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International Consensus Definition and Diagnostic Criteria for Generalized Pustular Psoriasis From the International Psoriasis Council

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IMPORTANCE Generalized pustular psoriasis (GPP) lacks internationally accepted definitions and diagnostic criteria, impeding timely diagnosis and treatment and hindering cross-regional clinical and epidemiological study comparisons.

OBJECTIVE To develop an international consensus definition and diagnostic criteria for GPP using the modified Delphi method.

EVIDENCE REVIEW The rarity of GPP presents a challenge in acquiring comprehensive published clinical data necessary for developing standardized definition and criteria. Instead of relying on a literature search, 43 statements that comprehensively addressed the fundamental aspects of the definitions and diagnostic criteria for GPP were formulated based on expert reviews of 64 challenging GPP cases. These statements were presented to a panel of 33 global GPP experts for voting, discussion, and refinements in 2 virtual consensus meetings. Consensus during voting was defined as at least 80% agreement; the definition and diagnostic criteria were accepted by all panelists after voting and in-depth discussion.

FINDINGS In the first and second modified Delphi round, 30 (91%) and 25 (76%) experts participated. In the initial Delphi round, consensus was achieved for 53% of the statements, leading to the approval of 23 statements that were utilized to develop the proposed definitions and diagnostic criteria for GPP. During the second Delphi round, the final definition established was, "Generalized Pustular Psoriasis is a systemic inflammatory disease characterized by cutaneous erythema and macroscopically visible sterile pustules." It can occur with or without systemic symptoms, other psoriasis types, and laboratory abnormalities. GPP may manifest as an acute form with widespread pustules or a subacute variant with an annular phenotype. The identified essential criterion was, "Macroscopically visible sterile pustules on erythematous base and not restricted to the acral region or within psoriatic plaques."

CONCLUSIONS AND RELEVANCE The achievement of international consensus on the definition and diagnostic criteria for GPP underscores the importance of collaboration, innovative methodology, and expert engagement to address rare diseases. Although further validation is needed, these criteria can serve as a reference point for clinicians, researchers, and patients, which may contribute to more accurate diagnosis and improved management of GPP.

Supplemental content

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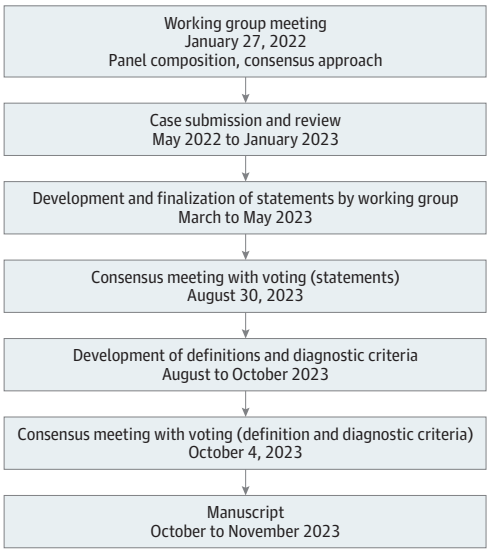
Generalized pustular psoriasis (GPP) is a rare and potentially life-threatening auto-inflammatory disease characterized by recurrent, sudden flares of widespread painful erythema studded with sterile pustules that may coalesce to form lakes of pus.[1-3] GPP is a heterogeneous disease with a wide range of clinical presentations, making accurate diagnosis and differentiation from other pustular dermatoses challenging. The severity and impact of GPP on patients' physical and mental health, as well as their overall quality of life, underscore the urgent need for prompt diagnosis and effective treatment to alleviate patients' suffering and mitigate potential life-threatening complications such as sepsis or kidney, liver, respiratory, and cardiovascular failure.[1,2,4] Reported mortality rates ranging from 4% to 24% emphasize the gravity of the condition.[2,4,5] A unified and precise set of diagnostic criteria is paramount to facilitate timely and accurate identification of GPP cases, enabling appropriate treatment and thereby reducing the risk of complications and improving patient outcomes. This becomes particularly pertinent with the recent approval of a highly efficacious targeted treatment for GPP.

In addition to the clinical imperative, obtaining reliable epidemiological data on GPP is crucial for assessing disease burden and allocating adequate resources for its management. However, quantifying the burden of GPP remains a formidable challenge, primarily due to the rarity of the disease and the absence of international consensus regarding its definition and diagnosis. Reported prevalence rates differ widely, ranging from 1.76 to 198 cases per million people.[6-12] This wide variation can be attributed to differences in study populations, designs, and settings as well as variations in data sources, case definitions, and diagnostic criteria. For example, the lower prevalence of GPP in Japan compared with Sweden (20-30 vs 90 cases per million population) is likely due to Japan's recommended practice of coding only biopsy-confirmed GPP with systemic manifestations for administrative claims.[9,11,13] In contrast, the European consensus on pustular psoriasis defines GPP as the presence of macroscopically visible sterile pustules on nonacral skin, with or without systemic inflammation and with or without associated psoriasis.[14] By this definition, neither systemic manifestation nor histologic confirmation is necessary for a diagnosis of GPP. Hence, establishing an internationally accepted standardized definition of GPP based on agreed-upon diagnostic criteria is essential for meaningful research. The aim of this study was to develop an international consensus definition and diagnostic criteria for GPP by using the modified Delphi method.

Methods

The International Psoriasis Council (IPC) established a Pustular Psoriasis Working Group to address the challenges GPP poses. Members of the working group were carefully chosen based on their experience in managing GPP, their involvement in GPP studies, and their publications on GPP (IPC Pustular Psoriasis Working group members are listed in Supplement 2). To ensure global representation, the 8 working group members are board members (S.E.C., J.E.G., C.d.l.C., A.M., and H.B.) or councilors (J.B., R.R., and F.C.) from diverse regions: Malaysia, the United States, Chile, the United Kingdom, Brazil, Japan, and France. This working group was tasked with developing an international definition and diagnostic criteria for GPP using the modified Delphi method.

Figure. Delphi Process to Develop an International Definition and Diagnostic Criteria for Generalized Pustular Psoriasis



The Delphi method, developed in the 1950s by the RAND Corporation, is a structured, iterative technique for forecasting or decision-making.[15] It gathers and distills knowledge and opinions from a group of experts on a specific subject, eliminating the need for face-to-face meetings. The modified Delphi, a variation, uses a more structured and facilitated technique, often involving interactive face-to-face or virtual group discussions. This enhances communication and interaction among experts, fostering a controlled environment for informed, collaborative decision-making.

The Delphi process commenced by gathering a set of complex GPP cases, which served as the foundation for crafting statements, refining definitions, and establishing diagnostic criteria for GPP. This iterative process involved 2 rounds of virtual consensus meetings with voting to solidify the outcomes (**Figure**). This study was conducted in compliance with the Standards for Quality Improvement Reporting Excellence (SQUIRE) reporting guideline.[16] Institutional review board review was not required, as this study did not meet the institutional definition of human participant research, per Monash University.

Formulation of Statements

Statements for voting and consensus were formulated based on expert reviews of multiple GPP cases with challenging diagnoses, submitted online by international colleagues between May and July 2022. IPC collaborated with Question Mark Media, LLC, to create a specialized online platform for case submissions aligned with the working group guidelines. The platform included detailed fields for gathering information and relevant documentation across 5 categories (eFigure in Supplement 1). No information that could lead to patient identification was collected to ensure patients' privacy and maintain strict confidentiality. A call for case submissions of challenging GPP cases was circulated via email to IPC councilors, board

members, fellows, and past participants of IPC psoriasis masterclasses, resulting in the receipt of 69 cases from 24 different countries (eTable 1 in Supplement 1).

From August 2022 to January 2023, 16 experts provided their opinion on the (1) characteristic features of GPP, (2) features that exclude GPP as the diagnosis, (3) features that could be part of but are not characteristic of GPP, and (4) their favored diagnosis of each case, including reasoning. After reviewing all cases, reviewers were asked (1) which clinical features are necessary for a diagnosis of GPP; (2) which clinical features may be present but are not necessary for a diagnosis of GPP; (3) which clinical features would rule out a diagnosis of GPP; (4) is biopsy mandatory to diagnose GPP; (5) if a biopsy is not mandatory, when should a biopsy be recommended; (6) is a genetic study necessary to diagnose GPP; (7) what are the clinical and histologic features that should prompt a search for differential diagnoses; and (8) in your opinion, what are the differential diagnoses that should be considered in a patient with GPP? From the wealth of insights gained through expert reviews and collective analysis of these cases, the working group meticulously curated a comprehensive set of 43 statements that were then presented for voting and dissection in a 2-round Delphi study, ensuring a thorough and iterative approach to consensus-building.

Panel Selection

Thirty-three GPP experts, identified by the IPC GPP Working Group members based on their clinical expertise on GPP and standing in different regions of the world, were invited via email to participate in 2 virtual consensus meetings. Twenty-five experts from various regions of the world agreed and participated (eTable 2 in Supplement 1). Together with 8 working group members, a panel of 33 GPP experts contributed actively to this consensus study.

Virtual Consensus Meetings

The aim of these meetings was to harness the collective expertise and insights of experts to refine the diagnostic statements and achieve consensus, with the end point being the definition and diagnostic criteria accepted by all panelists after voting and discussion. In the first virtual meeting, the experts used an online voting platform to vote on the 43 diagnostic statements. Consensus was defined as at least 80% agreement. The results of this voting were subsequently presented to the experts. These results served as the basis for a robust panel discussion during which experts provided comments and engaged in discussions to review the outcomes and refined some statements collaboratively. Refined statements that were not unanimously accepted were subjected to another round of voting. Building on the insights and feedback garnered from the first round, the working group developed 2 definitions and a list of diagnostic criteria for GPP. A summary of the outcomes of last meeting and the proposed definitions and list of diagnostic criteria were emailed to the panel to read in advance, with a request for submission of each expert's own definition of GPP based on the outcome of the first Delphi round before the second virtual meeting. One additional definition was submitted for consideration. During the second virtual meeting, the expert panel reviewed, voted on, and further refined the 3 proposed definitions and diagnostic criteria. One week later, the working group reconvened to finalize and recommend the definition and diagnostic criteria for GPP.

Results

Formulation of Statements

Among the 69 challenging cases received, 3 were erythroderma with pustulosis, while 2 cases each were identified as annular pustular psoriasis (APP), impetigo herpetiformis (IH), and subcorneal pustular dermatosis (SPD). Additionally, 1 case each was acute generalized exanthematous pustulosis (AGEP), pemphigus foliaceus, and IgA pemphigus. It is worth noting that of the 64 GPP cases (excluding 2 SPD, 2 pemphigus, and 1 AGEP), 50 (78%) involved patients with darker skin (eTable 1 in Supplement 1). Twenty patients (31%) had associated plaque psoriasis, and 9 (14%) had arthritis. Based on expert reviews and collective analysis of these cases, 43 statements that encompassed clinical, systemic, histological, and laboratory features crucial for the accurate diagnosis of GPP were developed (**Table 1**)

Expert Panel

Our panel consisted of 33 GPP experts representing diverse regions across the globe; 12 (36%) were based in Asia, 11 (33%) in Europe, 4 (12%) in South America, 3 (9%) in North America, and 3 (9%) in Africa (**Table 2**). More than half the panelists (24 [72%]) worked in an academic hospital setting; 2 (6%) in a public hospital; 2 (6%) in private setting; 1 (3%) in both academic and public hospitals, and 4 (12%) in both public and private hospitals. The majority (24 [75%]) had more than 20 years of clinical experience and had managed a mean (SD) of 22 (20) patients with GPP over the last 5 years. There were more male (24 [73%]) than female (9 [27%]) panelists, and all were older than 40 years. The first consensus meeting was attended by 30 experts, while 25 participated in the second meeting.

Results of Consensus Meetings

In the initial Delphi round, consensus was achieved for 51% of the statements, with 22 of 43 statements receiving at least 80% of votes, as detailed in Table 1. Among the 3 key cutaneous manifestations of GPP, namely pustules, erythema, and scaling, macroscopically visible sterile pustules and scaling reached a consensus. However, after extensive discussions, the panel agreed that desquamation, scaling, and crusting are indicative of the resolution of pustules but are not mandatory for diagnosing GPP. Nevertheless, erythema—although challenging to discern in individuals with darker skin—was deemed an important diagnostic criterion.

Another statement, "Annular pustular psoriasis should be considered a form of GPP," did not achieve consensus during the initial vote. After thorough deliberation, consensus remained elusive, and this statement was subjected to a second round of voting before being accepted by the panel. In the end, 23 statements were accepted and utilized in shaping the proposed definitions and diagnostic criteria for GPP, as outlined in **Table 3**.

During the second meeting, panel members were asked to choose their preferred definition from among the 3 proposed options. Definition 2, which received the highest number of votes, was revised and unanimously accepted. The subclassifiers within this definition did not require a separate vote and were accepted or rejected with minimal adjustments (Table 3) following in-depth discussions. After extensive deliberation, the proposed essential

Table 1. Results of First Consensus Meeting on the Definition and Diagnostic Criteria for Generalized Pustular Psoriasis (GPP)

No.	Statements	No./total No. (%) Vote 1	Vote 2
Accepted statements			
NA	Clinical features	NA	NA
1	Macroscopically visible sterile pustules are mandatory for the diagnosis of GPP.	23/27 (85)	NA
2	Erythema is mandatory for the diagnosis of GPP.	10/28 (36)[a]	NA
3	Hypopyon is not a clinical feature of GPP.	18/21 (86)	NA
4	Sneddon Wilkinson/subcorneal pustular dermatosis should not be classified as GPP.	23/24 (96)	NA
5	Pustules exclusively within psoriatic plaques should not be diagnosed as GPP.	21/25 (84)	NA
6	Annular pustular psoriasis should be regarded as a form of GPP.	17/23 (64)	21/23 (91)
7	Pustular psoriasis of pregnancy (IH) is not distinct from pregnancy induced GPP.	19/23 (83)	NA
8	Pustular lesions on acral regions may be present during flares and should not rule out a diagnosis of GPP.	22/22 (100)	NA
9	Widespread discrete pinpoint pustules may be seen initially in a GPP flare but over time at least some coalescence evolved.	19/20 (95)	NA
10	A history of flares supports the diagnosis of GPP but GPP may be diagnosed on first presentation.	21/21 (100)	NA
11	Mucosal involvement is not mandatory but supports the diagnosis of GPP.	15/18 (83)	NA
12	AGEP should be actively ruled out with thorough history and histology.	20/21 (95)	NA
13	Diagnosis of AGEP is based on numerous discrete pustules, history of exposure to common culprit drugs, fast onset and fast resolution, and histology.	21/22 (95)	NA
14	A personal or family history of psoriasis or GPP support diagnosis of GPP.	19/22 (86)	NA
15	Fever is not mandatory but supports a diagnosis of GPP.	18/19 (95)	NA
16	Fatigue is not mandatory but supports a diagnosis of GPP.	17/18 (94)	NA
17	Pain is not mandatory but supports a diagnosis of GPP.	19/19 (100)	NA
NA	Laboratory and histology	NA	NA
18	Skin biopsy is nonmandatory but useful to confirm the diagnosis of GPP and to rule out differential diagnoses.	20/20 (100)	NA
19	When eosinophils are present, particularly if within micro-abscesses, we should think about drug-induced pustulosis (AGEP).	18/20 (90)	NA
20	The presence of peripheral blood neutrophilia is not mandatory but supports a diagnosis of GPP.	15/17 (88)	NA
21	Elevated CRP serum level during a flare is not mandatory but supports a diagnosis of GPP.	17/18 (94)	NA
22	Abnormal laboratory tests such as hypocalcemia, hypoproteinemia/hypoalbuminemia, abnormal liver or renal functions are not mandatory for diagnosing GPP but need to be assessed regularly to detect potential complications.	17/17 (100)	NA
23	Genetic testing is not mandatory for diagnosing GPP.	17/17 (100)	NA
Rejected statements			
NA	Clinical features	NA	NA
24	Scaling is mandatory for the diagnosis of GPP.	24/27 (88)[b]	NA
25	Macroscopically visible sterile pustules on erythematous base are mandatory for the diagnosis of GPP.	17/27 (63)	NA
26	Macroscopically visible sterile pustules on erythematous base and with scaling are mandatory for the diagnosis of GPP.	6/23 (26)	NA
27	Widespread erythema with sterile pustules and/or lakes of pus, and with or without scaling are mandatory for the diagnosis of GPP.	19/25 (76)	NA
28	Widespread erythema with sterile pustules and/or lakes of pus and scaling are mandatory for the diagnosis of GPP.	10/27 (37)	NA
29	Lakes of pus are mandatory for the diagnosis of GPP.	6/24 (25)	NA
30	Erythrodermic psoriasis with pustulosis should not be classified as GPP.	14/23 (61)	NA
31	A minimum extent of area involved with pustules is mandatory for the diagnosis of GPP. (If Y, how much)	16/23 (70)	NA
32	Pustular lesions on acral regions rule out the diagnosis of GPP.	7/26 (27)	NA
33	Persistent, widespread, discrete pin-point pustules may be seen in GPP.	15/21 (71)	NA
34	GPP should only be diagnosed if it has recurred at least once.	7/21 (33)	NA
35	GPP may be diagnosed if pustules persist >3 mo.	11/21 (52)	NA
36	GPP may be diagnosed if pustules persist >1 mo.	11/20 (55)	NA
37	Fever is mandatory for diagnosing GPP.	5/23 (22)	NA
38	Fatigue is mandatory for diagnosing GPP.	2/19 (11)	NA
39	Pain is mandatory for diagnosing GPP.	2/18 (11)	NA

(continued)

Table 1. Results of First Consensus Meeting on the Definition and Diagnostic Criteria for Generalized Pustular Psoriasis (GPP) (continued)

No.	Statements	No./total No. (%) Vote 1	Vote 2
NA	Laboratory and histology	NA	NA
40	Skin biopsy is mandatory for diagnosing GPP.	6/20 (30)	NA
41	Subcorneal Kogoj spongiform pustules are mandatory for the diagnosis of GPP.	11/19 (58)	NA
42	Indirect immunofluorescence is mandatory to rule out the diagnosis of pemphigus.	6/19 (32)	NA
43	The presence of peripheral blood neutrophilia is mandatory for diagnosing GPP.	4/19 (21)	NA

Abbreviations: AGEP, acute generalized exanthematous pustulosis; CRP, C-reactive protein; IH, impetigo herpetiformis; NA, not applicable.

[a] Accepted after discussion; erythema is an essential feature which reflects the inflammatory nature of GPP although it may be difficult to discern on darker skin.

[b] Rejected after discussion; scaling is evolution of pustules and not mandatory for diagnosing GPP.

Table 2. Demographic Characteristics and Participation of Panelists

Characteristic	Panelists, No. (%) All (N = 33)	Consensus meeting 1 (n = 30)	Consensus meeting 2 (n = 25)
Age, median (IQR), y	59.5 (50.5-65.5)	61.0 (50.5-66.0)	59.0 (50.0-65.5)
Gender			
Male	24 (72)	21 (70)	18 (72)
Female	9 (88)	9 (30)	7 (28)
Geographic region			
North America	3 (9)	3 (10)	2 (8)
Europe	11 (33)	10 (33)	7 (28)
Asia	12 (36)	10 (33)	11 (44)
North Africa	3 (9)	3 (10)	1 (4)
South America	4 (12)	4 (13)	4 (16)
Primary specialty			
Dermatology	32 (97)	29 (97)	24 (96)
Rheumatology and dermatology	1 (3)	1 (3)	1 (4)
Practice setting			
Academic or university	24 (72)	21 (70)	17 (68)
Public hospital	2 (6)	2 (7)	2 (8)
Private practice	2 (6)	2 (7)	2 (8)
Academic and public hospitals	1 (3)	1 (3)	1 (4)
Public and private hospitals	4 (12)	4 (13)	3 (12)
Years in specialty practice, median (IQR)	32.0 (19.5-38.5)	32.0 (18.5-39.0)	32.0 (19.5-38.5)
No. of cases seen in last 5 y			
Median (IQR)	15.0 (9.5-30.0)	15.0 (8.5-40.0)	15.0 (8.5-25.0)
Mean (SD)	22.44 (20.10)	21.66 (20.48)	24.24 (22.13)

diagnostic criterion was revised and unanimously approved by the group. The **Box** shows the final recommended definition and diagnostic criteria for GPP.

Discussion

In this international consensus, a review of cases submitted by expert dermatologists was used as the basis for a Delphi consensus to establish definitions and diagnostic criteria for GPP. Reviewers highlighted the remarkable diversity in the clinical presentations of GPP and the inherent challenges in distinguishing it from common mimics, such as AGEP, SPD, and pustular forms of pemphigus. The submitted cases provided invaluable insights and made a compelling argument for the pivotal role of histopathology, complemented by direct immunofluorescence, in the accurate diagnosis of GPP. Although GPP may start with discrete pustules, these often evolve over time to form lakes of pus. The presence of numerous persistent discrete pustules without coalescence and hypopyon pustules should prompt dermatologists to consider performing a skin biopsy to confirm GPP and rule out potential mimicking conditions.

One notable challenge we encountered was the question of erythema, particularly in individuals with darker skin. While it initially did not achieve consensus due to the difficulty in appreciating erythema in individuals with darker skin tones, the panel eventually agreed that erythema, although potentially challenging to discern in individuals with darker skin, is an essential feature of GPP, reflecting the inflammatory nature of GPP, and should be included in the condition's definition aside from pustules that reflect the neutrophilic nature of the GPP. Moreover, it was established that features such as desquamation, scaling, and crusting, which represent the evolution of pustules, are not mandatory for diagnosing GPP. The extent of body surface area (BSA) affected and the duration of pustulation were also deemed nonessential for diagnosis because GPP is a life-threatening disease. Therefore, diagnosis should not

Table 3. Results of Second Consensus Meeting on the Definition and Diagnostic Criteria for Generalized Pustular Psoriasis (GPP)

No.	Definition or criteria	No./total No. (%)		
		Vote 1	Vote 2	Final
Definition of GPP				
1	GPP is a systemic inflammatory disease characterized by widespread cutaneous erythema studded/adorned with macroscopically visible sterile pustules with or without lakes of pus.	6/24 (25)	NA	Rejected
2	GPP is a systemic inflammatory disease characterized by macroscopically visible sterile pustules with or without lakes of pus on erythematous skin.	12/24 (50)	NA	Rejected
2[a]	GPP is a systemic inflammatory disease characterized by cutaneous erythema and macroscopically visible sterile pustules.	NA	21/23 (91)	Accepted
3	GPP is pustular psoriasis with widespread macroscopically visible sterile pustules and erythema, not localized to palmoplantar areas or preexisting psoriatic plaques. Symptoms and signs of systemic inflammation may be present.	6/24 (25)	NA	Rejected
Definitions for GPP: subclassifiers				
1	It may manifest with or without systemic symptoms and signs.	NA	NA	Accepted
2	Laboratory abnormalities may or may not be present.	NA	NA	Accepted
3	Recognizing erythema, especially in individuals with skin of color, can pose a diagnostic challenge.	NA	NA	Rejected[b]
4	Pustular lesions on acral regions may be present during acute flares and should not rule out a diagnosis of GPP.	NA	NA	Rejected[b]
5	Pustules solely on acral skin rule out GPP.	NA	NA	Rejected[b]
6	Pustular lesions on acral regions may precede and/or persist after acute flare. However, persistent acral pustular lesions at least 3 mo before or after acute GPP flares satisfied the ERASPEN criteria for the diagnosis of localized variants of pustular psoriasis.	NA	NA	Rejected[b]
6[a]	Pustular lesions on acral regions may precede and/or persist after acute flare.	NA	NA	Rejected[b]
7	The resolution of pustules involves desquamation, scaling, or crusts, which may or may not be evident.	NA	NA	Rejected[b]
8	GPP flares may manifest initially with discrete pustules, but they tend to coalesce to some extent over time.	NA	NA	Rejected[b]
9	A history of recurring flares supports the diagnosis of GPP but GPP may be diagnosed at the initial presentation.	NA	NA	Rejected[b]
10	GPP can present as acute form with widespread pustular eruption or subacute variant with annular phenotype, with tendency of transforming from one form to another.	NA	NA	Accepted
11[c]	It may or may not be associated with other type of psoriasis	NA	NA	Accepted
Essential diagnostic criteria				
1	Macroscopically visible sterile pustules with or without erythematous base.	NA	NA	Rejected
1[a]	Macroscopically visible sterile pustules on erythematous base and not restricted to the acral region or within psoriatic plaques.	NA	NA	Accepted
Supporting diagnostic criteria				
1	Lakes of pus	19/21 (90)	NA	Accepted
2	Pustules on erythematous skin	20/21 (95)	NA	Accepted
3	Desquamation, scaling, or crusts	16/21 (76)	NA	Rejected
4	Geographic tongue	10/21 (48)	NA	Rejected
5	Fissured tongue	4/21 (19)	NA	Rejected
6	Painful skin	17/21 (81)	NA	Accepted
7	Fever	20/21 (95)	NA	Accepted
8	Fatigue	14/21 (67)	NA	Accepted[d]
9	History of recurring flares	21/21 (100)	NA	Accepted
10	Positive personal or family history of psoriasis	17/21 (81)	NA	Accepted

(continued)

Table 3. Results of Second Consensus Meeting on the Definition and Diagnostic Criteria for Generalized Pustular Psoriasis (GPP) (continued)

No.	Definition or criteria	No./total No. (%)		
		Vote 1	Vote 2	Final
11	Elevated CRP	20/21 (95)	NA	Accepted
12	Leukocytosis	19/21 (90)	NA	Accepted
13	Neutrophilia	20/21 (95)	NA	Accepted
14	Abnormal laboratory tests such as hypocalcemia, hypoproteinemia, hypoalbuminemia, abnormal liver or renal functions	19/21 (90)	NA	Accepted
15	Biopsy confirmation with the presence of spongiform pustules of Kogoj	20/21 (95)	NA	Accepted
16	Any positive genetic finding (namely *IL36RN* mutation, *MPO*, *AP1S3*, *SERPINA*, *CARD14*)	16/21 (76)	NA	Accepted

Abbreviations: CRP, C-reactive protein; ERASPEN, European Rare and Severe Psoriasis Expert Network; NA, not applicable.

[a] Revised statement after discussion.

[b] Describing clinical presentations of GPP and rejected as subclassifiers.

[c] New statement added after discussion.

[d] Accepted after discussion.

Box. International Definition and Diagnostic Criteria for Generalized Pustular Psoriasis (GPP)

Definition

GPP is a systemic inflammatory disease characterized by cutaneous erythema and macroscopically visible sterile pustules.

Subclassifiers

1. It may manifest with or without systemic symptoms and signs.
2. It may or may not be associated with other types of psoriasis.
3. GPP can present as an acute form with widespread pustular eruption or a subacute variant with annular phenotype.
4. Laboratory abnormalities may or may not be present.

Diagnostic Criteria

Essential

Macroscopically visible sterile pustules on erythematous base and not restricted to the acral region or within psoriatic plaques

Supporting

- Lakes of pus
- Painful skin
- Fatigue
- Fever
- History of recurring flares
- Positive personal or family history of psoriasis
- Elevated CRP
- Leukocytosis
- Neutrophilia
- Abnormal laboratory tests such as hypocalcemia, hypoproteinemia, hypoalbuminemia, abnormal liver or renal functions
- Biopsy confirmation with the presence of spongiform pustules of Kogoj
- Any positive genetic finding (namely *IL36RN* mutation, *MPO*, *AP1S3*, *SERPINA*, *CARD14*)

Abbreviation: CRP, C-reactive protein.

be delayed by any predefined duration of pustulation or BSA.[2,3,17] Distribution on different anatomical sites and multiple erythematous patches with pustules were considered more important clues to diagnosing GPP. There was a 100% consensus that pustular lesions on acral regions may be present during flares and should not rule out a diagnosis of GPP. Acral pustular lesions may precede or persist after GPP flares, but persistent pustular lesions confined to the palms and soles should not be diagnosed as GPP.

The panel also came to a consensus that while systemic symptoms such as fever, fatigue, and laboratory abnormalities, including leucocytosis with neutrophilia and elevated C-reactive protein, are not mandatory for diagnosis, they do support the diagnosis of GPP. Skin biopsy was deemed nonmandatory but is highly recommended for confirming the diagnosis and ruling out differential diagnoses. Additionally, abnormal laboratory test results, such as hypocalcemia, hypoproteinemia and hypoalbuminemia, and abnormal liver or kidney functions, were not considered mandatory for diagnosing GPP but were advised to be assessed regularly to detect potential complications. Genetic testing for specific alterations, namely *IL36RN, MPO, AP1S3, SERPINA3* and *CARD14*, was not obligatory. However, *IL36RN* screening is recommended if available. *IL36RN* alterations have been associated with a more severe phenotype characterized by early disease onset,[18-20] more systemic inflammation,[18-20] and increased frequency of flares.[20] Patients with *IL36RN* alterations may need more vigilant monitoring and be prioritized for targeted therapy although variation in disease severity has been described in siblings harboring identical *IL36RN* alterations.[21]

APP was accepted as a variant of GPP due to its similar presentation and impact on quality of life, except for its annular morphology and lack of systemic manifestations.[2,22,23] Moreover, APP may evolve into GPP, and annular pustular lesions are common postflare manifestations of GPP. On the other hand, psoriasis with pustulosis (psoriasis *cum pustulatione*), characterized by pustules restricted to within psoriatic plaques, was excluded as a variant of GPP. As for erythrodermic psoriasis with pustulosis, the panel conceded that it is clinically impossible to distinguish it from erythrodermic GPP, highlighting the need for additional clinical data and genetic or molecular biomarkers to differentiate these conditions. The panel reached a consensus that IH is not a distinct entity but rather a manifestation of GPP induced by pregnancy. This conclusion was drawn from the panel's collective experience and limited published data, which showed that patients with IH also had GPP induced by other triggers.[2,24,25] The panel called for further studies on IH to enhance our understanding of this condition.

Additionally, the panel emphasized the importance of actively ruling out important differential diagnoses of GPP, including AGEP, SPD, and pemphigus, in patients with sterile pustular eruptions. AGEP, while presenting a similar sudden onset of pustular eruptions accompanied by fever and leucocytosis as GPP, may be distinguished by characteristics such as numerous persistent discrete pustules, a history of recent exposure to common culprit drugs, and fast resolution upon discontinuation of the triggering

medication.[26-28] There was high agreement (90%) that the presence of eosinophils, especially within micro-abscesses, supported a diagnosis of drug-induced pustulosis (AGEP).[27,28] Nevertheless, it was noted that *IL36RN* alterations may not serve as a reliable distinguishing factor, as they have been identified in cases of AGEP.[28,29] It was also agreed that hypopyon pustules, characterized by clear fluid in the upper half and purulent yellow fluid in the lower half, support the diagnosis of SPD, a rare, benign, relapsing pustular dermatosis without systemic symptoms.[30-32] While there was unanimous agreement (100%) that a biopsy should be performed to rule out differential diagnoses of GPP, there was no consensus (32%) on the use of direct immunofluorescence to identify or rule out pemphigus.

The final definition, "Generalized pustular psoriasis (GPP) is a systemic inflammatory disease characterized by cutaneous erythema and macroscopically visible sterile pustules," with its accompanying 4 subclassifiers (Box), reflects the culmination of collective expertise and refinement. GPP may manifest with or without (1) systemic symptoms and signs, (2) other types of psoriasis, and (3) laboratory abnormalities. GPP can present as (4) an acute form with widespread pustular eruption or a subacute variant with annular phenotype.

A notable aspect of the refinement process was the revision of the proposed essential diagnostic criterion, which evolved from "Macroscopically visible sterile pustules with or without erythematous base" to "Macroscopically visible sterile pustules on erythematous base and not restricted to the acral region or within psoriatic plaques." This modification underscores the importance of distinguishing GPP from non–life-threatening phenotypes of psoriasis, namely acrodermatitis continua of Hallopeau and psoriasis with pustulosis.

The consensus reached, with high agreement (≥90%), on various supporting criteria, including lakes of pus, fever, elevated C-reactive protein, leucocytosis, and neutrophilia, highlights the multifaceted nature of GPP diagnosis and the importance of considering both clinical and laboratory parameters. Notably, the incorporation of fatigue as a supporting criterion, despite initial divergence in consensus (94% and 67% in first and second consensus meeting rounds respectively), underscores its clinical relevance and the iterative nature of the consensus-building process. There was limited agreement on other features, such as "desquamation, scaling and crusts," geographic tongue, and fissured tongue. Of note, geographic tongue had recently been shown to be more common in patients carrying the *IL36RN* allele c.115 + 6C>T.[20,33-35] More evidence is needed to determine its prevalence in patients with GPP and its potential role as a marker of *IL36RN* alterations that are associated with more severe disease. Based on the results from the 2 consensus meetings, the panel successfully developed an international definition and the associated diagnostic criteria for GPP (Box).

Our consensus aligns with the European consensus on pustular psoriasis by recognizing acute and subacute annular GPP as distinct phenotypes. Both acknowledge GPP's potential manifestation with or without systemic features and other psoriasis types while excluding pustules confined to within psoriatic plaques as a variant of GPP. Nevertheless, differences exist, as the European criteria emphasize sterile pustules on nonacral skin and stipulate relapse or persistence over 3 months for diagnosis. IPC consensus accommodates acral lesions during flares but cautions against persistent acral pustules as GPP. Crucially, GPP, being potentially life-threatening, requires prompt diagnosis for timely intervention. Our consensus rejects imposing timelines on clinical features and allows diagnosis at the first flare. While the Japanese criteria require recurrent, biopsy-confirmed, systemic-featured, widespread pustules on erythematous skin for a definitive diagnosis, our consensus does not require systemic features and histologic confirmation for diagnosing GPP. Timeliness and accuracy in diagnosis are paramount for the effective treatment of this severe disease.

Strength and Limitations

This study possesses both strengths and limitations. Its primary strength lies in the unique approach of formulating statements based on expert reviews of complex GPP cases submitted by international colleagues, effectively bridging the gap in published clinical data for this rare disease. By synthesizing the collective expertise of GPP specialists and incorporating diverse clinical presentations observed in submitted cases, this collaborative initiative provided a more robust and comprehensive set of diagnostic criteria for the identification of GPP cases across global health care settings. The involvement of a panel of internationally recognized GPP experts with extensive experience in the field ensured that the diagnostic criteria were developed based on a wealth of clinical knowledge and expertise.

However, this study has limitations, including the relatively small number of global experts due to the rarity of GPP. Moreover, selection bias and voluntary participation may introduce unintentional biases. A validation study is needed to assess the proposed diagnostic standard's impact on patient outcomes and compare its accuracy and validity against the existing Japanese and European standards.

Conclusions

This study successfully achieved an international consensus on the definition and diagnostic criteria for GPP through the innovative use of the modified Delphi method with formal expert collaboration. The resulting definition and diagnostic criteria for GPP are intended to provide a clear and standardized framework for diagnosis, ultimately leading to improved patient care, enhanced epidemiological research, and a better understanding of the disease's impact on affected individuals.

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