Generalized pustular psoriasis: A consensus statement from the National Psoriasis Foundation

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Generalized pustular psoriasis (GPP) is a serious, immune-mediated inflammatory skin disease with significant morbidity and mortality. Estimates of GPP prevalence vary between 1.8 and 124 per million people.[1] GPP pathogenesis primarily involves abnormal activation of the interleukin (IL)-36 pathway of the innate immune system, with secondary contributions from the adaptive immune system. Through a validated Delphi method,[2,3] 32 physicians specializing in psoriatic diseases from the Medical Board of the National Psoriasis Foundation formulated the following consensus statements to guide clinicians, payors, and patients in GPP management.

Statement 1: GPP is a life-threatening disease that needs to be treated as quickly as possible. (High consensus)

Acute flares of GPP can be life-threatening, with one-half of patients requiring hospitalization and a mortality rate of approximately 3 deaths per 100 patient years.[4] These flares can occur spontaneously or be associated with infection, pregnancy, or discontinuation of systemic corticosteroids. The most common causes of mortality include sepsis and multiorgan failure. Patients receiving biologics have lower in-hospital mortality than those receiving oral agents or corticosteroids alone.[5]

Abbreviation used:

GPP: generalized pustular psoriasis

Statement 2: The diagnosis of GPP is made based on the assessment of clinical features. (High consensus)

GPP presents as recurrent episodes of disseminated, sterile, monomorphic pustules on a background of widespread erythema. Many patients are systemically ill, presenting with high-grade fever, pain, and arthralgias. Laboratory workup often reveals leukocytosis, elevated C-reactive protein levels, hypoalbuminemia, and microcytic anemia. Marked liver function enzyme abnormalities have been linked to neutrophilic cholangitis. Approximately 46% of patients with GPP have plaque psoriasis.[1] Although GPP can occur at any

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Table I. Differential diagnoses of generalized pustular psoriasis

Conditions	Distinguishing features from GPP
Acute generalized exanthematous pustulosis (AGEP)	-- Recent history of antimicrobials (tetracycline, sulfonamides, and terbinafine), calcium channel blockers, hydroxychloroquine, carbamazepine, or paracetamol. -- More abrupt onset, shorter duration, rarely recur; typically resolves within 2 wks of discontinuation of the offending drug. -- Histology shares many features with pustular psoriasis and can be indistinguishable. Features, such as eosinophilic spongiosis, vacuolar interface dermatitis, papillary dermal edema, and dermal eosinophilia, when present, may be more likely to be seen in AGEP than GPP. Acanthosis is less commonly seen than in GPP.
IgA Pemphigus	-- No systemic symptoms, such as fever and malaise. -- Typically has more subacute onset than AGEP or GPP. -- Flexural areas, including the axilla and groin are more preferentially involved than total body involvement. -- Flaccid pustules on an erythematous base that rupture to form annular crusts over the plaque. -- Intercellular IgA deposits are seen in the epidermis on direct immunofluorescence in both subtypes ([1] subcorneal pustular dermatosis-type IgA pemphigus and [2] intraepidermal neutrophilic type IgA pemphigus). -- Subcorneal pustular dermatosis-type IgA pemphigus is also responsive to dapsone, whereas GPP is not.
Subcorneal pustular dermatosis (SPD) or Sneddon-Wilkinson disease	-- Asymptomatic eruption of grouped pustules that evolve into half-pustular, half-clear fluid blisters and coalesce to form annular or serpiginous patterns (negative immunofluorescence in contrast to IgA pemphigus). -- Typically has more subacute onset and evolution than AGEP and GPP. -- Cannot be reliably distinguished histologically from GPP; lack spongiform pustules and epidermal changes of psoriasis. -- Responds to dapsone.

GPP, Generalized pustular psoriasis.

age, peak onset is between 40 and 59 years, and it may be associated with IL36RN mutations. Comorbidities include arthralgia/arthritis, diabetes, and metabolic syndrome.

Statement 3: Skin biopsy is not required for the diagnosis of GPP because histologic features may be nonspecific and it may delay treatment of this life-threatening condition. (Moderate consensus)

Histology in GPP shows subcorneal and intraepidermal pustules, which often does not provide additional information beyond what can be seen clinically. The histology is often identical to entities in the clinical differential diagnoses, including acute generalized exanthematous pustulosis.[6] The distinction between GPP and acute generalized exanthematous pustulosis is made, not histologically, but by evaluating clinical history, psoriasis history, and medication history (Table I). Therefore, patients with GPP require urgent treatments, and such treatments should not be delayed while waiting for histology.

Statement 4: Although GPP phenotype classification criteria from the European Rare and Severe Psoriasis Expert Network and Japanese Dermatological Association are informative for clinical trials, these criteria should not be used to deny or delay treatment in clinical practice. (High consensus)

The European Rare and Severe Psoriasis Expert Network criteria specify presentation of lesions on nonacral surfaces and discuss lesions lasting at least 3 months. Our US experience is that GPP can also occur on acral surfaces and may last shorter than 3 months. The Japanese criteria require fulfillment of multiple criteria, including having Kogoj's spongioform pustules on histology. Because we deem histologic confirmation not necessary for diagnosis of GPP, these criteria should not be used to deny or delay treatment. For example, in patients presenting with acute GPP, one should not wait to fulfill certain arbitrary definitions of GPP before initiating treatment.

Statement 5: We strongly advocate for timely access to US Food and Drug Administration-approved therapies for GPP because delays can increase the risk of mortality in patients with this rapidly progressing disease. (High consensus)

Therapeutic developments have been focused on modulating the aberrantly increased interleukin 36

signaling in GPP. Spesolimab is the first US Food and Drug Administration-approved treatment that is highly effective in the treatment of GPP flares in adults.[7] Timely access to approved therapies is critical to reducing morbidity and mortality in patients presenting with GPP.[8]

Conflicts of interest

Dr Armstrong has served as a research investigator, scientific advisor, and/or speaker to AbbVie, Almirall, Arcutis, ASLAN, Beiersdorf, BI, BMS, EPI, Incyte, Leo, UCB, Janssen, Lilly, Nimbus, Novartis, Ortho Dermatologics, Sun, Dermavant Sciences, Dermira, Sanofi, Regeneron, Pfizer, and Modmed. Dr Elewski has served as a research investigator and/or consultant for Boehringer Ingelheim, Pfizer, Lilly, Amgen, Novartis, UCB, and BMS. Dr Ferris has received compensation as an investigator from Amgen, AbbVie, UCB, Eli Lilly, Novartis, Janssen, Nimbus, Dermavant, and Arcutis. Dr Gottlieb has received honoraria as an advisory board member and consultant for Amgen, AnaptypsBio, Avotres Therapeutics, Boehringer Ingelheim, Bristol Myers Squibb, Dice Therapeutics, Eli Lilly, Janssen, Novartis, Sanofi, UCB, and Xbiotech and has received research/educational grants from AnaptypsBio, Moonlake Immunotherapeutics AG, Novartis, Bristol Myers Squibb, and UCB Pharma, (all paid to Mount Sinai School of Medicine). Dr Lebwohl is an employee of Mount Sinai which has received research funds from AbbVie, Amgen, Arcutis, Avotres, Boehringer Ingelheim, Cara therapeutics, Dermavant Sciences, Eli Lilly, Incyte, Inozyme, Janssen Research & Development, LLC, Ortho Dermatologics, Pfizer, Sanofi-Regeneron, and UCB, and he serves as a consultant for Almirall, AltruBio Inc, AnaptysBio, Arcutis, Inc., AstraZeneca, Avotres Therapeutics, Brickell Biotech, Boehringer Ingelheim, Bristol Myers Squibb, Castle Biosciences, Celltrion, Corevitas, Dermavant Sciences, EPI, Evommune, Inc, Facilitation of International Dermatology Education, Forte biosciences, Foundation for Research and Education in Dermatology, Galderma, Genentech, Incyte, LEO Pharma, Meiji Seika Pharma, Mindera, Pfizer, Seanergy, Strata, Trevi, and Verrica. Dr Calabrese has served as a consultant and/or speaker to Regeneron, Sanofi and AbbVie. Dr Desai has served as a research investigator, scientific advisor, consultant, and/or speaker to AbbVie, Galderma Laboratories, Foundation for Research & Education of Dermatology, Almirall, Dermavant Sciences, Ferndale Laboratories, Incyte, Gore Range Capital, AOBiome, BMS, Verrica Pharmaceuticals, UCB, Ortho Dermatologics, Scientis, EPI Health, Avita, Pfizer, Eli Lilly, LEO Pharma, L'Oreal USA, Beiersdorf, Johnson and Johnson, VYNE Therapeutics, Revision Skincare, Candela Corporation, Amgen, Cutera, and Hyphens Pharma; he is also the founder of Illuminate Skin Care. Dr Duffin has served on the advisory board or as a consultant and/or investigator for Stiefel, Novartis, Amgen, AbbVie, Celgene, Lilly, Ortho, Pfizer, Janssen, and Boehringer Ingelheim. Dr Feldman has received compensation from AbbVie, Accordant, Advance Medical, Almirall, Alovtech, Amgen, Arcutis, Arena, Argenx, Biocon, Boehringer Ingelheim, BMS, Caremark, Celgene, Dermavant, Eli Lilly, Galderma, GlaxoSmithKline/Stiefel, Helsinn, Informa, Janssen, LEO Pharma, Menlo, Merck, Mylan, National Biological Corporation, National Psoriasis Foundation, Novan, Novartis, Pfizer, Qurient Forte, Samsung, Regeneron, Sanofi, Sun Pharmaceutical, Suncare Research, UCB, UpToDate, Valeant, and vTv Therapeutics; he is also the founder and majority owner of www.DrScore.com and the founder and part owner of Causa Research. Dr Gladman has served as a consultant for Amgen, AbbVie, Eli Lilly, Novartis, Pfizer, UCB, BMS, Galapagos, Gilead Sciences, and Janssen. 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Dr Hsu has served as a consultant for Janssen, Lilly, and Boehringer Ingelheim; she has also served as a research investigator for Regeneron. Dr Kalb has served as a research investigator and/or consultant for Johnson and Johnson, AbbVie, UCB, Galderma, Novartis, Amgen, Menlo Therapeutics, and Boehringer Inhelheim. Dr Kircik has served as a consultant/speaker/ investigator/advisory board member for Abbott Laboratories, AbbVie, Ablynx, Aclaris, Acambis, Allergan, Almirall, Amgen, Anacor Pharmaceuticals, Anaptys, Arcutis, Arena, Assos Pharma, Astellas Pharma US, Asubio, Bausch Health, Berlex Laboratories (Bayer HealthCare Pharmaceuticals), Biogen-Idec, Biolife, Biopelle, Bristol Myers Squibb, Boehringer Ingelheim, Breckinridge Pharma, Cassiopea, Centocor, Cellceutix, Cipher, Coherus, Colbar, Combinatrix, Connetics Corporation, Coria, Dermavant Sciences, Dermira, Dermik Laboratories, Dow Pharmaceutical Sciences, Dr. Reddy's Lab, Dusa, Embil Pharmaceuticals, Eli Lilly, EOS, Exeltis, Ferndale Laboratories, Foamix, Ferrer, Galderma, Genentech, GlaxoSmithKline, PLC, Glenmark, Health Point, LTD, Idera, Incyte, Intendis, Innocutis, Innovail, Isdin, Johnson & Johnson, Kyowa Kirin, Laboratory Skin Care, LEO Pharma, L'Oreal, 3M, Maruho, Medical International Technologies, Merck, Medicis Pharmaceutical Corp, Merz, Nano Bio, Novartis AG, Noven Pharmaceuticals, Nucryst Pharmaceuticals Corp, Obagi, Onset, OrthoNeutrogena,

PediaPharma, Pfizer, Promius, PuraCap, PharmaDerm, QLT, Quinnova, Quatrix, Regeneron, Sanofi, Serono (Merck Serono International SA), SkinMedica, Stiefel Laboratories, Sun Pharma, Taro, TolerRx, Triax, UCB, Valeant Pharmaceuticals Intl, Warner-Chilcott, XenoPort, and ZAGE. Dr Koo has served as a scientific advisor and/or speaker to AbbVie, Amgen, Eli Lilly, UCB, Ortho Dermatologics, Sun Pharmaceutical Industries, Janssen, LEO Pharma, and EpiPharm. Dr Lewitt has served as a consultant, advisor, and/or speaker to AbbVie, Lilly, Janssen, Pfizer, Galderma, UCB, Dermavant, and Ortho Dermatologics. Dr Liao has received research grant funding from AbbVie, Amgen, Janssen, LEO Pharma, Novartis, Pfizer, Regeneron, and TRex Bio. Dr Liu has received research grant funding from and/or served as a speaker or scientific advisor to AbbVie, Janssen, Lilly, Sanofi-Regeneron, Arcutis, Dermavant, Pfizer, Bristol Myers Squib, UCB, Incyte, Amgen, and Evelo. Dr Merola has served as a research investigator and/or consultant for AbbVie, Amgen, Eli Lilly, Novartis, Janssen, UCB, Sanofi, Regeneron, Biogen, Pfizer, BMS, Dermavant, and LEO Pharma. Dr Prussick has served as a speaker to AbbVie, Jenssen, Pfizer, and Amgen. Dr Reddy has served as a consultant to Novartis, AbbVie, Janssen, UCB; he has also received research grant funding from Pfizer. Dr Schwartzman has served as a consultant and/or speaker to AbbVie, Janssen, Lilly, Pfizer, UCB, Myriad, Novartis, Regeneron, Sanofi, UCB, Stelexis, Jubilant, and Teijin. Dr Soung has received speaker honoraria from AbbVie, Actelion, Amgen, Celgene, Dermira, Eli Lilly, National Psoriasis Foundation, Novartis, Ortho Dermatologics, and Regeneron; has received consulting/advisory board honoraria from Eli Lilly, LEO Pharma, and Novartis; and has received grant/research grant funding from AbbVie, Actavis, Actelion, Allergan, Boehringer Ingelheim, Cassiopea, Dr. Reddy's, Galderma, GSK, Janssen, Kadmon, Kyowa Kirin, LEO Pharma, Menlo, Novan, Novartis, Ortho Dermatologics, Pfizer, and UCB. Dr van Voorhees has received grants and research support from Lilly and AbbVie; she has also served as a consultant for Amgen, Boehringer Ingelheim, BMS, UCB, and Novartis. Dr Wallace has served as a research investigator for Pfizer, Target RWE, Kyowa, Amgen, Arcutis, and Argenx. Dr Weinberg has received research grant funding from and/or served as a consultant or speaker to Novartis, Lilly, Amgen, AbbVie, Sun Pharmaceutical, Janssen, and BMS. Dr Wine Lee has served as a research investigator, scientific advisor, consultant, and/or speaker to Eli Lilly, Sanofi, Regeneron, Pfizer, Trevi Therapeutics, AbbVie, Mayne Pharmaceuticals, Incyte, Castle Creek, Pyramid Bioscience, Amyrt, Krystal Biotech, Arcutis, Celgene, Target Pharma, Amgen, Novartis, UCB, Galderma, Kiniksa, Avita, Janssen, MoonLake Pharmaceuticals, and Timber Pharmaceuticals. Dr Yamauchi has served as an investigator for Amgen, Celgene, Dermira, Eli Lilly, Galderma, Janssen, LEO Pharma, MedImmune, Novartis, Pfizer, Regeneron and Sandoz; he has also served as an advisor and/or speaker to AbbVie, Amgen, Baxter, Celgene, Dermira, Eli Lilly, Galderma, Janssen, LEO Pharma, Novartis, Pfizer, and Regeneron. The other authors have no other conflicts of interest to declare.

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