REVIEW ARTICLE

European consensus statement on phenotypes of pustular psoriasis

A.A. Navarini,[1,*,†] A.D. Burden,[2,†] F. Capon,[3,†] U. Mrowietz,[4,†] L. Puig,[5,†] S. Köks,[6] K. Kingo,[6] C. Smith,[3] J.N. Barker,[3] on behalf of the ERASPEN Network[‡]

[1]Department of Dermatology, University Hospital of Zurich, Zurich, Switzerland
[2]Institute of Infection Inflammation and Immunity, University of Glasgow, Glasgow, UK
[3]Division of Genetics and Molecular Medicine, King's College, London, UK
[4]Psoriasis Center at the Department of Dermatology, University Medical Center, Schleswig-Holstein, Campus Kiel,Kiel, Germany
[5]Department of Dermatology, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain
[6]Department of Dermatology and Venerology, Tartu University Hospital, Tartu, Estonia
*Correspondence: A.A. Navarini. E-mail: alexander.navarini@usz.ch

Abstract

Pustular psoriasis (PP) is a group of inflammatory skin conditions characterized by infiltration of neutrophil granulocytes in the epidermis to such an extent that clinically visible sterile pustules develop. Because of clinical co-incidence, PP is currently grouped with psoriasis vulgaris (PV). However, PP and PV are phenotypically different, respond differently to treatments and seem to be distinct on the genetic level. In contrast to PV, the phenotypes of PP are not well defined. Descriptions of each form of PP are discordant among standard dermatology textbooks [*Saurat Dermatologie* 2016, *Rook's Dermatology* 2016, *Fitzpatrick's* 2012 and *Braun-Falco* 2012], encumbering the collection of phenotypically well-matched groups of patients as well as clinical trials. The European Rare and Severe Psoriasis Expert Network (ERASPEN) was founded to define consensus criteria for diagnosis, deeply phenotype large groups of PP patients, analyse the genetics and pathophysiology and prepare for prospective clinical trials. This work reviews historical aspects of these conditions, new genetic findings and presents our initial considerations on the phenotypes of PP and a consensus classification of clinical phenotypes that will be used as a baseline for further, prospective studies of PP. Generalized pustular psoriasis (GPP) is defined as primary, sterile, macroscopically visible pustules on non-acral skin (excluding cases where pustulation is restricted to psoriatic plaques). GPP can occur with or without systemic inflammation, with or without PV and can either be a relapsing (>1 episode) or persistent (>3 months) condition. Acrodermatitis continua of Hallopeau (ACH) is characterized by primary, persistent (>3 months), sterile, macroscopically visible pustules affecting the nail apparatus. Palmoplantar pustulosis (PPP) has primary, persistent (>3 months), sterile, macroscopically visible pustules on palms and/or soles and can occur with or without PV.

Received: 21 December 2016; Accepted: 18 May 2017

Conflicts of interest

None declared.

Funding sources

None declared.

Introduction

Psoriasis traditionally comprises both erythrosquamous and pustular lesions. These are distinct both clinically and histologically, but both pustules and plaques can occur together. For example, pustules can be observed as an extreme phenotype within plaques of psoriasis. Indeed, plaques always have a measure of neutrophil granulocytes that can be detected histologically. When intense inflammation is present, collections of neutrophils (Munro's subcorneal microabscesses and Kogoj's spongiform pustules[1]) can form. It has not formally been proven whether these can turn into clinically observable pustules. But it is a not uncommon clinical observation to find some pustules in inflammatory plaques of PV (particularly by dermoscopy), as was described also by Barber[2] and Königsbeck. This ultimately led to the assumption that several primary pustular conditions are part of the psoriasis spectrum, which were thus labelled

†Shared authorship.

pustular psoriasis (PP). Newer data have revealed that some of the genetic variants underlying PP do not occur in non-pustular psoriasis. Therefore, the question arose whether these conditions should be regarded as diseases altogether separate from psoriasis. This prompted several groups to investigate these conditions closely for pathogenetic factors involved.

Unfortunately, the rarity of PP does not usually allow collection of sufficient sample numbers from a single centre. Therefore, pooling of samples among international centres is crucial. This is more difficult than might be expected, because the clinical criteria for description and diagnosis of pustular conditions including PP vary and no consensus has been developed. Therefore, basic science including genetic studies may reach diverging results depending on where patients are recruited from. Pooling heterogenous international groups of patients does not alleviate the problem and makes genetic discovery even more difficult. We therefore set out to find a European and ideally international consensus for clinical criteria of PP. The European Rare and Severe Psoriasis Expert Network (ERASPEN) was founded with a PPRC grant of the European Association of Dermatology and Venereology to address this unmet need and start unbiased collaborative investigation of the clinical phenotype and genotype of PP patients. Here, we present some considerations on the clinical features of PP and a consensus classification of phenotypes that will be utilized for further, unbiased study of PP and genetic studies, clinical trials, healthcare planning and prevalence/incidence studies.

Genetic architecture of PP

A minority of PP cases are caused by rare and damaging mutations of the *IL-36RN* gene, which encodes an anti-inflammatory protein known as the interleukin 36 receptor antagonist. This molecule inhibits the activation of NF-κB by interleukins 36 α, β and γ, by binding to the IL-1RL2 receptor and preventing its association with the IL-1RAP co-receptor.

IL-36RN defects were first identified in five unrelated individuals with GPP[3] and in nine Tunisian families with autosomal recessive transmission of the disease.[4] A total of 16 *IL-36RN* mutations have since been uncovered (p.Arg10X, p.Arg10ArgfsX1, p.Leu21Pro, p.Leu27Pro, p.His32Arg, p.Lys35Arg, p.Arg48Trp, p.Pro76Leu, p.Glu94X, p.Arg102Gln, p.Arg102Trp, p.Glu112Lys, p.Ser113Leu, p.Thr123Arg, p.Thr123Met and p.Gly141MefsX29) and listed in the Infevers database (http://fmf.igh.cnrs.fr/ISSAID/infevers/).[5] These disease alleles are found in both European and Asian populations, and account for approximately 25% of GPP,[6] 20% of ACH and 2% of PPP cases.[7] The latter, however, is somewhat controversial, as some studies found no association at all with PPP.[8]

Mutation status has also been found to correlate with clinical phenotype, as the age of disease onset tends to be higher[6] and systemic inflammation less frequent in those who lack *IL-36RN* defects. Also, 82% of GPP patients who did not suffer from concomitant PV had mutations in *IL-36RN* compared to 10% of those affected by GPP with PV.[9] The same pattern was confirmed by a European study finding *IL-36RN* mutations in 46% of GPP patients without PV and 17% in GPP with PV.[10] Finally, an interesting study from China found that about 93% of patients with GPP and features of ACH had a damaging *IL-36RN* mutation.[11]

Although *IL-36RN* alleles are mostly inherited in an autosomal recessive fashion, the disease can also occur in persons with single heterozygous mutations. In total, more than 10 patients with GPP and heterozygous *IL-36RN* changes have been reported, which could be explained by additional mutations at a second locus.[12] Heterozygous *IL-36RN* alleles were also found in some cases[13,14] of the pustular drug rash AGEP, which could suggest a close relation or overlap with PP.

IL-36 is close to IL-1 that has been implicated as the early pathogenetic mechanism in the model of bimodal immune activation in psoriasis,[15] acting as autoinflammatory factor. Whilst in PV this is followed by an adaptive immune response, it remains unclear what role adaptive immunity plays in PP.

Another gene involved in GPP, PPP and ACH is *AP1S3*.[16] It encodes a subunit of the adaptor protein complex 1 (AP-1), which is an evolutionary conserved heterotetramer that promotes vesicular trafficking between the trans-Golgi network and the endosomes. The exact expression pattern of *AP1S3* in skin is yet unknown. Two *AP1S3* founder mutations (c.11T>G [p.Phe4Cys] and c.97C>T [p.Arg33Trp]) were identified in GPP/ACH or PPP individuals of European descent but not in Asian patients. Potential clinical relevance was confirmed by *AP1S3* silencing that disrupted the endosomal translocation of the innate pattern-recognition receptor TLR-3 (Toll-like receptor 3) and resulted in a marked inhibition of downstream signalling.

CARD14[5,17] mutations have also been found in GPP and PPP[8] as well as in PV.[18] *CARD14* is also localized in keratinocytes and encodes for the caspase recruitment domain family, member 14. It mediates aggregation of CARD protein complexes that play a role in apoptosis and NF-kB signalling. The two mutations (p.Glu138Ala and p.Asp176His) described in PP are gain-of-function changes which result in abnormal activation of NF-kB.

Historical considerations

We reviewed the definitions of PP in standard dermatology textbooks and found several discrepancies on subtypes, localizations, pain, presence of arthritis and other features (Table 1). This prompted us to review the first descriptions of PP, which revealed that our current understanding of these conditions has drifted somewhat away from these first observations.

The condition known today as generalized pustular psoriasis was described by Leopold von Zumbusch.[19] Two siblings with stable PV had been treated with pyrogallic acid applications.

Table 1 Textbook definitions of pustular psoriasis

		Braun-Falco 6th Ed.[39]	Rook 9th Ed.[38]	Fitzpatrick 8th Ed.[40,41]	Saurat 3rd Ed.[37]	Baker/Ryan[43]
Generalized pustular psoriasis	Fever	+	+	+	+	+
	Generalized pustules	+	+	+	+	+
	Sterile pustules	+	+	+	+	+
	Arthritis	–	(+)	–	(+)	(+)
	Localization Trunk	+	+	+	+	+
	Localization intertriginous	+	+	–	?	(+)
	Subtypes	2	4	4	5	4
Acrodermatitis continua suppurativa	Finger > Toes	+	+	+	+	
	Pustules	+	+	+	+	
	Atrophy	+	+	+	+	
	Nail loss	+	+	+	+	
	Pain	+	?	?	–	
Palmoplantar pustulosis	Palms, Feet	+	+	+	+	
	Pustules	+	+	+	+	
	Smoking	+	+	+	?	
	Nail loss	+	+	+	+	
	Pain	+	?	?	–	
	Inflamed skin	+*	+	+	+	

*changed to + since 6th edition.

Subsequently, they developed recurrent episodes of bright erythema and oedema, which then became studded with multiple pustules (Fig. 1a). The flares were almost universal and constantly accompanied by fever (40°C) and other signs of systemic inflammation. Each attack was short-lived, the inflamed skin becoming paler as the pustules gave way to peeling and desquamation. Even though the first attacks were temporally associated with the pyrogallic acid treatments, subsequently they reoccurred without obvious causes. The eruptions paralleled the activity of psoriasis. In a period of 10 years, nine flares occurred. Subsequent descriptions of GPP featured many patients without PV. Also, trigger factors for GPP other than pyrogallic acid were identified, namely infections, pregnancy, hypocalcaemia associated with hypoparathyroidism and drugs. In particular, streptococcal infection has been noted as a provocative factor. Some of these triggers have prompted the definition of distinct conditions[20,21] (see below).

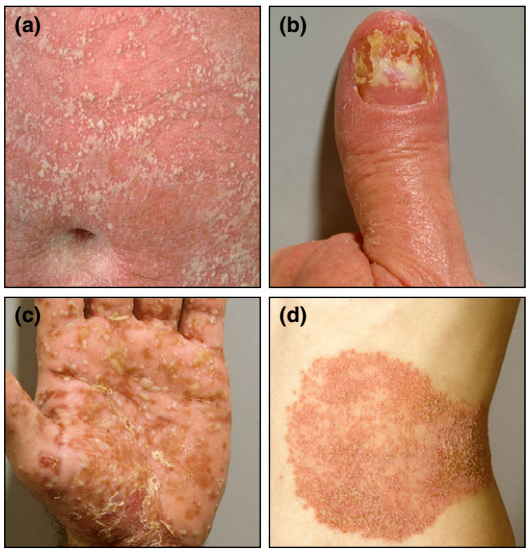

Figure 1 Generalized pustular psoriasis (a), *Acrodermatitis continua of* Hallopeau (b), Palmoplantar pustulosis (c) and an unclear case of a single episode of a sterile, localized pustular eruption that would be classified as undifferentiated pustulosis (d).

Acrodermatitis continua of Hallopeau[22] (ACH) was described in 1890 in a 69-year-old glove maker, shortly after Radcliffe Crocker had described similar cases in 1888.[23] Since infancy, the patient had suffered repeatedly with peripheral hypoxia. Hallopeau interpreted the condition as Raynaud's phenomenon. The toes, ears and nose were also affected from time to time upon exposure to cold. The patient suddenly developed a red and painful lesion on the palm, as well as purulent inflammation of the same fingers that had been affected by the cyanosis. This inflammation started at the matrix of the nails. Months after the first presentation, the patient's toe nail turned red and whitish islets with polycyclic borders developed on the nail, representing subungual pus. Subsequently, the patient lost several toenails and the periungual tissues were greatly inflamed. The disease then spread to involve the whole body with sheets of pustules that only abated after a period of 6 months. The oral mucosa

was involved as well. Interestingly, during a period of influenza and pulmonary congestion, the pustules resolved briefly. Hallopeau interpreted his observation that pustular lesions were causally connected to the hyperaemia that he had observed after the attacks of Raynauds' phenomenon and he suggested in his case discussion that this might have led to the inflammation. Other authors' later descriptions did not include a vascular component but rather seemingly spontaneous neutrophil inflammation of the distal fingers (Fig. 1b) and toes. Barber stated 'true *acrodermatitis continua vel perstans* begins on the extremity of a digit, either as an infected traumatic sore, or as a whitlow. From this localized and unilateral site the eruption spreads'.[24] Also, in some patients, ACH tends to generalize and overlap with GPP.

Palmoplantar pustulosis (PPP) is the most common of the three archetypical forms of pustular psoriasis. Barber at St John's Institute of Dermatology in London[2] described a series of patients in great detail. He observed that PV is often associated with PPP and can precede it. The age of onset varied from of 7 to 74 years, and a familial association was often present. Sometimes, pustules developed within psoriatic plaques (a phenomenon we nowadays call '*psoriasis cum pustulatione*', or 'psoriasis with pustules'). Pustules developed also on the lateral surfaces of the hands and feet, on the wrists, over the Achilles tendons and upwards around the ankles. He observed that the neutrophilic infiltration destroys the microarchitecture of the epidermis and that upon evacuation of the pus, the pustules in PPP leave a visible cavity behind. When they are not evacuated, the pustules dry up and form brownish scabs (Fig. 1c) that subsequently exfoliate. Barber also noted that sometimes, the fluid is at first serous and not pustular. Invariably, the pus was sterile. He was convinced that PPP is a pustular form of psoriasis and as evidence cited, the co-incidence of the two conditions, mixed lesions with features of both conditions, familial occurrence and onset triggered by streptococcal infection. Later, it was substantiated that tonsillectomy is a beneficial measure in PPP.[25] On the other hand, he strictly set ACH apart from GPP/PPP, as shown in Table S1.

Uncommon forms of PP exist that partially overlap with GPP, ACH or PPP.

The drug-triggered acute generalized exanthematous pustulosis (AGEP) is clinically very similar to GPP, and recently, the same mutations in *IL-36RN* were found in some cases of AGEP.[13,14,26] *Pustulosis acuta generalisata* (PAG) is clinically related to GPP and AGEP.[20,27,28] PAG produces scattered subcorneal pustules with red halo on normal skin, with acral predominance. Leucocytosis and sometimes leucocytoclastic vasculitis and fever are present. The antistreptolysin titres are elevated. *Impetigo herpetiformis* (IH) was described in 1872 by von Hebra and is a generalized pustular eruption anytime during pregnancy. It remits postpartum. Some cases have been found to have *IL-36RN* mutations,[29,30] suggesting that IH and GPP are the same disease.

The pustular bacterid[31] that was identified by Andrews and Machacek is also triggered by streptococcal infection, usually of the throat. It is exquisitely rare but continues to be described every few years. It affects the palms and soles with multiple tense monomorphic pustules without erythema or scale[32] and occurs together with systemic symptoms including fever. The sudden onset, the invariable association with streptococcal infection and the fever set it apart from palmoplantar pustulosis.[32,33] A condition that is almost forgotten today is Radcliffe Crocker's *dermatitis repens* that he described in 1888 in three patients.[34] He noted a slowly progressing erosive dermatitis on the fingers that he thought to be elicited by injury. This condition, comparably to ACH, affected first the nail apparatus and indeed led to loss of fingernails, but never became generalized. Barber, in a detailed and painstaking comparison,[35] concluded that this condition is identical with ACH.

There are many other pustuloses[36] not associated with psoriasis. Pustules can develop as a response to bacterial, viral or fungal infection, but they can also form without apparent cause and remain sterile (Fig. 1d). The latter are the central feature observed in primary pustuloses. At least 29 different primary pustuloses have been described over the years (Table 2), and all three PP types can be classified in this list as well. These conditions can involve all areas of the skin, have been described in all age groups and have a wide range of possible associated clinical features. The pustuloses comprise a variety of conditions that were thought to merit consideration as separate entities based on a distinct phenotype, specific trigger factors or for being a part of a complex syndrome's clinical manifestation. Many of the pustuloses described over the years are exquisitely rare, to the point that their existence has been discussed controversially.

Taken together, it is not surprising that the first descriptions of PP and later observations do not completely overlap. This suggests a clear unmet need for a consensus definition of phenotypes and later validation or adaptation of these definitions by prospective evaluation of a sufficient number of PP patients.

Methods

Determination of consensus criteria

Identification of expert group: Among five representative European countries, clinicians known as experts for PP were asked to participate (LP, ADB, UM, AN, AC). In addition, a geneticist (FC) was invited. These experts met as a 'core phenotyping group' with the specific agenda of finding consensus on phenotypic descriptions of PP and condensing the peer-reviewed as well as textbook-derived literature in simple and universally applicable diagnostic criteria. Four widely used textbooks were chosen as sources of clinical descriptions of PP representing the dermatological perspective from France (Saurat 3rd Ed.[37]), UK

Table 2 Pustular dermatoses (historical classification)

Pustular dermatoses	
Localized	
Paediatric	
	Infantile acropustulosis[44]
	Transient neonatal cephalic pustulosis[45]
	Parakeratosis pustulosa[46]
Adult	
	Acrodermatitis continua suppurativa Hallopeau[22]
	Dermatitis repens Radcliffe Crocker[34]
	Palmoplantar pustulosis (PPP)[2]
	Andrew's pustular bacterid[31]
	Erosive pustular dermatosis of the scalp[47]
	Dermatitis cruris pustulosa et atrophicans[48]
Syndrome	Amicrobial intertriginous pustulosis Oberlin[49]
Syndrome	SAPHO syndrome[50]
Syndrome	*Keratoderma blenorrhagicum*[51]
Generalized	
Paediatric	
	Erythema toxicum neonatorum[52]
	Transient neonatal pustular melanosis[53]
	Acute neonatal pustulosis in Down Syndrome[54]
	Eosinophilic pustular folliculitis in infancy[55]
Syndrome	*Miliaria pustulosa (rubra)*[56]
Syndrome	Congenital Langerhans cell histiocytosis[57]
Syndrome	*Incontinentia pigmenti* Bloch Sulzberger[58]
Syndrome	*Acrodermatitis enteropathica*[59]
Adult	
	Generalized pustular psoriasis von Zumbusch[60]
	Impetigo herpetiformis[21]
	Pemphigus vegetans[36]
	Pustulosis acuta generalisata[20]
	Acute generalized exanthematous pustulosis[61]
	Intraepidermal neutrophil IgA Dermatosis[62]
	Pustulosis subcornealis Sneddon Wilkinson[63]
	Erythema anulare-like psoriasis[64]
	Eosinophilic pustular folliculitis[65]

(Rook 9th Ed.[38]), Germany (Braun-Falco 5th and 6th Ed.[39]) and USA (Fitzpatrick 8th Ed.[40,41]).

In preparation for the meeting, the medical literature was searched for 'phenotype/clinical features' in 'pustular psoriasis/acrodermatitis continua/palmoplantar pustulosis' and synonyms. Clinical features and photographs of typical and atypical cases were reviewed collectively to generate consensus diagnostic criteria. The method to generate consensus was a modified nominal group process. Each expert prepared one predefined main aspect most relevant for phenotyping of PP and subsequently contributed all relevant points in his or her view. The group then discussed all points and finally defined consensus definitions and diagnostic criteria for PP. A consensus level of 100% was both required and reached. Diagnostic criteria were circulated within the wider ERASPEN network, and comments were integrated in a revised version of the diagnostic criteria, again based on unanimous consensus of the core group.

ERASPEN network and membership

ERASPEN (www.eraspen.eu) is an open, collaborative network for clinicians caring for PP patients. Its main aims are harmonization of phenotyping of PP across Europe and collection of liquid and standard biopsies (esp. DNA) to achieve better clinical and pathophysiologic understanding of these conditions. Membership is free and allows access to several tools to collect data and collaborate with others. Ethical permissions are managed on the national level, and all data shared on the European level in ERASPEN's core electronic clinical database are anonymized. The sponsor-PI (AN, JB) are responsible for the ERASPEN infrastructure.

Results

Diagnostic criteria and terminology of pustular psoriasis

Pustules are macroscopically visible epidermal or subcorneal accumulations of neutrophil granulocytes with (not predominating) or without eosinophils. Very small pustules not visible with the naked eye are compatible with PP, but also with other conditions including PV. Primary pustular conditions including all forms of PP should be considered related diseases. Pustules in PP are considered primary lesions, whereas non-sterile secondary pustules do not form part of PP. This includes pustules in for instance bullous impetigo or in superinfected dyshidrotic eczema, but not pustules triggered by a distant streptococcal infection. Pustules drying out may form brownish scabs that are slowly cast off. These brown scabs are considered evidence of pustulation in situations when no fresh pustules are detectable. For chronic disease, the threshold of 3-month duration of lesions was used as defined by the U.S. National Center for Health Statistics. For systemic inflammation, we used the American Society of Chest Physicians definition of fever >38°C and leucocytosis (WBC $> 12 \times 10^9$/L).[42]

As to terminology of PP subtypes, the expert group agreed that the mostly historical labelling of GPP, ACH and PPP as psoriasis is insufficiently evidence-based but still has clinical utility. The terminology should not be abandoned lightly, but only when new clinical groupings based on robust evidence will be defined by the ERASPEN consortium and further validated by other studies. Each subtype of PP is subclassified on the basis of the presence or absence of associated features (see Table 3). Thus for instance, a complete clinical diagnosis might be 'generalized pustular psoriasis, with systemic inflammation, without plaque psoriasis, relapsing type'.

Relationship of PV to PP

PV is a distinct entity that has neutrophil granulocytes at the microscopic level, including microabscesses of Munro. However,

Table 3 Consensus definitions for the diagnosis of pustular psoriasis

Generalized pustular psoriasis	
Primary, sterile, macroscopically visible pustules on non-acral skin (excluding cases where pustulation is restricted to psoriatic plaques)	
Subclassifier	With or without systemic inflammation
Subclassifier	With or without psoriasis vulgaris
Subclassifier	Either relapsing (>1 episode) or persistent (>3 months)
Palmoplantar pustulosis	
Primary, persistent (>3 months), sterile, macroscopically visible pustules on palms and/or soles	
Subclassifier	With or without psoriasis vulgaris
Acrodermatitis continua of Hallopeau	
Primary, persistent (>3 months), sterile, macroscopically visible pustules affecting the nail apparatus	
Subclassifier	With or without psoriasis vulgaris

primary pustules do not form part of the spectrum of PV except when pustules arise within or at the edge of psoriasis plaques. In these cases, the term to be used is '*psoriasis cum pustulatione*' (psoriasis with pustules). All experts agreed that this should not be considered pustular psoriasis.

Generalized pustular psoriasis

Macroscopically visible primary sterile pustules occurring on non-acral skin and not within psoriasis plaques characterize generalized pustular psoriasis. GPP should only be diagnosed when the condition has relapsed at least once or when it persists for more than 3 months. Also, a drug reaction such as AGEP should be actively ruled out. GPP can occur with or without PV, and with or without systemic inflammation. Although it is known that GPP can be triggered by provocative factors, this is not considered a criterion for the diagnosis. Also, the expert group decided against actual counting of pustules as a measure of intensity, as the spectrum varies from discrete to confluent forms. However, an unmet need for development of a new score to measure GPP severity was noted.

Acrodermatitis continua of Hallopeau (ACH)

ACH is a chronic condition that evolves slowly. It forms primary, persistent (>3 months), sterile, macroscopically visible pustules affecting the nail apparatus. ACH is not restricted to the nail apparatus, but by the experts' consensus, it is the key structure that is always involved. It can occur with or without PV. Pustules not affecting the nail apparatus are not considered ACH but rather PPP or undifferentiated pustulosis.

Mixed forms

A large part of PP is expected to be forms with mixed clinical features, for example ACH with GPP. By consensus, these are to be grouped by the predominant feature. Later analysis of collected phenotypes will reveal whether some overlap patterns are sufficiently frequent to warrant the creation of additional entities. Cases that do not conform to the archetypal description given above may be considered 'undifferentiated primary pustulosis'.

Discussion and outlook

Research on PP is still at its beginning. Revision of the genetic findings reveals that some mutations seem to be enriched in mixed phenotypes not well captured by our traditional PP trinity of GPP, ACH and PPP. In addition, some other entities[13] might be added to the realm of PP. Even though interest is rekindled with the new genetic findings that promise potential new treatments, we are very far away from systematic trials as are available for PV. However, by combining efforts and multicentre studies powered by efficient data collection, solid advances in this field are within our reach.

Acknowledgements

ERASPEN is supported by a PPRC grant from the European Association of Dermatology and Venereology (EADV) to AN and JB. AN is supported by the Bruno Bloch and Promedica Foundation and HSM-2 from the Kanton of Zurich, Switzerland. FC is supported by The Psoriasis Association.

Author contributions

AN wrote the manuscript; FC, ADB, LP, UM and AN determined the consensus definitions; JB, CS and all others critically revised and added to the manuscript.

References

1 Steffen C. William John Munro and Munro's abscess, and Franz Kogoj and Kogoj's spongiform pustule. *Am J Dermatopathol* 2002; **24**: 364–368.
2 Barber HW. Pustular psoriasis of the extremities. *Guy's Hospital Rep* 1936; **86**: 108–119.
3 Onoufriadis A, Simpson Michael A, Pink Andrew E *et al.* Mutations in IL36RN/IL1F5 are associated with the severe episodic inflammatory skin disease known as generalized pustular psoriasis. *Am J Hum Genet* 2011; **89**: 432–437.
4 Marrakchi S, Guigue P, Renshaw BR *et al.* Interleukin-36-receptor antagonist deficiency and generalized pustular psoriasis. *N Engl J Med* 2011; **365**: 620–628.
5 Sugiura K. The genetic background of generalized pustular psoriasis: IL36RN mutations and CARD14 gain-of-function variants. *J Dermatol Sci* 2014; **74**: 187–192.
6 Hussain S, Berki DM, Choon SE *et al.* IL36RN mutations define a severe autoinflammatory phenotype of generalized pustular psoriasis. *J Allergy Clin Immunol* 2015; **135**: 1067–1070.e9.
7 Setta-Kaffetzi N, Navarini AA, Patel VM *et al.* Rare pathogenic variants in IL36RN underlie a spectrum of psoriasis-associated pustular phenotypes. *J Invest Dermatol* 2013; **133**: 1366–1369.
8 Mossner R, Frambach Y, Wilsmann-Theis D *et al.* Palmoplantar pustular psoriasis is associated with missense variants in CARD14, but not with loss-of-function mutations in IL36RN in European patients. *J Invest Dermatol* 2015; **135**: 2538–2541.
9 Sugiura K, Takemoto A, Yamaguchi M *et al.* The majority of generalized pustular psoriasis without psoriasis vulgaris is caused by deficiency of interleukin-36 receptor antagonist. *J Invest Dermatol* 2013; **133**: 2514–2521.

10 Korber A, Mossner R, Renner R *et al.* Mutations in IL36RN in patients with generalized pustular psoriasis. *J Invest Dermatol* 2013; **133**: 2634–2637.
11 Wang TS, Chiu HY, Hong JB, Chan CC, Lin SJ, Tsai TF. Correlation of IL36RN mutation with different clinical features of pustular psoriasis in Chinese patients. *Arch Dermatol Res* 2016; **308**: 55–63.
12 Capon F. IL36RN mutations in generalized pustular psoriasis: just the tip of the iceberg? *J Invest Dermatol* 2013; **133**: 2503–2504.
13 Navarini AA, Valeyrie-Allanore L, Setta-Kaffetzi N *et al.* Rare variations in IL36RN in severe adverse drug reactions manifesting as acute generalized exanthematous pustulosis. *J Invest Dermatol* 2013; **133**: 1904–1907.
14 Navarini AA, Simpson MA, Borradori L, Yawalkar N, Schlapbach C. Homozygous missense mutation in IL36RN in generalized pustular dermatosis with intraoral involvement compatible with both AGEP and generalized pustular psoriasis. *JAMA Dermatol* 2015; **151**: 452–453.
15 Christophers E, Metzler G, Rocken M. Bimodal immune activation in psoriasis. *Br J Dermatol* 2014; **170**: 59–65.
16 Setta-Kaffetzi N, Simpson Michael A, Navarini Alexander A *et al.* AP1S3 mutations are associated with pustular psoriasis and impaired toll-like receptor 3 trafficking. *Am J Hum Genet* 2014; **94**: 790–797.
17 Berki DM, Liu L, Choon SE *et al.* Activating CARD14 mutations are associated with generalized pustular psoriasis but rarely account for familial recurrence in psoriasis vulgaris. *J Invest Dermatol* 2015; **135**: 2964–2970.
18 Jordan CT, Cao L, Roberson ED *et al.* Rare and common variants in CARD14, encoding an epidermal regulator of NF-kappaB, in psoriasis. *Am J Hum Genet* 2012; **90**: 796–808.
19 Von Zumbusch L. Psoriasis und pustuloses Exanthem. *Arch Dermatol Syphilol* 1910; **99**: 335–346.
20 Braun-Falco O, Luderschmidt C, Maciejewski W, Scherer R. Generalized acute pustulosis. An unusual presentation of leukocytoclastic vasculitis. *Hautarzt* 1978; **29**: 371–377.
21 von Hebra F. On some affections of the skin occurring in pregnant and puerperal women. *Wien Med Wchnschr* 1872; **48**: 1197.
22 Hallopeau MH. Sur une asphyxie locale des extremities avec polydactylite suppurative chronique et poussées éphémères de dermatite pustuleuse disséminée et symétrique. *Bull Soc Fr Dermatol Syphiligr* 1890; **1**: 39–45.
23 Radcliffe-Crocker H. Recent Literature Diseases of the Skin. By H. Radcliffe Crocker. Third edition, revised and enlarged. Philadelphia: P. Blakiston's Son & Company. 1903. *Boston Med Surg J* 1903; **148**: 624.
24 Barber HW. Acrodermatitis continua vel perstans (dermatitis repens) and psoriasis pustulosa*. *Br J Dermatol* 1930; **42**: 500–518.
25 Mrowietz U, van de Kerkhof PC. Management of palmoplantar pustulosis: do we need to change? *The British journal of dermatology.* 2011; **164**: 942–946.
26 Navarini AA, Valeyrie-Allanore L, Setta-Kaffetzi N *et al.* Generalised pustular eruptions-time to adapt the disease taxonomy to the genetic architecture? *J Invest Dermatol* 2014; **134**: 580–581.
27 Patrizi A, Savoia F, Giacomini F, Neri I, Ricci G. Diffuse acute pustular eruption after streptococcal infection–a new instance of pustulosis acuta generalisata. *Pediatr Dermatol* 2007; **24**: 272–276.
28 Auer-Grumbach P, Pfaffenthaler E, Soyer HP. Pustulosis acuta generalisata is a post-streptococcal disease and is distinct from acute generalized exanthematous pustulosis. *Br J Dermatol* 1995; **133**: 135–139.
29 Sugiura K, Nakasuka A, Kono H, Kono M, Akiyama M. Impetigo herpetiformis with IL36RN mutations in a Chinese patient: a founder haplotype of c.115 + 6T>C in East Asia. *J Dermatol Sci* 2015; **79**: 319–320.
30 Sugiura K, Oiso N, Iinuma S *et al.* IL36RN mutations underlie impetigo herpetiformis. *J Invest Dermatol* 2014; **134**: 2472–2474.
31 Andrews GC, Machacek GF. Pustular bacterids of the hands and feet. *Arch Derm Syphilol* 1935; **32**: 837–847.
32 Murakami M, Ishida-Yamamoto A, Morhenn VB, Sayama K. Acute generalised pustular bacterid. *Lancet Infect Dis* 2013; **13**: 655–656.
33 Bacharach-Buhles M, el Gammal S, Altmeyer P. The pustular bacterid (Andrews). Are there clinical criteria for differentiating from psoriasis pustulosa palmaris et plantaris? *Hautarzt* 1993; **44**: 221–224.
34 Radcliffe-Crocker H. Diseases of the Skin, 1st edn. HK Lewis, London, 1888.
35 Barber HW, Eyre JWH. Acrodermatitis continua (hallopeau) vel dermatitis repens (crocker). *Br J Dermatol* 1927; **39**: 485–520.
36 Leroy D, Lebrun J, Maillard V, Mandard JC, Deschamps P. Pemphigus vegetans, a clinical type of chronic pustular dermatitis of Hallopeau. *Ann Dermatol Venereol* 1982; **109**: 549–555.
37 Navarini AA, Borradori L, Saurat JH. Dermatologie – Pustuloses Amicrobiennes., 2016.
38 Burden AD, Kirby B. Rook's Dermatology - Pustular Psoriasis, 9th edn., 2016. DOI: 10.1002/9781118441213.rtd0036
39 Christophers E, Mrowietz U. Dermatologie, 6th edn., 2005.
40 Gudjonsson J, Elder JT. Fitzpatrick's Dermatology in General Medicine – Psoriasis, 8th edn. McGraw-Hill, New York, NY, 2012.
41 Mrowietz U. Fitzpatrick's Dermatology in General Medicine – Pustular Eruptions of Palms and Soles, 8th edn. McGraw-Hill, New York, NY, 2012.
42 Bone RC, Balk RA, Cerra FB *et al.* Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest* 1992; **101**: 1644–1655.
43 Baker H, Ryan TJ. Generalized pustular psoriasis. A clinical and epidemiological study of 104 cases. *Br J Dermatol* 1968; **80**: 771–793.
44 Jarratt M, Ramsdell W. Infantile acropustulosis. *Arch Dermatol* 1979; **115**: 834–836.
45 Aractingi S, Cadranel S, Reygagne P, Wallach D. Neonatal pustulosis induced by Malassezia furfur. *Ann Dermatol Venereol* 1991; **118**: 856–858.
46 Hjorth N, Thomsen K. Parakeratosis pustulosa. *Br J Dermatol* 1967; **79**: 527–532.
47 Pye RJ, Peachey RD, Burton JL. Erosive pustular dermatosis of the scalp. *Br J Dermatol* 1979; **100**: 559–566.
48 Clarke GHV. A note on dermatitis cruris pustulosa et atrophicans. *Trans R Soc Trop Med Hyg* 1952; **46**: 558–559.
49 Oberlin P, Bagot M, Perrussel M, Leteinturier F, Wechsler J, Revuz J. Amicrobial pustulosis and systemic lupus erythematosus. *Ann Dermatol Venereol* 1991; **118**: 824–825.
50 Chamot AM, Benhamou CL, Kahn MF, Beraneck L, Kaplan G, Prost A. Acne-pustulosis-hyperostosis-osteitis syndrome. Results of a national survey. 85 cases. *Rev Rhum Mal Osteoartic* 1987; **54**: 187–196.
51 Reiter H. Ueber eine bisher unerkannte Spirochäteninfektion (*Spirochaetosis arthritica*). *Deutsch Med Wochenschr* 1916; **42**: 1535–1536.
52 Finlay HV, Bound JP. Urticaria neonatorum (erythema toxicum neonatorum). *Arch Dis Child* 1953; **28**: 404–408.
53 Ramamurthy RS, Reveri M, Esterly NB, Fretzin DF, Pildes RS. Transient neonatal pustular melanosis. *J Pediatr* 1976; **88**: 831–835.
54 Rosner F, Lee SL. Down's syndrome and acute leukemia: myeloblastic or lymphoblastic? Report of forty-three cases and review of the literature. *Am J Med* 1972; **53**: 203–218.
55 Lucky AW, Esterly N, Heskel N, Krafchik BR, Solomon LM. Eosinophilic pustular folliculitis in infancy. *Pediatr Dermatol* 1984; **1**: 202–206.
56 Urbatsch A, Paller AS. Pustular miliaria rubra: a specific cutaneous finding of type I pseudohypoaldosteronism. *Pediatr Dermatol* 2002; **19**: 317–319.
57 Gottlober P, Weber L, Behnisch W, Bezold G, Peter RU, Kerscher M. Langerhans cell histiocytosis in a child presenting as a pustular eruption. *Br J Dermatol* 2000; **142**: 1234–1235.
58 Eigentumliche BB. bisher nicht beschriebene Pigmentaffektion (incontinentia pigmenti). *Schweiz Med Wochenschr* 1926; **56**: 404–405.
59 Danbolt N, Closs K. Akrodermatitis enteropathica. *Acta Dermatol Venereol* 1942; **23**: 127–169.
60 Zumbusch LR. Psoriasis und pustulöses Exanthem. *Arch f Dermat* 1909; **99**: 335–346.
61 Beylot C, Bioulac P, Doutre MS. Acute generalized exanthematic pustuloses (four cases) (author's transl). *Ann Dermatol Venereol* 1980; **107**: 37–48.

62 Wallach D, Foldes C, Cottenot F. Subcorneal pustulosis, superficial acantholysis and monoclonal IgA. *Ann Dermatol Venereol* 1982; **109**: 959–963.
63 Sneddon IB, Wilkinson DS. Subcorneal pustular dermatosis. *Br J Dermatol* 1956; **68**: 385–394.
64 Resneck JS, Cram DL. Erythema annulare-like pustular psoriasis. *Arch Dermatol* 1973; **108**: 687–688.
65 Ofuji S, Ogino A, Horio T, Oseko T, Uehara M. Eosinophilic pustular folliculitis. *Acta Derm Venereol* 1970; **50**: 195–203.

Appendix 1

‡The ERASPEN network

Herve Bachelez, Saint Louis University Hospital, Paris, France; Jonathan Barker, Division of Genetics and Molecular Medicine, King's College, London, UK; A. David Burden, Institute of Infection Inflammation and Immunity, University of Glasgow, UK; Andrea Chiricozzi, University of Pisa, Nepi, Italy; Francesca Capon, Division of Genetics and Molecular Medicine, King's College, London, UK; Antonio Costanzo, Humanitas Research Hospital, Milano, Italy; Kilian Eyerich, Technische Universität München, Munich, Germany; Lars E. French, UniversitätsSpital Zürich, Zürich, Switzerland; Kamran Ghoreschi, University Department of Dermatology, Tübingen, Germany; Michel Gilliet, Centre hospitalier universitaire vaudois, Lausanne, Switzerland; Giampiero Girolomoni, Universit degli studi di Verona, Verona, Italy; Robert Gniadecki, Bispebjerg Hospital, Copenhagen University, Copenhagen, Denmark; Christopher Griffiths, The University of Manchester, Manchester, UK; Külli Kingo, Tartu University Hospital, Tartu, Estonia; Hong Yi Koh, Singapore General Hospital, Singapore, Singapore; Sulev Koeks, Tartu University Hospital, Tartu, Estonia; Dan Lipsker, Faculté de Médecine de l Université de Strasbourg, Strasbourg, France; University Medical Center, Kiel, Germany; Luigi Naldi, Centro Studi GISED, Bergamo, Italy; Ele Prans, Tartu University, Tartu, Estonia; Lluis Puig, Hospital de la Santa Creu i Sant Pau, Universitat Autonoma de Barcelona, Spain; Jörg Prinz, University Hospital LMU Munich, Munich, Germany; Kristian Reich, Dermatologikum hamburg, Hamburg, Germany; Martin Röcken, University Department of Dermatology, Tübingen, Germany; Lone Skov, Gentofte Hospital, University of Copenhagen, Copenhagen, Denmark; Catherine Smith, Division of Genetics and Molecular Medicine, King's College, London, UK; George Sorin, Carol Davila University of Medicine, Bucharest, Romania; Mona St_ahle, Karolinska University Hospital, Stockholm, Sweden; Georg Stingl, Medical University of Vienna, Vienna, Austria; Peter Van de Kerkhof, Universitair Medisch Centrum St Radboud, Nijmegen, Netherlands; Richard Warren, The University of Manchester, Manchester, UK.

Supporting information

Additional Supporting Information may be found in the online version of this article:

Table S1. H.W. Barber [29] (as read at British Association of Dermatology Meeting 1930)