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European Consensus Statement on Phenotypes of Pustular Psoriasis

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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 [1-5], 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.

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

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detected histologically. When intense inflammation is present, collections of neutrophils (Munro's subcorneal microabscesses and Kogoj's spongiform pustules [6]) 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 [7] and Königsbeck. This ultimately led to the assumption that several primary pustular conditions are part of the psoriasis spectrum, which were thus labelled 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 *IL36RN* gene, which encodes an anti-inflammatory protein known as the interleukin 36 receptor antagonist. This molecule inhibits the activation of NF- κ B by interleukins 36 α , β and γ , by binding to the IL1RL2 receptor and preventing its association with the IL1RAP co-receptor.

IL36RN defects were first identified in 5 unrelated individuals with GPP [8] and in 9 Tunisian families with autosomal recessive transmission of the disease [9]. A total of 16 *IL36RN*

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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/>) [10]. These disease alleles are found in both European and Asian populations, and account for approximately 25% of GPP [11], 20% of ACH and 2% of PPP cases [12]. The latter, however, is somewhat controversial, as some studies found no association at all with PPP [13].

Mutation status has also been found to correlate with clinical phenotype, as the age of disease onset tends to be higher [11] and systemic inflammation less frequent in those who lack *IL36RN* defects. Also, 82% of GPP patients who did not suffer from concomitant PV had mutations in *IL36RN* compared to 10% of those affected by GPP with PV [14]. The same pattern was confirmed by a European study finding *IL36RN* mutations in 46% of GPP patients without PV and 17% in GPP with PV [15]. Finally, an interesting study from China found that about 93% of patients with GPP and features of ACH had a damaging *IL36RN* mutation [16].

Although *IL36RN* 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 *IL36RN* changes have been reported, which could be explained by additional mutations at a second locus [17]. Heterozygous *IL36RN* alleles were also found in some cases [18, 19] 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 [20], 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* [21]. 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 at 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 signaling.

CARD14 [10, 22] mutations have also been found in GPP and PPP [13] as well as in PV [23]. *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-κB signaling. The two mutations (p.Glu138Ala and p.Asp176His) described in PP are gain-of-function changes which result in abnormal activation of NF-κB.

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 [24]. Two siblings with stable PV had been treated with pyrogalllic acid applications. Subsequently, they developed recurrent episodes of bright erythema and oedema, which then became studded with multiple pustules (Figure 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 pyrogalllic acid treatments, subsequently they re-occurred without obvious causes. The eruptions paralleled the activity of psoriasis. In a period of 10 years, 9 flares occurred. Subsequent descriptions of GPP featured many patients without PV. Also, trigger factors for GPP other than pyrogalllic acid were identified, namely infections, pregnancy, hypocalcaemia associated with hypoparathyroidism, and drugs. Especially streptococcal infection has been noted as a provocative factor. Some of these triggers have prompted the definition of distinct conditions [25, 26] (see below).

Acrodermatitis continua of Hallopeau [27] (ACH) was described in 1890 in a 69 year old glove maker, shortly after Radcliffe-Crocker had described similar cases in 1888 [28]. 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 (Figure 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" [29]. 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 [7] 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 (Figure 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 [30]. On the other hand, he strictly set ACH apart from GPP / PPP, as shown in Supplementary Table 1.

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 *IL36RN* were found in some cases of AGEP [18, 19, 31]. **Pustulosis acuta generalisata** (PAG) is clinically related to GPP and AGEP [25, 32, 33]. PAG produces scattered subcorneal pustules with red halo on normal skin, with acral predominance. Leukocytosis and sometimes leukocytoclastic vasculitis and fever are present. The anti-streptolysin titers are elevated. **Impetigo herpetiformis** (IH) was described in 1872 by von Hebra and is a generalized pustular eruption anytime during pregnancy. It remits post-partum. Some cases have been found to have *IL36RN* mutations [34, 35], suggesting that IH and GPP are the same disease.

The **pustular bacterid** [36] 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 [37] and occurs together with systemic symptoms including fever. The sudden onset, the invariable association with streptococcal infection and the fever sets it apart from palmoplantar pustulosis [37, 38]. A condition that is almost forgotten today is Radcliffe-Crocker's **dermatitis repens** that he described in 1888 in three patients [39]. 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 [40], concluded that this condition is identical with ACH.

There are many **other pustuloses** [41] 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 (Figure 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 5 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. [5]), UK (Rook 9th Ed. [2]), Germany (Braun-Falco 5th Ed. [1]) and USA (Fitzpatrick 8th Ed. [3, 4]).

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 pre-defined 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

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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 months 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 $>38^{\circ}\text{C}$ and leukocytosis ($\text{WBC} > 12 \times 10^9/\text{L}$) [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 sub-classified on the basis of the presence or absence of associated features (see Table 3). Thus for instance a complete clinical diagnosis might be 'generalised 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, 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 characterise 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, e.g. 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 [18] 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.

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Author contributions:

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

Figure legend:

Figure 1:

Generalized pustular psoriasis (A), *Acrodermatitis continua* 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).

Table 1: Textbook definitions of pustular psoriasis

	Braun-Falco 5th Ed. [1]	Rook 9th Ed. [2]	Fitzpatrick 8th Ed. [3, 4]	Saurat 3rd Ed. [5]	Baker / Ryan [43]
Generalized pustular psoriasis	Fever	+	+	+	+
	Generalized pustules	+	+	+	+
	Sterile pustules	+	+	+	+
	Arthritis	-	(+)	-	(+)
	Localization Trunk	+	+	+	+
	Localization intertriginous	+	+	-	?
	Subtypes	2	4	4	5
Acrodermatitis continua suppurativa	Finger > Toes	+	+	+	+
	Pustules	+	+	+	+
	Atrophy	+	+	+	+
	Nail loss	+	+	+	+
	Pain	+	?	?	-
Palmoplantar pustulosis	Palms, Feet	+	+	+	+
	Pustules	+	+	+	+
	Smoking	+	+	+	?
	Nail loss	+	+	+	+
	Pain	+	?	?	-
	Inflamed skin	-	+	+	+

Table 2: Pustular dermatoses (historical classification)

Pustular dermatoses	
Localized	
	Paediatric
	Infantile acropustulosis [44]
	Transient neonatal cephalic pustulosis [45]
	<i>Parakeratosis pustulosa</i> [46]
	Adult
	<i>Acrodermatitis continua suppurativa</i> Hallopeau [27]
	<i>Dermatitis repens</i> Radcliffe-Crocker [39].
	Palmoplantar pustulosis (PPP) [7]
	Andrew's pustular bacterid [36]
	Erosive pustular dermatosis of the scalp [47]
	<i>Dermatitis cruris pustulosa et atrophicans</i> [48]
	<i>Syndrome</i> Amicrobial intertriginous pustulosis Oberlin [49]
	<i>Syndrome</i> SAPHO-Syndrome [50]
	<i>Syndrome</i> <i>Keratoderma blenorrhagicum</i> [51]
Generalized	
	Paediatric
	<i>Erythema toxicum neonatorum</i> [52]
	Transient neonatal pustular melanosis [53]
	Acute neonatal pustulosis in Down Syndrome [54]
	Eosinophilic pustular folliculitis in infancy [55]
<i>Syndrome</i> <i>Miliaria pustulosa (rubra)</i> [56]	

<i>Syndrome</i>	Congenital Langerhans-cell histiocytosis [57]
<i>Syndrome</i>	<i>Incontinentia pigmenti</i> Bloch Sulzberger [58]
<i>Syndrome</i>	<i>Acrodermatitis enteropathica</i> [59]
Adult	Generalized pustular psoriasis von Zumbusch [60]
	<i>Impetigo herpetiformis</i> [26]
	<i>Pemphigus vegetans</i> [41]
	<i>Pustulosis acuta generalisata</i> [25]
	Acute generalized exanthematous pustulosis [61]
	Intraepidermal neutrophil IgA-Dermatosis [62]
	<i>Pustulosis subcornealis</i> Sneddon Wilkinson [63]
	<i>Erythema anulare</i> -like psoriasis [64]
	Eosinophilic pustular folliculitis [65]

Table 3: Consensus definitions for the diagnosis of pustular psoriasis**Generalised 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

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