) of 101 patients on prednisolone, an adjusted difference of 18·6% (90% CI 11·1–26·1) favouring prednisolone (upper limit of 90% CI, 26·1%, within the predefined 37% margin). Related severe, life-threatening, and fatal events at 52 weeks were 18% (22 of 121) for those starting doxycycline and 36% (41 of 113) for prednisolone (mITT), an adjusted difference of 19·0% (95% CI 7·9–30·1), p=0·001.

Interpretation Starting patients on doxycycline is non-inferior to standard treatment with oral prednisolone for short-term blister control in bullous pemphigoid and significantly safer in the long-term.

American Journal of Clinical Dermatology
https://doi.org/10.1007/s40257-018-0401-6

SYSTEMATIC REVIEW

Rituximab and Omalizumab for the Treatment of Bullous Pemphigoid: A Systematic Review of the Literature

Noa Kremer[1,2] · Igor Snast[1,2] · Efrat Solomon Cohen[1,2] · Emmilia Hodak[1,2] · Daniel Mimouni[1,2] · Moshe Lapidoth[1,2] · Sigal Mazor[3] · Assi Levi[1,2]

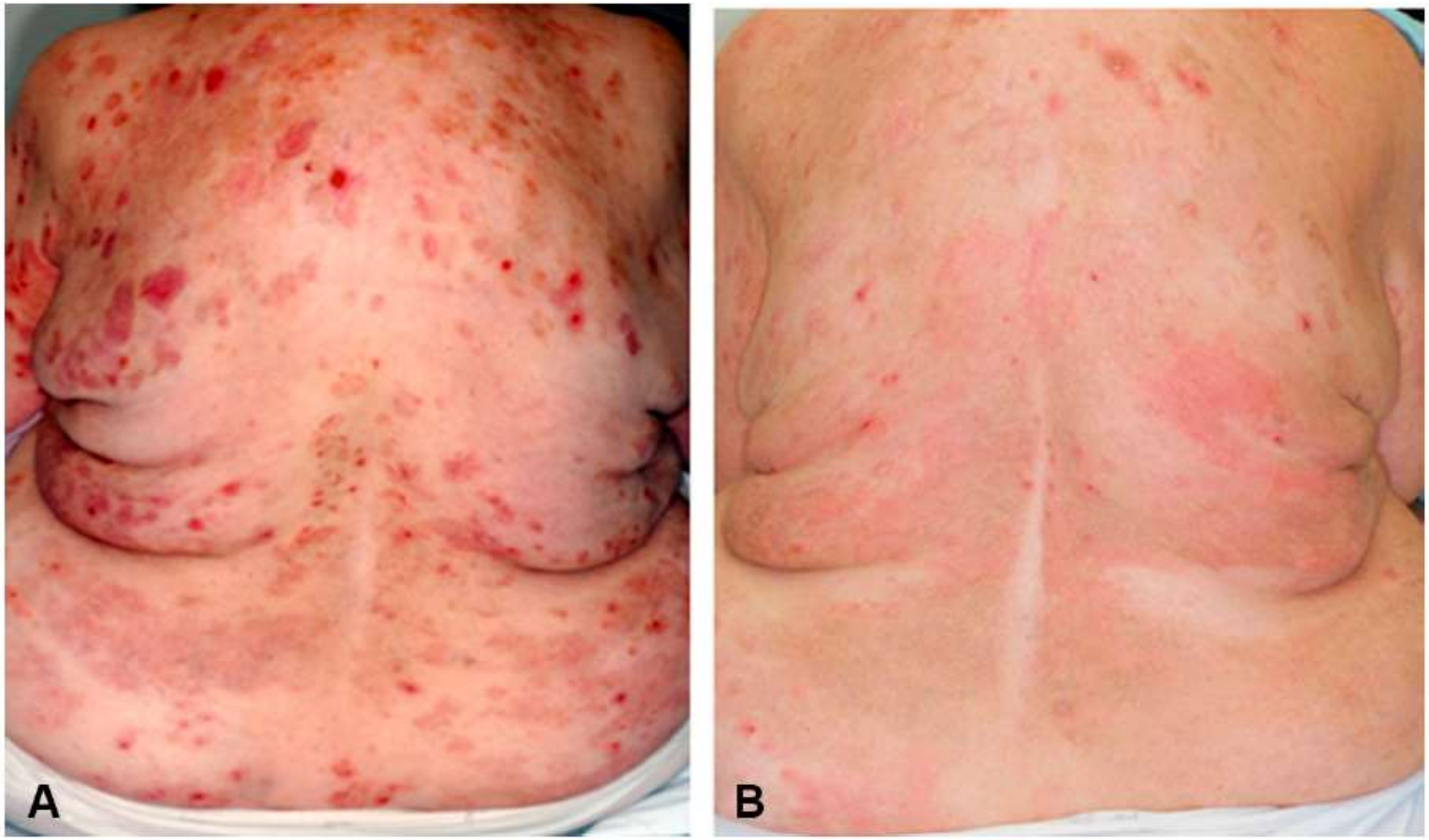

Fig 1. Response of a patient with bullous pemphigoid (BP) after 6 omalizumab injections as monotherapy. **A**, Involvement of the back of a steroid-refractory patient with BP before omalizumab treatment. **B**, Four months after beginning omalizumab as monotherapy, the inflammatory plaques have largely resolved, leaving postinflammatory hyperpigmentation and a small number of erosions and mild, transient erythema. The patient cleared completely after a second cycle of omalizumab treatment.

(J Am Acad Dermatol 2014;71:468-74.)

Drug-induced pemphigoid

Vildagliptin Significantly Increases the Risk of Bullous Pemphigoid: A Finnish Nationwide Registry Study

Journal of Investigative Dermatology (2018) **138**, 1659–1661; doi:10.1016/j.jid.2018.01.027

Bullous disorders associated with anti–PD-1 and anti–PD-L1 therapy: A retrospective analysis evaluating the clinical and histopathologic features, frequency, and impact on cancer therapy

Jacob Siegel, MD,[a] Mariam Totonchy, MD,[a] William Damsky, MD, PhD,[a] Juliana Berk-Krauss, BA,[a] Frank Castiglione, Jr, MD,[a] Mario Sznol, MD,[b] Daniel P. Petrylak, MD,[b,c] Neal Fischbach, MD,[b] Sarah B. Goldberg, MD, MPH,[b] Roy H. Decker, MD, PhD,[d] Angeliki M. Stamatouli, MD,[b] Navid Hafez, MD, MPH,[b] Earl J. Glusac, MD,[a] Mary M. Tomayko, MD, PhD,[a] and Jonathan S. Leventhal, MD[a]
New Haven, Connecticut

Background: Bullous disorders associated with anti–programmed cell death 1 (PD-1)/programmed cell death ligand 1 (PD-L1) therapy are increasingly reported and may pose distinct therapeutic challenges. Their frequency and impact on cancer therapy are not well established.

Objective: To evaluate the clinical and histopathologic findings, frequency, and impact on cancer therapy of bullous eruptions due to anti–PD-1/PD-L1 therapy.

Methods: We retrospectively reviewed the medical records of patients evaluated by the oncodermatology clinic and consultative service of Yale New Haven Hospital from 2016 to 2018.

Results: We identified 9 of 853 patients who developed bullous eruptions (~1%) that were treated with an–PD-1/PD-L1 therapy at our institution during the study period: 7 presented with bullous pemphigoid, 1 presented with bullous lichenoid dermatitis, and 1 presented with linear IgA bullous dermatosis in the context of vancomycin therapy. In all, 8 patients required systemic steroids, 5 required maintenance therapy, and 8 required interruption of immunotherapy. All 9 patients had an initial positive tumor response or stable disease, but 4 went on to develop disease progression.

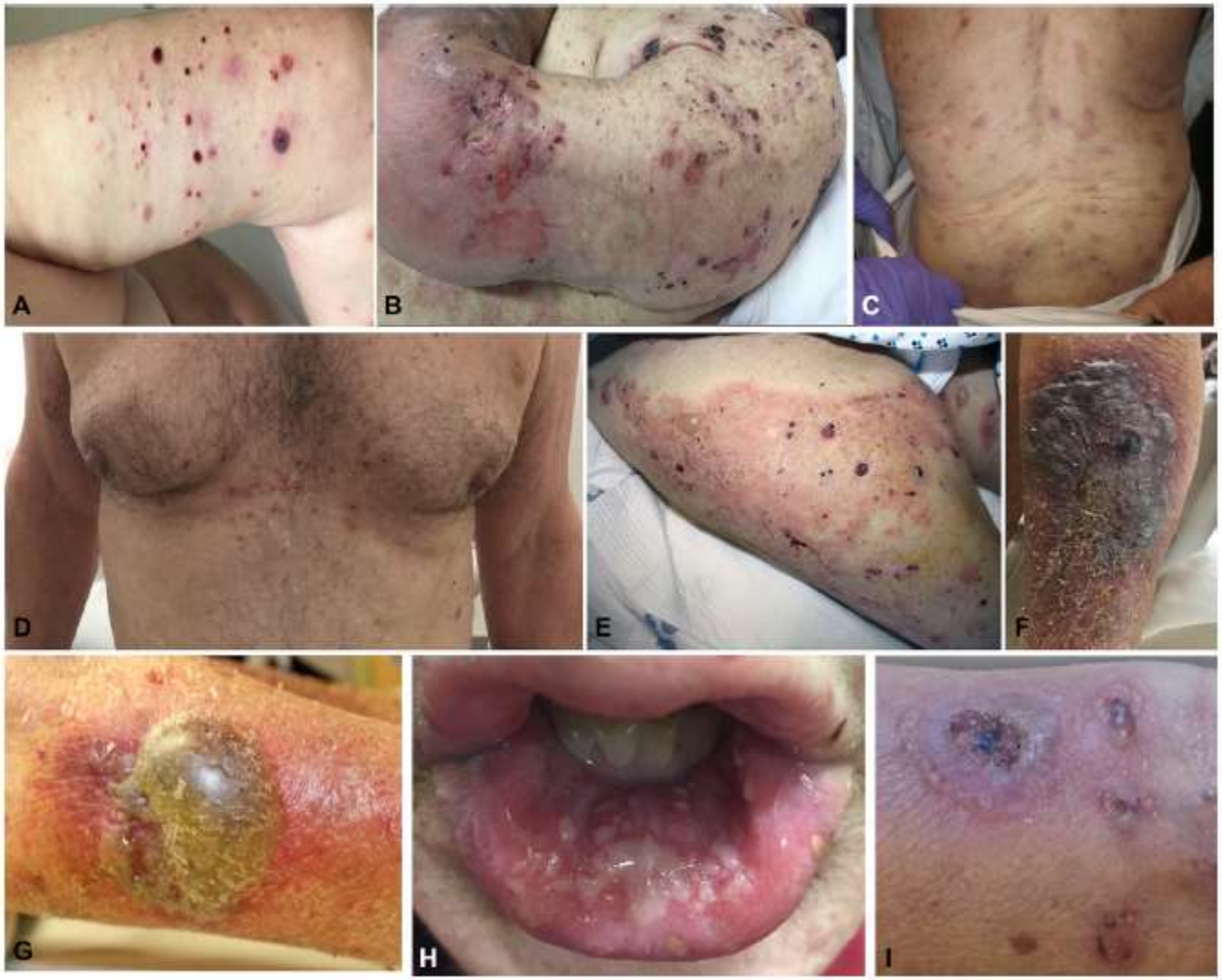

Fig 1. Immunotherapy-associated bullous disorders. **A-I,** Spectrum of mucocutaneous findings in patients with bullous eruptions that developed during anti–programmed cell death 1 (PD-1)/programmed cell death ligand 1 (PD-L1) therapy.

Take home messages

- Increasing prevalence of pemphigoid
- Minimal criteria: 2-out-of-3
  Pruritus and/or bullae on the skin
  DIF linear (n-serrated)
  IIF Salt split epidermal
- Nonbullous pemphigoid a new disease
- Associations, e.g. neurological diseases
- OBS drug-induced pemphigoid