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CHAPTER 8

Unmet needs in pemphigoid diseases: an international survey amongst patients, clinicians and researchers

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Introduction

Pemphigoid diseases are subepidermal autoimmune bullous diseases, characterized by autoantibodies against structural proteins of the dermal-epidermal junction.¹ Symptoms of severe pruritus, with or without tense blistering of the skin or mucosa, cause a high disease burden.² Basic and clinical research led to better understanding of disease mechanisms, and novel therapies emerged.³ Nonetheless, gaps in knowledge exist, and several disease areas are understudied. These unmet needs have not been well-characterized. While in research available time and resources are often limited, it is essential to address research topics relevant to both patients and health care professionals.⁴ Nowadays, it is widely recognized that patients play an important role in setting the research agenda.⁵ This study sought to explore and prioritize unmet needs in pemphigoid diseases from the perspective of patients, clinicians and researchers, with the intent to guide future research towards important research topics. A secondary aim was to identify points of improvement in patient care.

Methods

A steering group was established in February 2017, consisting of a project coordinator (AL), experts on pemphigoid diseases (SAG, BH, DZ, MFJ) and a patient representative (MY; director of the International Pemphigus and Pemphigoid Foundation (IPPF)). A preliminary list of unmet needs was composed and discussed by the steering group during a kick-off meeting in June 2017 that took place at the IPPF conference in Lübeck. An online anonymous survey was developed using Qualtrics survey software (supplement 1), containing questions on participants characteristics, and unmet needs in pemphigoid diseases. Seven or eight pre-listed needs were provided and participants were asked whether they recognized the needs as unmet, to designate a top three of the most urgent unmet needs, and to complement the list. In addition, patients received questions about patient care satisfaction, and their reasons for (dis)satisfaction.

The survey was distributed internationally between October 2017 and April 2018. Patients were invited by email via the International Pemphigus and Pemphigoid Foundation, and national German and Dutch patient organizations. Clinicians and researchers were invited by email via pemphigoid research groups, and via the European Academy of Dermatology and Venereology. Data was exported from Qualtrics directly into SPSS Statistics version 23 (IBM, Chicago, USA).

Descriptive and qualitative statistics were used for data analysis. An overall ranking score was calculated by awarding three points every time unmet needs were ranked highest, two points if ranked second, and one point if ranked third.

Results

The in- and exclusion process is shown in figure 1. The clinicians and researchers response rate was 36/99 (36%). The patients response rate was unknown.

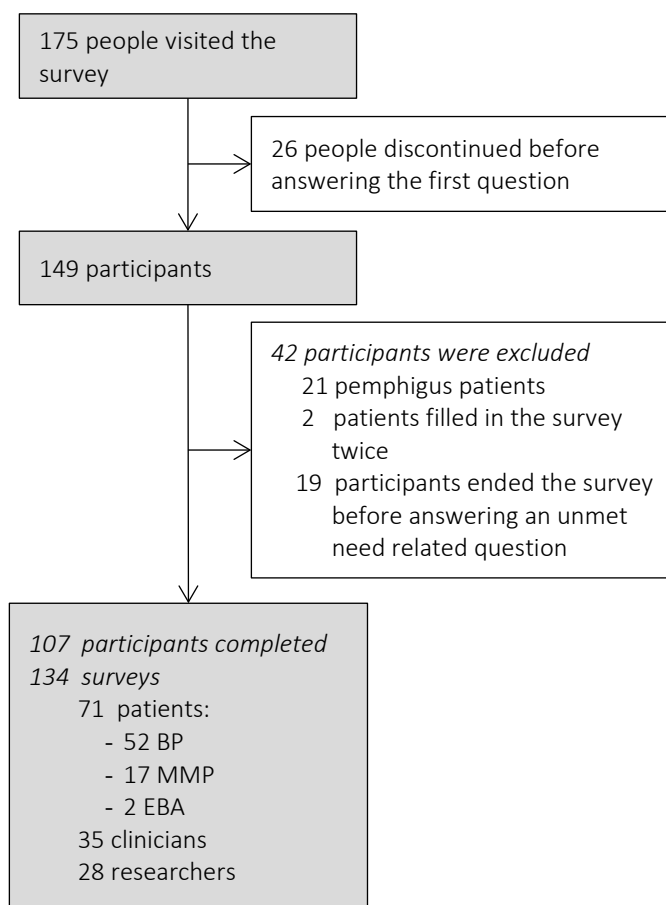


Figure 1. Flowchart of in- and exclusion of study participants. BP, bullous pemphigoid; MMP, mucous membrane pemphigoid; EBA, epidermolysis bullosa acquisita.

Participants characteristics and the top three of most urgent needs are displayed in table 1. Patients, clinicians and researchers agreed that the most urgent need is the improvement of therapeutic options for pemphigoid diseases (table 1). Additionally, patients expressed the need for more public information most frequently (n=9) (supplemental table 1).

Data on patient satisfaction showed that half of the patients were unsatisfied with patient care during the diagnostic process, mainly due to misdiagnosis and long doctors delay (mentioned by 88% of unsatisfied patients; table 2). Six patients visited more than five doctors before a correct diagnosis was made. Patients with epidermolysis bullosa acquisita and mucous membrane pemphigoid reported a longer diagnostic delay (mean 90.3 ± 127 and 19.7 ± 23 months), compared to patients with bullous pemphigoid (9.0 ± 22 months). Most patients (76%) were satisfied with current patient care, especially due to successful treatment (mentioned by 41% of satisfied patients) in centers of expertise (mentioned by 37% of satisfied patients) (table 2). Treatment side effects, insurance issues, and poor disease knowledge by doctors were main reasons for unsatisfactory current patient care.

Discussion

Our survey data confirmed that a long diagnostic delay and suboptimal treatment are important concerns in pemphigoid diseases. Though our results were not surprising, this study is the first to explore patients priorities in the field of pemphigoid diseases. Our method has some resemblance to the James Lind Alliance (JLA) methodology of prioritisation of research topics.⁵ The greatest difference is the lack of a finalisation workshop, where patients and health professionals discuss the final prioritisation of uncertainties face-to-face. In our study we choose for prioritisation by survey, considering that pemphigoid diseases are rare, and therefore a low attendance and a high geographic selection bias would be expected. Still, the risk of selection bias was not completely prevented, as participants from only three continents were included. Other limitations of this study include a relatively low sample size and missing values. Geographical differences might have caused small deviations in the ranked needs (supplemental tables 2, 3, 4).

Table 1. Participants characteristics and top three ranking of unmet needs in pemphigoid diseases.

Participants characteristics (n=107)				
<i>Patients (n=71)</i>	<i>Clinicians (n=35)</i>	<i>Researchers (n=28)</i>		
Mean age: 66.6 years (R 34-94)	Mean age 51.9 (R 28-65)	Mean age 51.6 (R 28-65)		
Mean diagnostic delay: 14.1 months (R 1 day-15 years)	Setting: Academic 34 (97%) Peripheral 1 (3%)	Research experience: >10 years: 20 (71%)		
Mean disease duration: 4.7 years (R 0-20)	Consider yourself AIBD expert? Yes: 35 (100%)	AIBD main research topic? Yes: 21 (75%), No: 7 (25%)		
<i>Continent of origin:</i> Europe: 22 (31%) Northern America: 48 (68%) Asia: 1 (1%)	<i>Continent of origin:</i> Europe: 21 (60%) Northern America: 7 (20%) Asia: 4 (11%)	<i>Continent of origin:</i> Europe: 18 (64%) Northern America: 6 (21%) Asia: 4 (14%)		
Overall top three ranking of unmet needs	<i>Unmet need recognized?</i>			
	<i>Yes, n (%)</i>	<i>No, n (%)</i>	<i>Missing, n (%)</i>	<i>Ranking score*</i>
<i>Patients (n=71)</i>				
1. Need for better treatment options	48 (68)	5 (7)	18 (25)	92
2. Need for quicker diagnosis	47 (66)	9 (13)	15 (21)	84
3. Need for more disease awareness	46 (65)	8 (11)	17 (24)	81
<i>Clinicians (n=35)</i>				
1. Need for labeling of new drugs for the indication pemphigoid (anti- CD20, anti-complement, anti-FcRn, anti-neutrophil activating pathways)	30 (86)	4 (11)	1 (3)	53
2. Need for easy laboratory tests to diagnose pemphigoid diseases	27 (77)	5 (14)	3 (9)	38
3. Need for better recognition of nonbullous pemphigoid	30 (86)	3 (9)	2 (6)	37
<i>Researchers (n=28)</i>				
1. Need for more head-to-head randomized controlled trials comparing the effectiveness and safety of current treatments	25 (89)	1 (4)	2 (7)	51
2. Need for understanding of the pathophysiology of pemphigoid for drug development	27 (96)	0 (0)	1 (4)	38
3. Need for understanding trigger mechanism (e.g., infections, drugs) in addition to genetic predisposition	27 (96)	0 (0)	1 (4)	30

*R, range; AIBD, autoimmune blistering diseases; * Ranking score was calculated by awarding three points for every time an unmet needs was ranked highest, two points if ranked second highest and one point if ranked third highest.*

Table 2. Satisfaction of patients (n=71) with patient care during the diagnostic process, and their current patient care.

Patients satisfied with diagnostic process (n=36, 51%)		Patients unsatisfied with diagnostic process (n=35, 49%)	
<i>Reasons categorized</i>	<i>Times mentioned</i>	<i>Reasons categorized</i>	<i>Times mentioned</i>
Quick diagnosis	10	Misdiagnosis/mistreatment	31
Good disease recognition	5	- lack of recognition of nonbullous variant (n=2)	
Good awareness	3	High number of doctors seen before diagnosis	6
Disease information provided	3	Lack of disease knowledge	5
Good treatment	3	Symptoms were not taken seriously	2
Good disease knowledge	2	Side effects of steroids	2
Doctor was determinate after unspecific results of biopsy	2	Long waiting time for referral to specialist	2
		Lack of information	2
		Doctor induced bullous pemphigoid by drug prescription	1
		Poor treatment	1
		Many referrals, thereby high costs of care	1
		No biopsy was taken	1
Patients satisfied with current patient care (n=54, 76%)		Patients unsatisfied with current patient care (n=17, 24%)	
<i>Reasons categorized</i>	<i>Times mentioned</i>	<i>Reasons categorized</i>	<i>Times mentioned</i>
Satisfied with therapy/ in remission	22	Side effects - steroids (n=3)/ other therapy (n=1)	5
Experienced/professional dermatologist/care center	20	Little disease knowledge by doctor	5
Happy with correct diagnosis	3	Insurance issues - insurance does not cover therapy (n=3)	4
Disease information provided	2	- specialist did not accept the medical insurance (n=1)	
		Not satisfied with interaction with specialist	2
		No information/support for patients in remission still dealing with skin issues	1
		No satisfying treatment for itching	1

BP, bullous pemphigoid.

Patients from Northern America ranked the need for better treatment availability fourth, in contrast to European patients that rated the urgency of this need second last. This might be explained by lower health care availability in Northern America than in Europe (supplemental table 2).

Another interesting finding is the higher need for easy diagnostic laboratory tests expressed by clinicians in Northern America and Asia, in comparison with European clinicians (supplemental table 3). Whether this difference is caused by approachability, laboratory equipment, or by the use of different diagnostic techniques cannot be concluded based on our survey data.

In conclusion, our data shows that future studies are needed to improve and widen the currently available treatment options for pemphigoid diseases. Moreover, patients point out a high need for shortening the diagnostic delay. Therefore, more awareness for pemphigoid diseases should be pursued. Data on patient satisfaction showed that after the correct diagnosis was established, patients were most satisfied with care in centers of expertise. Focus group sessions might be useful to provide extended information in order to formulate concrete interventions for patient care improvement.

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Supplemental tables

Supplemental table 1. Additional unmet needs in pemphigoid diseases by patients, clinicians and researchers

	<i>Times mentioned, n</i>
<i>Categorized additional unmet needs in pemphigoid diseases of patients</i>	
Need for more (public) information	9
Need for more awareness amongst doctors/medical staff	7
Need for better disease knowledge by doctors	7
Need for better health care organization	5
Need for attention and care for intense itching post BP (after blistering stage; after remission)	4
Need for better medicine	4
Need for more information/guidance	4
Need for research	4
Need for more local support groups	2
Need for guidance of frail elderly population (caregiver to help with nutrition/self-care)	1
<i>Categorized additional unmet needs in pemphigoid diseases of clinicians</i>	
	<i>Times mentioned, n</i>
Need for better therapies:	11
Need for resolving issues with coverage of medication by insurance companies	4
Need for better diagnostics:	3
Need for a centralized national serum database/DNA bank and need for registries	2
Need for nosology for linear IgA disease and pemphigoid (not a synonym for bullous pemphigoid)	1
Need for guideline for diagnosis/treatment of MMP and treatment of BP	1
Need for better education of patients on their disease	1
Need for transfer of knowledge to GP's on the nonbullous stages of disease	1
Need for access to nursing support in outpatient setting	1
<i>Categorized additional unmet needs in pemphigoid diseases of researchers</i>	
	<i>Times mentioned, n</i>
Need for animal/ ex-vivo model of human pemphigoid	2
Need for research on pemphigoid diseases pathogenesis	2
Need for research on brain and skin associations in BP	2
Need for research; why is BP a self-limiting disorder	1
Need for research on cytokine network in amplifying blistering development	1

BP, bullous pemphigoid; RCT, randomized controlled trial; DNA, deoxyribonucleic acid; MMP, mucous membrane pemphigoid; GP, general practitioner.

Supplemental table 2. Patients' ranking of unmet needs in pemphigoid diseases per continent

	<i>Unmet need recognized?</i>			<i>Ranking score*</i>
	<i>Yes, n (%)</i>	<i>No, n (%)</i>	<i>Missing, n (%)</i>	
<i>Europe (n=22)</i>				
1. Need for better treatment options	16 (73)	3 (14)	3 (14)	34
2. Need for awareness	15 (68)	6 (27)	1 (5)	30
3. Need for quicker diagnosis	15 (68)	6 (27)	1 (5)	29
4. Need for guidance of psychological impact	14 (64)	7 (32)	1 (5)	24
5. Need for easy assessable information	12 (55)	9 (41)	1 (5)	21
6. Need for knowledge on impact on comorbidities	15 (68)	5 (23)	2 (9)	16
7. Need better treatment availability	8 (36)	13 (59)	1 (5)	8
8. Need for self-assessment tool	9 (41)	12 (55)	1 (5)	7
<i>Northern America (n=48)</i>				
1. Need for better treatment options	31 (65)	2 (4)	15 (31)	54
2. Need for quicker diagnosis	31 (65)	3 (6)	14 (29)	52
3. Need for awareness	30 (63)	2 (4)	16 (33)	45
4. Need better treatment availability	19 (40)	4 (8)	25 (52)	33
5. Need for easy assessable information	22 (46)	5 (10)	21 (44)	32
6. Need for self-assessment tool	19 (40)	4 (8)	25 (52)	22
7. Need for guidance of psychological impact	18 (38)	5 (10)	25 (52)	21
8. Need for knowledge on impact on comorbidities	21 (44)	3 (6)	24 (50)	16
<i>Asia (n=1)</i>				
No preference noted				

* *Ranking score was calculated by awarding three points for every time an unmet needs was ranked highest, two points if ranked second highest and one point if ranked third highest.*

Supplemental table 3. Clinicians' ranking of unmet needs in pemphigoid diseases per continent

	<i>Unmet need recognized?</i>			<i>Ranking score*</i>
	<i>Yes, n (%)</i>	<i>No, n (%)</i>	<i>Missing, n (%)</i>	
<i>Europe (n=21)</i>				
1. Need for labeling of new drugs for the indication pemphigoid	16 (76)	4 (19)	1 (5)	31
2. Need for better recognition of nonbullous cutaneous pemphigoid	17 (81)	3 (14)	1 (5)	24
3. Need for a multidisciplinary approach: building multidisciplinary teams	15 (71)	4 (19)	2 (10)	17
3. Need for easy laboratory tests to diagnose pemphigoid diseases	13 (62)	5 (24)	3 (14)	17
4. Need for consensus on minimal requirements for diagnosis of pemphigoid	16 (76)	4 (19)	1 (5)	16
5. Need for definition of the treatment goal at certain time points during treatment (e.g. at 3 months)	14 (67)	5 (24)	2 (10)	13
6. Need for standardized use of PROMS during treatment	15 (71)	4 (19)	2 (10)	11
7. Need for low threshold for detection of autoantibodies in referral laboratories	12 (57)	7 (33)	2 (10)	0
<i>Asia (n=4)</i>				
1. Need for easy laboratory tests to diagnose pemphigoid diseases	4 (100)	0 (0)	0 (0)	7
1. Need for a multidisciplinary approach: building multidisciplinary teams	4 (100)	0 (0)	0 (0)	7
2. Need for labeling of new drugs for the indication pemphigoid	4 (100)	0 (0)	0 (0)	6
3. Need for consensus on minimal requirements for diagnosis of pemphigoid	4 (100)	0 (0)	0 (0)	5
4. Need for better recognition of nonbullous cutaneous pemphigoid	4 (100)	0 (0)	0 (0)	4
5. Need for definition of the treatment goal at certain time points during treatment (e.g. at 3 months)	4 (100)	0 (0)	0 (0)	3
6. Need for standardized use of PROMS during treatment	4 (100)	0 (0)	0 (0)	3
7. Need for low threshold for detection of autoantibodies in referral laboratories	3 (75)	0 (0)	1 (25)	2
<i>Northern America (n=7)</i>				
1. Need for labeling of new drugs for the indication pemphigoid	7 (100)	0 (0)	0 (0)	14
2. Need for easy laboratory tests to diagnose pemphigoid diseases	7 (100)	0 (0)	0 (0)	9
3. Need for better recognition of nonbullous cutaneous pemphigoid	6 (86)	0 (0)	1 (14)	7
4. Need for low threshold for detection of autoantibodies in referral laboratories	5 (71)	2 (29)	0 (0)	4
4. Need for consensus on minimal requirements for diagnosis of pemphigoid	5 (71)	2 (29)	0 (0)	4
4. Need for definition of the treatment goal at certain time points during treatment (e.g. at 3 months)	5 (71)	2 (29)	0 (0)	4
5. Need for a multidisciplinary approach: building multidisciplinary teams	3 (43)	4 (57)	0 (0)	3
6. Need for standardized use of PROMS during treatment	5 (71)	2 (29)	0 (0)	0

*PROMS, patient reported outcome measurements. * Ranking score was calculated by awarding three points for every time an unmet needs was ranked highest, two points if ranked second highest and one point if ranked third highest.*

Supplemental table 4 – part 1. Researchers' ranking of unmet needs in pemphigoid diseases per continent

	<i>Unmet need recognized?</i>			<i>Ranking score*</i>
	<i>Yes, n (%)</i>	<i>No, n (%)</i>	<i>Missing, n (%)</i>	
<i>Europe (n=18)</i>				
1. Need for more head-to-head randomized controlled trials comparing the effectiveness and safety of current treatments	15 (83)	1 (6)	2 (11)	33
2. Need for understanding of the pathophysiology of pemphigoid for drug development	17 (94)	0 (0)	1 (6)	26
3. Need for understanding trigger mechanism (e.g., infections, drugs) in addition to genetic predisposition	17 (94)	0 (0)	1 (6)	20
4. Need for studies on personalized treatment based on patients characteristics	15 (83)	1 (6)	2 (11)	16
5. Need for humanized animal models that simulate the human eosinophilic pathogenesis and the interactions between human IgG/IgA/IgE with human Fc receptors	11 (73)	3 (17)	4 (22)	10
6. Need for animal models for studying the break of tolerance to desmosomal and hemidesmosomal constituents	12 (67)	3 (17)	3 (17)	5
7. Need for consensus on BPDAI cut-off values for staging disease severity	13 (72)	3 (17)	2 (11)	4
<i>Asia (n=4)</i>				
1. Need for more head-to-head randomized controlled trials comparing the effectiveness and safety of current treatments	4 (100)	0 (0)	0 (0)	11
2. Need for studies on personalized treatment based on patients characteristics	4 (100)	0 (0)	0 (0)	6
2. Need for animal models for studying the break of tolerance to desmosomal and hemidesmosomal constituents	4 (100)	0 (0)	0 (0)	6
3. Need for consensus on BPDAI cut-off values for staging disease severity	4 (100)	0 (0)	0 (0)	4
4. Need for understanding trigger mechanism (e.g., infections, drugs) in addition to genetic predisposition	4 (100)	0 (0)	0 (0)	3
4. Need for understanding of the pathophysiology of pemphigoid for drug development	4 (100)	0 (0)	0 (0)	3
4. Need for humanized animal models that simulate the human eosinophilic pathogenesis and the interactions between human IgG/IgA/IgE with human Fc receptors	3 (75)	0 (0)	1 (25)	3

BPDAI, bullous pemphigoid disease activity index.

** Ranking score was calculated by awarding three points for every time an unmet needs was ranked highest, two points if ranked second highest and one point if ranked third highest.*

Supplemental table 4 – part 2. Researchers' ranking of unmet needs in pemphigoid diseases per continent

	<i>Unmet need recognized?</i>			<i>Ranking score*</i>
	<i>Yes, n (%)</i>	<i>No, n (%)</i>	<i>Missing, n (%)</i>	
<i>Northern America (n=6)</i>				
1. Need for understanding of the pathophysiology of pemphigoid for drug development	6 (100)	0 (0)	0 (0)	9
2. Need for animal models for studying the break of tolerance to desmosomal and hemidesmosomal constituents	5 (83)	1 (17)	0 (0)	8
3. Need for humanized animal models that simulate the human eosinophilic pathogenesis and the interactions between human IgG/IgA/IgE with human Fc receptors	6 (100)	0 (0)	0 (0)	7
3. Need for understanding trigger mechanism (e.g., infections, drugs) in addition to genetic predisposition	6 (100)	0 (0)	0 (0)	7
3. Need for more head-to-head randomized controlled trials comparing the effectiveness and safety of current treatments	6 (100)	0 (0)	0 (0)	7
4. Need for studies on personalized treatment based on patients characteristics	5 (83)	1 (17)	0 (0)	1
5. Need for consensus on BPDAI cut-off values for staging disease severity	5 (83)	1 (17)	0 (0)	0

BPDAI, bullous pemphigoid disease activity index.

** Ranking score was calculated by awarding three points for every time an unmet needs was ranked highest, two points if ranked second highest and one point if ranked third highest.*

