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Evaluation of a Case Series of Patients With Generalized Pustular Psoriasis in the United States

Megan H. Noe, MD, MPH, MSCE; Marilyn T. Wan, MBChB, MPH; Arash Mostaghimi, MD, MPH, MPA; Joel M. Gelfand, MD, MSCE; and the Pustular Psoriasis in the US Research Group

IMPORTANCE Generalized pustular psoriasis (GPP) is a chronic, orphan disease with limited epidemiological data.

OBJECTIVE To describe the clinical characteristics, treatments, longitudinal disease course, and disease-specific health care utilization among patients with GPP across the United States.

DESIGN, SETTING, AND PARTICIPANTS A retrospective longitudinal case series involving 95 adults who met the European Rare and Severe Psoriasis Expert Network consensus definition for GPP and were treated at 20 US academic dermatology practices between January 1, 2007, and December 31, 2018.

MAIN OUTCOMES AND MEASURES The primary outcome is to describe the patient characteristics, associated medical comorbidities, treatment patterns complications, and GPP-specific health care utilization.

RESULTS Sixty-seven of 95 patients (70.5%) were women (mean age, 50.3 years [SD, 16.1 years]). In the initial encounter, 35 patients (36.8%) were hospitalized and 64 (67.4%) were treated with systemic therapies. In total, more than 20 different systemic therapies were tried. During the follow-up period, 19 patients (35.8%) reported hospitalizations at a median rate of 0.5 hospitalizations per year (IQR, 0.4-1.6). Women had a decreased risk of an emergency department or hospital encounter (odds ratio, 0.19; 95% CI, 0.04-0.83).

CONCLUSIONS AND RELEVANCE Generalized pustular psoriasis is a rare, chronic disease without standard treatment and is associated with continued health care utilization over time.

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Editorial page 13
Related article page 68
Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The Pustular Psoriasis in the US Research Group members appear at the end of this article.

Corresponding Authors: Joel M. Gelfand, MD, MSCE, Departments of Dermatology and Epidemiology, University of Pennsylvania Perelman School of Medicine, 3400 Civic Center Blvd, Philadelphia, PA 19104 (joel.gelfand@pennmedicine.upenn.edu); and Megan H. Noe, MD, MPH, MSCE, Department of Dermatology, Brigham and Women's Hospital, Harvard Medical School, 221 Longwood Ave, Boston, MA 02215 (mnoe2@bwh.harvard.edu).

Generalized pustular psoriasis (GPP) is an orphan disease characterized by the rapid appearance of sterile pustules and generalized erythema. Patients are often systemically ill and may experience severe organ dysfunction and rarely death. The genetic risk factors for pustular psoriasis are different from other types of psoriasis. To date, variations have been identified in the following genes: *IL36RN* (interleukin-36 receptor antagonist), *CARD14* (caspase recruitment domain family member 14), *AP1S3* (adapter related protein complex 1 subunit sigma 3), *SERPINA3* (serpin family A member 3), and *MPO* (myeloperoxidase); however, the majority of patients do not have a known genetic variant.[1] Owing to the rarity of GPP, there is limited information about the natural disease course. The only epidemiological data from the United States is a report of 63 patients seen over 29 years at a single institution.[2] The objective of this study is to describe the clinical characteristics, natural disease course, treatments, and health care utilization of patients with GPP across the United States.

Methods

Study Design and Population

This is a retrospective, longitudinal case series of adults (≥18 years) with a diagnosis of GPP confirmed by a dermatologist (January 1, 2007-December 31, 2018) (**Table 1**). Up to 5 potential cases were identified from each of 20 participating sites' electronic health records or site-specific databases, starting with cases seen most recently. All diagnoses were confirmed by the principal investigator at each site at the time of data entry. Only patients who met the European Rare and Severe Psoriasis Expert Network (ERASPEN) consensus definition of GPP with documentation of "primary, sterile, macroscopically visible pustules on nonacral skin, excluding cases where pustulation is restricted to psoriatic plaques"[3] and had had a dermatology encounter with active pustular disease during the study period were included.

Table 1. Baseline Characteristics of Patients With Generalized Pustular Psoriasis

Characteristic	No. (%) of patients (N = 95)
Women	67 (70.5)
Men	28 (29.5)
Age at presentation, y	
Mean (SD) [range]	50.3 (16.1) [18-90]
Median (IQR)	50 (37-63)
Follow-up time, mo	
Mean (SD) [range]	19.8 (25.3) [0-98.8]
Median (IQR)	9.5 (1.7-28.7)
Year of first visit	
2007-2010	6 (6.3)
2011-2014	25 (26.3)
2015-2018	64 (67.4)
BMI, mean (SD)	31.9 (9.8)
Missing	36 (37.9)
Race	
Asian	6 (6.3)
Black or African American	11 (11.6)
White	51 (53.7)
Unknown or not reported	27 (28.4)
Smoking history	
Current	13 (13.7)
Former	19 (20.0)
Never	50 (52.6)
Unknown or not reported	13 (13.7)
Alcohol use	
Current	20 (21.1)
Former	9 (9.5)
Never	35 (36.8)
Unknown or not reported	31 (32.6)
Prior history of psoriasis and pustular psoriasis	
Psoriasis	36 (37.9)
Duration prior to presentation, median (IQR) [range], y	12 (8-25) [0-32][a]
Psoriatic arthritis	9 (9.5)
Duration prior to presentation, median (IQR) [range], y	11 (4.5-25) [0-37][a]
Generalized pustular psoriasis	38 (40.0)
Duration prior to presentation, median (IQR) [range], y	2.5 (1-10) [0-48][a]

Abbreviation: BMI, body mass index, calculated as weight in kilograms divided by height in meters squared.

[a] Information available for 15 patients with psoriasis, 4 with psoriatic arthritis, and 28 with generalized pustular psoriasis.

Data Collection

The index date or "initial encounter" was the first date of active disease within the reporting institution. Information about demographics, medical history, and disease course, including initial encounter and all subsequent encounters, during the study period were abstracted from the medical record into standardized data collection forms.

Sample Size

A target sample size of 100 patients was calculated to allow for the prevalence of associated covariates to be estimated with a 95% CI and maximum margin of error of 10%. The final sample size of 95 reflects that not all sites had 5 patients with active disease during the study period.

Key Points

Question What are the patient characteristics and the disease course in adults with generalized pustular psoriasis in the United States?

Findings In this retrospective case series of 95 adults with generalized pustular psoriasis, 70.5% of patients were women with a mean age of 50.3 years. On initial presentation, more than one-third of patients were hospitalized, and two-thirds were treated with systemic therapies; over time, 35.8% of patients reported hospitalizations for disease flares.

Meaning Generalized pustular psoriasis is a rare, chronic disease, and patients experience periodic flares where they become systemically ill and may require hospitalization.

Analysis

Descriptive statistics were used to summarize the baseline patient characteristics, past medical history, and information regarding clinical encounters and treatments. Duration of therapy was calculated for each patient and each systemic therapy for all patient-drug combinations with at least 1 subsequent visit after initiation of therapy. For patients without an identified end date, the last visit in the study period where the therapy was continued was used. In patients with at least 6 months of follow-up, GPP-specific health care utilization was also descriptively examined, including the number of dermatology visits, emergency department encounters, and hospitalizations for GPP. Logistic regression was used to evaluate the association of age and sex with hospitalization or emergency department visit during follow-up. This study was granted exempt status by the University of Pennsylvania Institutional Review Board. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

Results

Ninety-five patients met the inclusion criteria, with a mean (SD) follow-up of 19.8 (25.3) months. The median year of first encounter was 2016. Five study sites (25%) did not have 5 cases who met the inclusion criteria during the 10-year study period (Table 1). On the initial presentation, 35 patients (36.8%) presented during an inpatient admission, 9 (9.5%) in the emergency department, and 51 (53.7%) during an outpatient or ambulatory dermatology office visit. Among 57 patients who had no prior history of GPP, 29 (50%) were inpatient admissions or emergency department encounters. Most patients had pustules on the trunk and extremities, but pustules were also reported on the scalp, face, genitals, nail unit, and mucous membranes in a minority of patients. Symptoms of GPP were common with 59 patients (62.1%) reporting skin pain and 25 (26.2%) reporting joint pain. Additionally, 16 (16.8%) had tachycardia and 9 (9.5%) had a

Table 2. Treatments Reported in the Index Encounter

Treatment	No. (%)		
	All patients (n = 95)	Inpatients and ED encounters (n = 44)	Outpatient encounters (n = 51)
No GPP-specific treatment[a]	1 (1.0)	0	1 (2.0)
Topical treatments only	31 (32.3)	14 (31.8)	17 (33.3)
Topical steroids[b]	82 (86.3)	42 (95.5)	40 (78.4)
Low potency	21	12	9
Mid potency	51	33	18
High potency	35	14	21
Other topical medications[c]	12 (12.6)	3 (96.8)	9 (17.6)
Antibiotics	6	3	3
Antifungals	6	2	4
Tar	2	1	1
Vitamin D analog	6	4	2
Systemic antibiotics[d]	15 (15.8)	12 (27.3)	3 (5.9)
β-Lactam	1	1	0
Cephalosporin	9	7	2
Clindamycin	3	3	0
Fluoroquinolone	1	1	0
Linezolid	1	1	0
Sulfa	1	0	1
Tetracycline	1	1	0
Vancomycin	5	5	0
Systemic antiviral	2 (2.1)	2 (4.5)	0 (0)
Systemic antifungal	1 (1.1)	0 (0)	1 (2.0)
Systemic steroids	19 (20.0)	11 (25.0)	8 (15.7)
Phototherapy			
Oral PUVA	1 (1.1)	0 (0)	1 (2.0)
Narrowband UV-B	5 (5.3)	1 (2.3)	4 (7.8)
Oral systemic treatments			
Acitretin	23 (24.2)	7 (15.9)	16 (31.4)
Apremilast	3 (3.2)	0 (0)	3 (5.9)
Cyclosporine	21 (22.1)	14 (31.8)	7 (13.7)
Dapsone	1 (1.1)	1 (2.3)	0 (0)
Isotretinoin	2 (2.1)	0 (0)	2 (3.9)
Methotrexate	13 (13.7)	9 (20.5)	4 (7.8)
Biologics			
Abatacept	1 (1.1)	0 (0)	1 (2.0)
Adalimumab	4 (4.2)	2 (4.5)	2 (3.9)
Etanercept	1 (1.1)	1 (2.3)	0 (0)
Infliximab	4 (4.2)	3 (6.8)	1 (2.0)
Secukinumab	1 (1.1)	0 (0)	1 (2.0)
Ustekinumab	3 (3.2)	1 (2.3)	2 (3.9)

Abbreviations: ED, emergency department; GPP, generalized pustular psoriasis; PUVA, psoralen–UV-A.

[a] Patient received systemic antibiotics only.

[b] Eighty-two patients received at least 1 topical steroid. The sum of patients in each steroid class is more than 82 because some patients received more than 1 topical steroid, so percentages are not reported for individual treatments.

[c] Twelve patients were prescribed at least 1 other topical medication. The sum of patients in each medication category is more than 12 because some people received more than 1 type of topical medication, so percentages are not reported for individual treatments.

[d] Eleven patients were prescribed 1 antibiotic; 2 were prescribed 2; and 1 person each was prescribed 3 and 4 antibiotics during the initial encounter. The sum of patients is greater than 15 because some patients received more than 1 treatment, so percentages are not reported for individual treatments.

fever. The most common comorbidities identified were hypertension, depression, diabetes, chronic kidney disease, and hypothyroidism (eTable 2 in the Supplement). Additionally, 13 patients (13.7%) reported a history of cancer. Additional details regarding the clinical presentation, hospital complications, and likely disease triggers can be found in the eResults section of the Supplement.

During the initial encounter, most patients (n = 64; 67.4%) were treated with systemic therapies (**Table 2**). Systemic antibiotics were used in 15 patients (15.8%), and systemic steroids were given to 19 (20.0%). Other systemic therapies were administered: 23 patients (24.2%) received acitretin; 21 (21.1%), cyclosporine; 13 (13.7%), methotrexate; and 6 (6.3%), phototherapy. Of biologic treatments, 4 patients received infliximab; 4, adalimumab; and 3, ustekinumab. In total, 17 different systemic therapies were used during the index visit. Additional details about the duration of therapy is in the eResults section of the Supplement.

Finally, health care utilization was examined for 53 patients with at least 6 months of follow-up time (**Table 3**). In follow-up, 19 patients (35.8%) were hospitalized for GPP symptoms experienced a median rate of 0.5 hospitalizations per year (IQR, 0.4-1.6). Eight patients had additional GPP-specific emergency department encounters (median, 0.5; IQR, 0.4-1.3). The median number of dermatology visits reported was 3.2 per year (IQR, 2.2-6.1) with a maximum of 18 visits per year of follow-up time. In age- and sex-adjusted models, women had a decreased risk of emergency department encounter or hos-

Table 3. Follow-up Health Care Utilization in Patients With Generalized Pustular Psoriasis With at Least 6 Months of Follow-up

	Median (IQR) [range]
Patients with ≥ 6 mo of follow-up time	53
Follow-up time, mo	27.4 (14.2-48.1) [7.4-98.8]
Total encounters per year	4.4 (3.1-6.9) [0.9-21.4]
Patients with office visits in follow-up, No. (%)	51 (96.2)
No. of office visits per year	3.2 (2.2-6.1) [0.4-18.0]
Patients with ED visits in follow-up, No. (%)	8 (15.1)
No. of ED visits per year	0.5 (0.4-1.3) [0.1-3.0]
Patients with hospitalization in follow-up, No. (%)	19 (35.8)
No. of hospitalizations per year	0.5 (0.4-1.6) [0.1-3.4]
Patients with ED visits or hospitalization in follow-up, No. (%)	21 (39.6)
No. of ED visits or hospitalizations per year	0.7 (0.4-2.2) [0.2-3.9]

Abbreviation: ED, emergency department.

pital admission during follow-up (odds ratio, 0.19; 95% CI, 0.04-0.83).

Discussion

These results further support prior findings that GPP is a rare disease and treatment is highly variable, with more than 20 different systemic therapies reported. Patients reported continued GPP-specific health care utilization including 19 patients (35.8%) who reported hospitalizations during the follow-up period, suggesting that few therapies prove consistently effective. Additionally, this study confirms many of the associations previously reported in the prior US cohort and in other larger international cohorts, including a female predominance and a prior history of plaque psoriasis.[2,4-8] Cancer was rarely reported in previous cohorts, but in this study 13 patients (13.7%) reported a history of cancer, a numerically higher rate than the 5.1% estimated in the general population.[4,9]

There is no consensus for the most effective therapy for GPP, and as a result more than 20 treatments with relatively short treatment durations were reported across patients. Among oral therapies, the median duration of treatment was from 6 to 13 months, a short amount of time for a chronic disease. Biologic use was uncommon, and only etanercept had a median treatment duration longer than 1 year. The variability in treatments used is consistent with international practice. In data from the Japanese National Clinical Database, etretinate accounted for 35.6% of all oral medications, with an efficacy rate of 87.1%.[10] Cyclosporine, methotrexate, oral steroids, and psoralen-UV-A (PUVA) radiation were also reported to be effective.[10] Oral retinoids were the most common treatment reported in a study from Korea.[4] Small case series have reported efficacy of biologic therapies, including tumor necrosis factor α inhibitors, interleukin (IL)-23 inhibitors, and IL-17 inhibitors, but information from large, randomized clinical trials is lacking.[11-14] Additionally, results of a phase 1 study (n = 7) showed that a monoclonal antibody targeting the IL-36 receptor may be an emerging treatment mechanism in patients with and without a variation in the *IL36RN* gene,[15] and phase 2 and 3 trials are ongoing.

Limitations

The retrospective study design creates some limitations, including nonstandardized and missing information in the medical record. Patients were all identified from academic medical centers with inclusion criteria favoring patients seen most recently and therefore may not be generalizable to all patients with GPP in the United States. Additionally, the lack of standardized follow-up visits does not allow for measurement of treatment response.

Conclusions

The results of this case series evaluation support prior findings that GPP is a rare, chronic disease without standard treatment and is associated with continued health care utilization over time. Further prospective research is necessary to better understand treatment efficacy in patients with GPP.

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Author Affiliations: Department of Dermatology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts (Noe, Mostaghimi); Department of Dermatology, Perelman School of Medicine, University of Pennsylvania, Philadelphia (Wan, Gelfand); Department of Internal Medicine, Memorial Hospital West, Pembroke Pines, Florida (Wan); Associate Editor, *JAMA Dermatology* (Mostaghimi); Department of Biostatistics, Epidemiology and Informatics, University of Pennsylvania Perelman School of Medicine, Philadelphia (Gelfand).

Pustular Psoriasis in the US Research Group: Ritesh Agnihothri, MD; April W. Armstrong, MD, MPH; Tina Bhutani, MD, MAS; Alina Bridges, DO; Nicholas Brownstone, MD; Melissa Butt, MPH; Kristina P. Callis Duffin, MD, MS; Christian Carr, MPH; Andrew Creadore, BS; Katherine L. DeNiro, MD; Sheena Desai, BA; Arturo R. Dominguez, MD; Emily K. Duffy, MD; Janet A. Fairley, MD; Alisa Femia, MD; Johann E. Gudjonsson, MD, PhD; Jessica A. Kaffenberger, MD; Kimberly L. Katz, MD; Stephanie T. Le, MD; Edgar Martinez, BS; Emanual Maverakis, MD; Bridget Myers, BS; Haley B. Naik, MD, MHSc; Caroline A. Nelson, MD; Alex G. Ortega-Loayza, MD, MCR; Molly E. Plovanich, MD; Lauren K. Rangel, BA; Vignesh Ravi, BA; Vidhatha D. Reddy, BA; Jamal Z. Saleh, MD, MS; Joslyn S. Kirby, MD, MEd, MS; Jeena K. Sandhu, MD; Hadir Shakshouk, MBBS; Bridget E. Shields, MD; Zakariyah Sharif-Sidi, BA; Jacob Smith, BA; Amanda Steahr, MPH; Atrin Toussi, BS, BA; Karolyn A. Wanat, MD; Bo Wang, MD, PhD; Brian M. Wei, BS; Annika Weinhammer, MD; Scott D. Worswick, MD; Alexander Yang, ScB.

Affiliations of Pustular Psoriasis in the US Research Group: Department of Dermatology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts (Creadore, Desai); Associate Editor, *JAMA Dermatology* (Naik, Kirby); Department of Dermatology, University of Rochester, School of Medicine & Dentistry, Rochester, New York (Agnihothri, Plovanich); Department of Dermatology, Keck Hospital of USC, University of Southern California Keck School of Medicine, Los Angeles (Armstrong, Worswick); Department of Dermatology, UCSF Medical Center, University of California, San Francisco School of

Medicine (Bhutani, Naik); Department of Dermatology, Mayo Clinic Graduate School of Education, Rochester, Minnesota (Bridges); Richfield Laboratory of Dermatopathology, Dermpath Diagnostics, Cincinnati, Ohio (Bridges); Department of Dermatology, Psoriasis and Skin Treatment Center, University of California, San Francisco (Brownstone); Department of Dermatology, Pennsylvania State Hershey Medical Center, Hershey (Butt, Kirby); Department of Dermatology, University of Utah, Salt Lake City (Duffin); University of Texas Southwestern Medical Center, Dallas (Carr, Martinez); Boston University School of Medicine, Boston, Massachusetts (Creadore); Division of Dermatology, Department of Medicine, University of Washington, Seattle (DeNiro, Duffy, Nelson); Tufts University School of Medicine, Boston, Massachusetts (Desai); Departments of Dermatology and Internal Medicine, University of Texas Southwestern Medical Center, Dallas (Dominguez); Department of Dermatology, University of Iowa Carver College of Medicine, Iowa City (Fairley, Steahr); Ronald O. Perelman Department of Dermatology, NYU Langone Hospitals, New York University Grossman School of Medicine, New York (Femia); Department of Dermatology, University of Michigan, Ann Arbor (Gudjonsson, Wang); Division of Dermatology, The Ohio State University Wexner Medical Center, Columbus (Kaffenberger); Department of Dermatology, Medical College of Wisconsin, Milwaukee (Katz, Saleh, Sharif-Sidi, Wanat); Department of Dermatology, University of California, Davis, Sacramento (Le); Department of Dermatology, University of California, Davis School of Medicine, Sacramento (Maverakis); University of California, San Francisco School of Medicine, San Francisco (Myers, Reddy); Department of Dermatology, Oregon Health and Science University School of Medicine, Portland (Ortega-Loayza); New York University Grossman School of Medicine, New York (Rangel); University of Southern California Keck School of Medicine, Los Angeles (Ravi); Department of Dermatology, University of Southern California Keck School of Medicine, Los Angeles (Sandhu); Division of Dermatology, John H. Stroger Jr. Hospital of Cook County, Chicago, Illinois (Sandhu); Department of Dermatology, Mayo Clinic, Rochester, Minnesota (Shakshouk); Department of Dermatology, School of Medicine and Public Health, University of Wisconsin–Madison (Shields); Oregon Health and Science University School of Medicine, Portland (Smith); University of California, Davis School of Medicine, Sacramento (Toussi); Yale School of Medicine, New Haven, Connecticut (Wei, Yang); Department of Dermatology, University of Wisconsin–Madison (Weinhammer).

Author Contributions: Drs Noe and Gelfand had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Noe, Wan, Mostaghimi, Gelfand, Duffin, Creadore, Le, Sandhu, Steahr.
Acquisition, analysis, or interpretation of data: Noe, Wan, Mostaghimi, Gelfand. Agnihothri, Armstrong, Bhutani, Bridges, Brownstone, Butt, Duffin, Carr, Creadore, DeNiro, Desai, Dominguez, Duffy, Fairley, Femia, Gudjonsson, Kaffenberger, Katz, Kirby, Le, Martinez, Maverakis, Myers, Naik, Nelson, Ortega-Loayza, Plovanich, Rangel, Ravi, Reddy, Saleh, Sandhu, Shakshouk, Shields, Sharif-Sidi, Smith, Toussi, Wanat, Wang, Wei, Weinhammer, Worswick, Yang, Mostaghimi, Gelfand.
Drafting of the manuscript: Noe, Wan, Le, Rangel, Worswick.
Critical revision of the manuscript for important intellectual content: Noe, Wan, Mostaghimi, Gelfand, Agnihothri, Armstrong, Bhutani, Bridges, Brownstone, Butt, Duffin, Carr, Creadore, DeNiro, Desai, Dominguez, Duffy, Fairley, Femia, Gudjonsson, Kaffenberger, Katz, Le, Martinez, Maverakis, Myers, Naik, Nelson, Ortega-Loayza, Plovanich, Ravi, Reddy, Saleh, Sandhu, Kirby, Shakshouk, Shields, Sharif-Sidi, Smith, Steahr, Toussi, Wanat, Wang, Wei, Weinhammer, Worswick, Yang.
Statistical analysis: Noe, Wan, Shakshouk, Gelfand.
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Supervision: Mostaghimi, Gelfand, Bridges, DeNiro, Gudjonsson, Shields.

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