JAMA Dermatology | Consensus Statement

Diagnostic Criteria of Ulcerative Pyoderma Gangrenosum
A Delphi Consensus of International Experts

Emanual Maverakis, MD; Chelsea Ma, MD; Kanade Shinkai, MD, PhD; David Fiorentino, MD, PhD; Jeffrey P. Callen, MD; Uwe Wollina, MD; Angelo Valerio Marzano, MD; Daniel Wallach, MD; Kyoungmi Kim, PhD; Courtney Schadt, MD; Anthony Ormerod, MD; Maxwell A. Fung, MD; Andrea Steel, BA; Forum Patel, MD; Rosie Qin, MD; Fiona Craig, MRCP; Hywel C. Williams, DSc; Frank Powell, FRCPI; Alexander Merleev, PhD; Michelle Y. Cheng, MD

IMPORTANCE Pyoderma gangrenosum is a rare inflammatory skin condition that is difficult to diagnose. Currently, it is a "diagnosis of exclusion," a definition not compatible with clinical decision making or inclusion for clinical trials.

OBJECTIVE To propose and validate diagnostic criteria for ulcerative pyoderma gangrenosum.

EVIDENCE REVIEW Diagnostic criteria were created following a Delphi consensus exercise using the RAND/UCLA Appropriateness Method. The criteria were validated against peer-reviewed established cases of pyoderma gangrenosum and mimickers using k-fold cross-validation with methods of multiple imputation.

FINDINGS Delphi exercise yielded 1 major criterion—biopsy of ulcer edge demonstrating neutrophilic infiltrate—and 8 minor criteria: (1) exclusion of infection; (2) pathergy; (3) history of inflammatory bowel disease or inflammatory arthritis; (4) history of papule, pustule, or vesicle ulcerating within 4 days of appearing; (5) peripheral erythema, undermining border, and tenderness at ulceration site; (6) multiple ulcerations, at least 1 on an anterior lower leg; (7) cribriform or "wrinkled paper" scar(s) at healed ulcer sites; and (8) decreased ulcer size within 1 month of initiating immunosuppressive medication(s). Receiver operating characteristic analysis revealed that 4 of 8 minor criteria maximized discrimination, yielding sensitivity and specificity of 86% and 90%, respectively.

CONCLUSIONS AND RELEVANCE This Delphi exercise produced 1 major criterion and 8 minor criteria for the diagnosis of ulcerative pyoderma gangrenosum. The criteria may serve as a guideline for clinicians, allowing for fewer misdiagnoses and improved patient selection for clinical trials.

JAMA Dermatol. doi:10.1001/jamadermatol.2017.5980
Published online February 14, 2018.

Editorial
Related article
Supplemental content

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

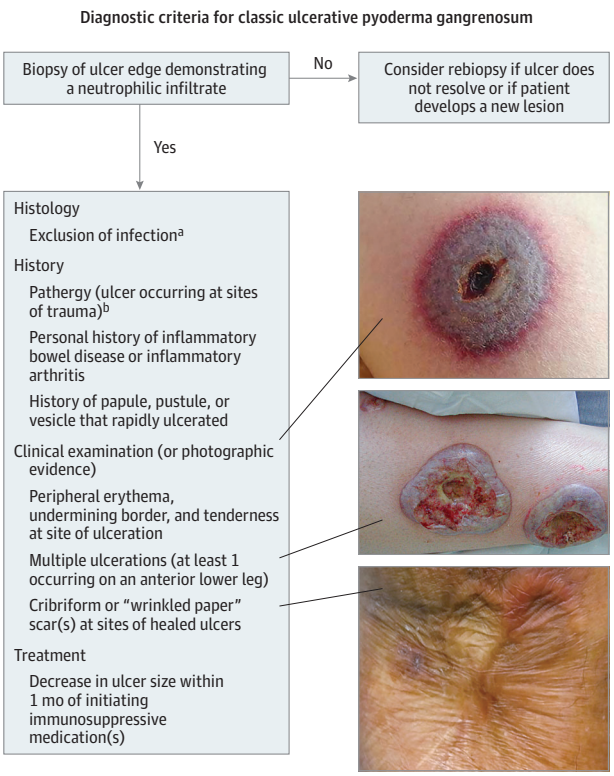
Corresponding Author: Emanual Maverakis, MD, Department of Dermatology, University of California, Davis, 3301 C St, Ste 1400, Sacramento, CA 95816 (emaverakis@ucdavis.edu).

Pyoderma gangrenosum (PG) is a rare inflammatory skin condition with an estimated incidence of 3 to 10 cases per million people per year. It was first described in 1908 as a "geometric phagedena" (*phagédénisme géométrique*)[1] and was later redefined as PG in 1930.[2] Multiple variants of PG exist, but ulcerative PG typically presents as tender papules or pustules that evolve into painful and rapidly expanding ulcers. Initially thought to be of infectious etiology, the pathogenesis of PG is still not well understood. Currently, most consider PG to be a prototypic neutrophilic dermatosis, possibly driven by an autoinflammatory process.[3]

Diagnosis of PG has been challenging owing to its variable presentation, clinical overlap with other conditions, association with several systemic diseases, and absence of defining histopathologic or laboratory findings. For example, ulcerations may be seen in other neutrophilic disorders, vascular disorders, malignancy, and infections. Although the histopathology of PG typically shows neutrophilic inflammation, this manifestation is nonspecific and may vary based on PG subtype, ulcer stage, and timing of biopsy. Misdiagnosis and delayed diagnosis are common; in 1 retrospective study,[4] 39% of patients who initially received a diagnosis of PG were ultimately found to have an alternative diagnosis. Importantly, misdiagnosis may present substantial risks to patients because some PG treatments are contraindicated in cases of active infection or malignancy.

There are currently no uniformly accepted diagnostic criteria for PG. Previously published criteria by Su et al[5] maintain ulcerative PG as a diagnosis of exclusion, which may be impractical and impede diagnosis. Also, to our knowledge, there have been no publications using a systematic approach to develop diagnostic criteria for PG. This lack of structure in approaching diagnosis makes patient selection for clinical trials particularly difficult and

Figure 1. Diagnostic Criteria for Classic Ulcerative Pyoderma Gangrenosum



In addition to a biopsy demonstrating a neutrophilic infiltrate, patients must have at least 4 minor criteria to meet diagnostic criteria.

[a] Including histologically indicated stains and tissue cultures.

[b] Ulcer should extend past area of trauma.

prone to misclassification. For example, in the largest of the 2 clinical trials conducted to date, clinical PG diagnosis in 9 of 121 participants was later revised after randomization.[6] To bridge this clinical gap, we assembled a set of diagnostic criteria for ulcerative PG using the Delphi method following the RAND/UCLA Appropriateness Method[7] and subsequently validated the criteria against published cases of PG and its mimickers.

Methods

Panel Selection

Panel members were selected based on first or last authorship on PG publications in high-impact medical journals, as identified through the Web of Science using the search term *pyoderma gangrenosum*, in August 2015. Case reports and minor publications were not considered. In addition, participating physicians were allowed to recommend other PG experts for the panel.[7] This process yielded 15 physicians representing 6 countries and 10 universities. Three physicians did not respond to the invitation, and the remaining 12 agreed to participate.

Delphi Exercise

First Round

In the first round of the Delphi exercise, the participating 12 committee members were sent an online survey consisting of 21 statements regarding the diagnosis of PG. The panel evaluated the level of appropriateness of statements in relation to PG on a scale of 1 (extremely inappropriate) to 9 (extremely appropriate). Participants were given the option of selecting "N/A" if they felt they did not have the necessary expertise to rank a particular statement. Statements presented for criteria were assembled from Scopus and Web of Science literature searches of highly cited manuscripts about PG and included prior suggested diagnostic criteria.[4,5,8,9] The search was conducted in August 2015 using the term *pyoderma gangrenosum*. Results were deidentified prior to releasing them to the panel, and participants were able to suggest new statements.

Statistics

Results were analyzed using the RAND/UCLA Appropriateness Method.[7] For each statement, the median rating for appropriateness, interpercentile range (IPR), interpercentile range adjusted for symmetry (IPRAS), and disagreement index (DI) were calculated (DI = IPR/IPRAS).[7] A median rating of 1.0 to 3.4 was considered to be "inappropriate," 3.5 to 6.9 to be "uncertain," and 7.0 to 9.0 to be "appropriate." A (DI) value greater than or equal to 1 ($DI \geq 1$) indicated a lack of consensus among the participants regarding the appropriateness of the statement. For further details, please see eAppendix 1 in the Supplement.

Second and Third Rounds

During the second and third rounds, participants ranked new suggested statements and revised statements that failed the previous rounds.

Fourth Round

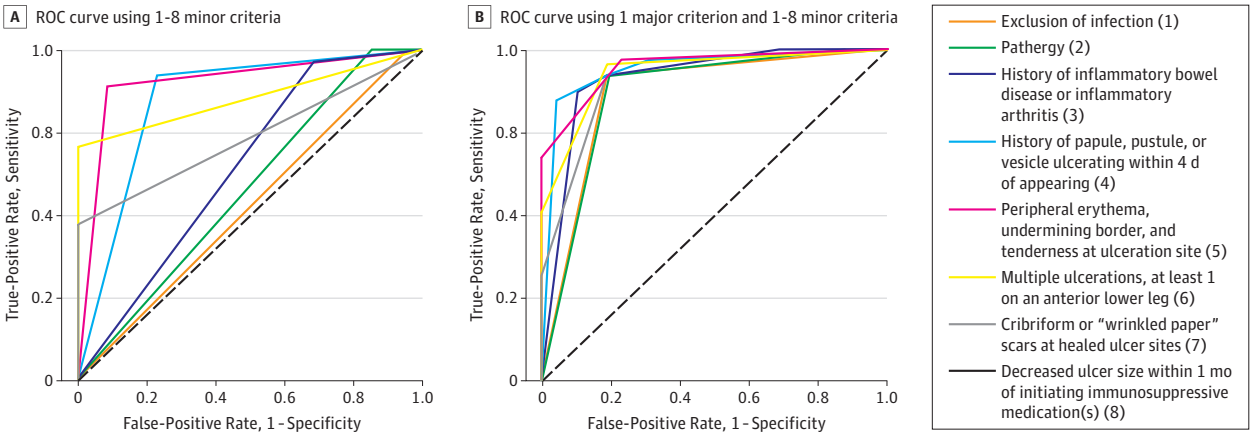
Statements that were agreed on ($DI < 1$) to be appropriate were used to develop a set of diagnostic criteria for PG (**Figure 1**). Statements that the panel agreed to be required for diagnosis were designated as major criteria, whereas those that were deemed to be helpful but not required were designated as minor criteria. The panel was asked to rate the appropriateness or usefulness of the new criteria using the same scale.

Validation

Case reports of ulcerative PG and mimickers were collected through a PubMed search for cases published in respected peer-reviewed medical journals chosen by impact factor (*Journal of the American Academy of Dermatology*, *JAMA Dermatology*, *British Journal of Dermatology*, *Journal of the European Academy of Dermatology and Venereology*, and *Acta Dermato-Venereologica*) from 2001 to 2016.[10-47] To balance the number of PG cases and mimics, additional cases of non-PG ulcers were found using the search terms *ulcer* and *vasculitis*, *ulcer* and *venous*, and *ulcer* and *calciphylaxis* because such ulcers are often misdiagnosed as PG (eAppendix 2 in the Supplement).[4] Case series were excluded if they contained grouped data and lacked patient-specific details. When necessary, corresponding authors were contacted in an attempt to recover diagnostic information missing from the publications.

Subsequently, the data from the case reports underwent multiple imputation to address data missing from the case reports using the missing at random and missing completely at random

Figure 2. Receiver Operating Characteristic (ROC) Curve From k-Fold Cross-Validation



A, ROC curve using 1 to 8 minor criteria as the threshold for diagnosis, in which biopsy is designated as a minor criterion. B, ROC curve using 1 major and 1 to 8 minor criteria as the threshold for diagnosis, in which biopsy is designated as a major criterion. Biopsy as a major criterion improved the performance of all diagnostic models. The 8 minor criteria are as follows: (1) exclusion of infection; (2) pathergy; (3) history of inflammatory bowel disease or inflammatory arthritis; (4) history of papule, pustule, or vesicle ulcerating within 4 days of appearing; (5) peripheral erythema, undermining border, and tenderness at ulceration site; (6) multiple ulcerations, with at least 1 on an anterior lower leg; (7) cribriform or "wrinkled paper" scar(s) at healed ulcer sites; and (8) decreased ulcer size within 1 month of initiating immunosuppressive medication(s).

assumptions. Diagnostic model performance was evaluated by calculating the area under the receiver operating characteristic curve (AUC) and validated by k-fold cross-validation (**Figure 2**). For details on these statistical analyses, see eAppendix 3 in the Supplement.

Results

Delphi Exercise

All 12 physicians responded to every round of the Delphi exercise (100% response rate). The results of the first 3 rounds are tabulated in eAppendix 4 in the Supplement.

Afterward, the statements that the panel "agreed" were "appropriate" were used to develop a total of 9 criteria (1 major criterion and 8 minor criteria) for the diagnosis of ulcerative PG. The panel then subsequently "agreed" (DI = 0.22) that the final criteria were "appropriate or useful" (median rating of 7).

Diagnostic Criteria

During the first round of the Delphi exercise, biopsy was proposed as a minor criterion, but the panel could not agree on the appropriateness of this statement (DI = 1.3). Instead, they agreed that a biopsy should be required in diagnosing PG. Thus, biopsy was made into a major criterion and is the first step of our diagnostic criteria. Importantly, a biopsy at the ulcer edge was agreed to be superior to a biopsy made at an alternative ulcer site.

In addition, the panel strongly agreed that histologic features seen in PG included dermal edema with neutrophilic inflammation. Absence of infection was deemed helpful but not required in diagnosing PG. Biopsy demonstrating leukocytoclastic vasculitis was not thought to exclude a diagnosis of PG because this finding can be seen in PG lesions.[48]

While the rate of ulcer progression and the presence of an undermining border were considered major criteria for ulcerative PG per Su et al,[5] these features were deemed to be helpful but not required by our expert panel, and thus they were designated as minor criteria. Other clinical findings that the panel agreed were helpful but not required included peripheral erythema and pain at the ulcer site.

With regard to patient history, pathergy has been described as an important trigger for PG, with 20% to 30% of PG cases reportedly occurring after minor trauma.[49] The panel was in agreement that pathergy was helpful but not required for PG diagnosis. History of an inflammatory papule, pustule, or vesicle that rapidly ulcerates was also thought to be helpful. The panel also agreed that history of inflammatory bowel disease or inflammatory arthritis would assist in diagnosis, which is supported by literature showing a strong association between these 2 conditions and PG.[50]

During the second round of the Delphi exercise, the panel approved a newly introduced statement that decreased ulcer size after immunosuppressive therapy is useful in diagnosing PG. The panel also reached an agreement confirming that the diagnosis may be supported by the presence of multiple ulcers, particularly on the anterior legs. During the third round, the panel agreed that either cribriform or wrinkled paper scarring may be useful in the diagnosis of PG.

Agreed on items were then used to generate the proposed diagnostic criteria for PG, which included 1 major criterion and 8 minor criteria. Some statements were revised based on patient and expert panel comments. The set of criteria was then submitted to the participants, who approved the new diagnostic criteria.

Validation

Our approved diagnostic criteria were then tested and validated against 113 case reports. Of these, 65 pertained to PG and 48

Table 1. Presence of Criteria in 113 Case Reports and Statistical Significance Using MAR and MNAR Assumptions

Criteria	Case Reports, No. (%)		Significance[a]	
	PG Cases Fulfilling Criterion (n = 65)	Mimics Fulfilling Criterion (n = 48)	Under MAR Assumption	Under MNAR Assumption
Biopsy with neutrophilic infiltrate	51 (78)	7 (15)	100	100
Exclusion of infection on histology	17 (26)	7 (15)	38	26
Pathergy	23 (35)	4 (8)	87	94
Personal history of IBD or inflammatory arthritis	15 (23)	9 (19)	0	0
Papule, pustule, or vesicle that rapidly ulcerates	27 (42)	0	95	72
Peripheral erythema, undermining border, and tenderness at site of ulceration	59 (91)	12 (25)	100	100
Multiple ulcerations (at least one occurring on an anterior lower leg)	36 (55)	20 (42)	3	0
Cribriform or wrinkled paper scars at healed ulcer sites	25 (38)	4 (8)	100	100
Decrease in ulcer size after immunosuppressive treatment	55 (85)	10 (21)	100	100

Abbreviations: IBD, inflammatory bowel disease; MAR, missing at random; MNAR, missing not at random; PG, pyoderma gangrenosum.

[a] Number of times predictor was statistically significant ($P < .05$) for the PG model.

Table 2. Performance of the Best Models Under MAR, MNAR, and Single Imputation Assumptions

Parameter	MAR	MNAR	Single Imputation
Minor criteria, No.	5	4	3
Area under the curve, mean (SD)	0.95 (0.02)	0.94 (0.02)	0.92 (0.02)
Sensitivity, mean (SD), %	0.80 (0.04)	0.86 (0.06)	0.80 (0.05)
Specificity, mean (SD), %	0.95 (0.03)	0.90 (0.03)	0.88 (0.05)

Abbreviations: MAR, missing at random; MNAR, missing not at random.

pertained to PG mimickers. The frequency with which each criterion is present in the cases is summarized in **Table 1**. k-Fold cross-validation confirmed the use of biopsy as a major rather than minor criterion because it increased the performance of all models. In addition, 5 minor criteria were determined to be optimal under the missing at random assumption (AUC = 0.95, sensitivity = 80%, and specificity = 95%), 4 minor criteria were determined to be optimal under the missing completely at random assumption (AUC = 0.93, sensitivity = 86%, and specificity = 90%), and 3 minor criteria were determined to be optimal under a single imputation (AUC = 0.92, sensitivity = 80%, and specificity = 88%) (**Table 2**). Four minor criteria were ultimately determined as the threshold for PG diagnosis given the optimal combination of sensitivity and specificity and similar AUCs under the missing at random and missing completely at random assumptions compared with 5 minor criteria.

Discussion

This study calculates the optimal diagnostic criteria to maximize discrimination in ulcerative PG, yielding sensitivity and specificity of 86% and 90%, respectively. In addition, this work consolidates the relevant clinical and histopathologic findings using expert panel consensus.

The greatest benefit of these diagnostic criteria compared with previous standards[5] is that PG will no longer be a diagnosis of exclusion. Instead, diagnosis rests on clinical history, presentation, histopathology, and resolution pattern. Importantly, biopsy of the ulcer edge must demonstrate a neutrophilic infiltrate to establish the diagnosis of PG. However, the presence of a mixed infiltrate or a diagnosis of leukocytoclastic vasculitis does not completely exclude the possibility of PG. Exclusion of infection through histologically indicated stains and tissue cultures aids in diagnosis but is not required because superinfection is possible.[22,46] Therefore, exclusion of infection is best done through histology. Although superficial wound cultures could be obtained on a case-by-case basis, it is not part of our diagnostic criteria because it may overestimate bacterial colonization and superinfection while underestimating slow-growing bacteria, fungus (eg, *Sporothrix schenckii*), mycobacteria, and viruses. This emphasis on histopathology is unlike previously suggested diagnostic approaches, which relied predominantly on clinical features.[5,8,9] Also, positive findings are as useful as negative findings on biopsy in our diagnostic criteria.

Although the association between malignancy and PG has been demonstrated in the literature,[49] malignancy history did not pass as a minor criterion. However, some panel members felt strongly that history of malignancy aids in PG diagnosis. Finally, it is important to underscore that if biopsy is determined to show an alternative diagnosis by the pathologist, our diagnostic criteria need not be applied.

Our diagnostic criteria were validated against published PG case reports. Case reports were used as the criterion standard diagnosis because they receive higher scrutiny and peer review prior to publication. However, a limitation of the data are the limited validation set. Additional validation testing in broader mimicking populations may be valuable. A further limitation was that some case reports did not contain sufficient information to use all components of the criteria. We addressed this issue by contacting corresponding authors for the missing information and by performing statistical analyses that accounted for the missing data.

While these criteria have demonstrated high sensitivity and specificity for the diagnosis of ulcerative PG, atypical cases may be missed—in particular, cases in which a biopsy was obtained after initiation of immunosuppressive therapy or during spontaneous resolution. Biopsies taken at such time points may fail to demonstrate a neutrophilic infiltrate. Thus, it is important to rebiopsy patients during subsequent flares if diagnosis remains uncertain.

Our diagnostic criteria remove ulcerative PG as a diagnosis of exclusion and will change how physicians approach this challenging disease. It will also allow for more accurate patient selection for clinical trials.

Conclusions

Rather than maintain PG as a diagnosis of exclusion, this set of criteria is unique and practical in its ability to diagnose PG using clear major and minor criteria. Furthermore, the diagnostic model of 1 major criterion and 4 of 8 minor criteria as the threshold for diagnosis was validated, achieving high sensitivity and specificity. We expect these criteria to gain wide acceptance and serve as a guideline for clinicians, allowing for fewer misdiagnoses and improved patient selection for clinical trials. Future research directions in this area involve further clinical validation of the diagnostic criteria in prospective studies.

ARTICLE INFORMATION

Accepted for Publication: February 14, 2017.

Published Online: February 14, 2018. doi:10.1001/jamadermatol.2017.5980

Author Affiliations: Department of Dermatology, University of California, Davis, Sacramento (Maverakis, Ma, Fung, Steel, Patel, Qin, Merleev, Cheng); Department of Dermatology, University of California, San Francisco (Shinkai); Division of Immunology and Rheumatology, Department of Dermatology, Stanford University, Stanford, California (Fiorentino); Division of Immunology and Rheumatology, Department of Internal Medicine, Stanford University, Stanford, California (Fiorentino); Division of Dermatology, Department of Medicine, University of Louisville, Louisville, Kentucky (Callen, Schadt); Associate Editor, *JAMA Dermatology* (Callen); Department of Dermatology and Allergology, Academic Teaching Hospital Dresden, Dresden, Germany (Wollina); UOC di Dermatologia, IRCCS Fondazione Ca' Granda Ospedale Maggiore Policlinico, Milano–Dipartimento di Fisiopatologia Medico-Chirurgica e dei Trapianti, Università degli Studi di Milano, Milano, Italy (Marzano); Department of Dermatology, Paris Hospitals, Paris, France (Wallach); Division of Biostatistics, Department of Public Health Sciences, University of California, Davis (Kim); Department of Dermatology, School of Medicine and Dentistry, University of Aberdeen, Aberdeen, United Kingdom (Ormerod, Craig); Centre of Evidence Based Dermatology, King's Meadow Campus, University of Nottingham, United Kingdom (Williams); Charles Institute of Dermatology, University College, Dublin, Ireland (Powell).

Author Contributions: Drs Maverakis and Ma are co-first authors. Drs Ma and Maverakis 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.
Study concept and design: Maverakis, Ma, Marzano, Kim, Schadt, Patel, Qin, Craig, Cheng.
Acquisition, analysis, or interpretation of data: Maverakis, Ma, Shinkai, Fiorentino, Callen, Wollina, Marzano, Wallach, Kim, Ormerod, Fung, Steel, Qin, Williams, Powell, Merleev, Cheng.
Drafting of the manuscript: Maverakis, Ma, Wollina, Marzano, Kim, Steel, Qin, Powell, Cheng.
Critical revision of the manuscript for important intellectual content: Maverakis, Ma, Shinkai, Fiorentino, Callen, Wollina, Marzano, Wallach, Kim, Schadt, Ormerod, Fung, Patel, Craig, Williams, Powell, Merleev, Cheng.
Statistical analysis: Maverakis, Ma, Kim, Merleev, Cheng.
Obtained funding: Maverakis.
Administrative, technical, or material support: Maverakis, Steel, Patel, Cheng.
Supervision: Maverakis, Marzano, Cheng.

Conflict of Interest Disclosures: Dr Callen received consulting fees from XOMA, CSL International, and Abbvie. Drs Williams, Ormerod, and Craig were investigators for the STOP GAP (Study of Treatments for Pyoderma Gangrenosum Patients) clinical trial funded by the UK National Institute of Health Research under its program grants for applied research (RP-PG-0407-10177). No other disclosures were reported.

Funding/Support: Dr Maverakis was supported by career awards from the Howard Hughes Medical Institute and the Burroughs Wellcome Fund. This work was supported by the National Institutes of Health grant DP2OD008752.

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer: The views expressed in this publication are those of the authors and not necessarily those of the National Health Service, the National Institute for Health Research, or the Department of Health. Dr Callen is Associate Editor of *JAMA Dermatology*, but he was not involved in any of the decisions regarding review of the manuscript or its acceptance.

REFERENCES

1. Brocq L, Simon CL. Contribution à l'étude du phagédénisme. *Bull Soc Méd Hop Paris*. 1908:290-307.

2. Brunsting LA, Goeckerman WH, O'Leary PA. Pyoderma (ecthyma) gangrenosum. *Arch Derm Syphilol*. 1930;22(4):655-680.

3. Marzano AV, Cugno M, Trevisan V, et al. Role of inflammatory cells, cytokines and matrix metalloproteinases in neutrophil-mediated skin diseases. *Clin Exp Immunol*. 2010;162(1):100-107.

4. Weenig RH, Davis MD, Dahl PR, Su WP. Skin ulcers misdiagnosed as pyoderma gangrenosum. *N Engl J Med*. 2002;347(18):1412-1418.

5. Su WP, Davis MD, Weenig RH, Powell FC, Perry HO. Pyoderma gangrenosum: clinicopathologic correlation and proposed diagnostic criteria. *Int J Dermatol*. 2004;43(11):790-800.

6. Ormerod AD, Thomas KS, Craig FE, et al; UK Dermatology Clinical Trials Network's STOP GAP Team. Comparison of the two most commonly used treatments for pyoderma gangrenosum: results of the STOP GAP randomised controlled trial. *BMJ*. 2015;350:h2958.

7. Fitch K. *The RAND/UCLA Appropriateness Method User's Manual*. Santa Monica, CA: RAND Corporation; 2001.

8. Al Ghazal P, Klode J, Dissemond J. Diagnostic criteria for pyoderma gangrenosum: results of a survey among dermatologic wound experts in Germany. *J Dtsch Dermatol Ges*. 2014;12(12):1129-1131.

9. Powell FC, Su WP, Perry HO. Pyoderma gangrenosum: classification and management. *J Am Acad Dermatol*. 1996;34(3):395-409.

10. Crittenden SC, Gilbert JE, Callen JP. Hydroxyurea-induced leg ulceration in a patient with a homozygous MTHFR polymorphism misdiagnosed as pyoderma gangrenosum. *JAMA Dermatol*. 2014;150(7):780-781.

11. Samlaska CP, Smith RA, Myers JB, Bottini AG, Person DA. Pyoderma gangrenosum and cranial osteolysis: case report and review of the paediatric literature. *Br J Dermatol*. 1995;133(6):972-977.

12. Fremlin GA, Rawlings C, Livingstone JA, Bray AP. An unusual case of bilateral pyoderma gangrenosum with Achilles tendon rupture. *Br J Dermatol*. 2015;172(2):522-526.

13. Coors EA, von den Driesch P. Pyoderma gangrenosum in a patient with autoimmune haemolytic anaemia and complement deficiency. *Br J Dermatol*. 2000;143(1):154-156.

14. Hubbard VG, Friedmann AC, Goldsmith P. Systemic pyoderma gangrenosum responding to infliximab and adalimumab. *Br J Dermatol*. 2005;152(5):1059-1061.

15. Kaur MR, Lewis HM. Severe recalcitrant pyoderma gangrenosum treated with infliximab. *Br J Dermatol*. 2005;153(3):689-691.

16. Moreno-Ramírez D, Herrera-Saval A, Ríos-Martín JJ, Blasco-Esquivias I, Camacho F. Multiple lesions of pyoderma gangrenosum in association with hyper-reactive malarial splenomegaly. *Br J Dermatol*. 2004;150(3):605-607.

17. Haga N, Iwata H, Yamaguchi Y, et al. Mucocutaneous pyoderma gangrenosum due to trisomy 8 neutrophilic infiltrates in a patient with myelodysplastic syndrome. *Br J Dermatol*. 2016;174(1):239-241.

18. Boussofara L, Gammoudi R, Ghariani N, et al. Familial pyoderma gangrenosum in association with common variable immunodeficiency. *Br J Dermatol*. 2013;169(4):944-946.

19. ten Freyhaus K, Homey B, Bieber T, Wilsmann-Theis D. Pyoderma gangrenosum: another cutaneous side-effect of sunitinib? *Br J Dermatol*. 2008;159(1):242-243.

20. Fujimoto E, Fujimoto N, Kuroda K, Tajima S. Leukocytapheresis treatment for pyoderma gangrenosum. *Br J Dermatol*. 2004;151(5):1090-1092.

21. Kerr OA, Bong C, Wallis C, Tidman MJ. Primary cutaneous mucormycosis masquerading as pyoderma gangrenosum. *Br J Dermatol*. 2004;150(6):1212-1213.

22. Yang CC, Hsieh FS, Lee JY. Pyoderma gangrenosum complicated by ecthyma gangrenosum. *Br J Dermatol*. 2004;150(5):1025-1026.

23. Ghislain PD, De Decker I, Lachapelle JM. Efficacy and systemic absorption of topical tacrolimus used in pyoderma gangrenosum. *Br J Dermatol*. 2004;150(5):1052-1053.

24. Ho KK, Browne A, Fitzgibbons J, Carney D, Powell FC. Mycosis fungoides bullosa simulating pyoderma gangrenosum. *Br J Dermatol*. 2000;142 (1):124-127.

25. New D, Eaton P, Knable A, Callen JP. The use of B vitamins for cutaneous ulcerations mimicking pyoderma gangrenosum in patients with *MTHFR* polymorphism. *Arch Dermatol*. 2011;147(4):450-453.

26. Murray PR, Jain A, Uzel G, et al. Pyoderma gangrenosum–like ulcer in a patient with X-linked agammaglobulinemia: identification of *Helicobacter bilis* by mass spectrometry analysis. *Arch Dermatol*. 2010;146(5):523-526.

27. Heffernan MP, Anadkat MJ, Smith DI. Adalimumab treatment for pyoderma gangrenosum. *Arch Dermatol*. 2007;143(3):306-308.

28. Liaqat M, Elsensohn AN, Hansen CD, Maughan JA, Petersen MJ. Acute postoperative pyoderma gangrenosum case and review of literature identifying chest wall predominance and no recurrence following skin grafts. *J Am Acad Dermatol*. 2014;71(4):e145-e146.

29. Hong JB, Su YN, Chiu HC. Pyogenic arthritis, pyoderma gangrenosum, and acne syndrome (PAPA syndrome): report of a sporadic case without an identifiable mutation in the CD2BP1 gene. *J Am Acad Dermatol*. 2009;61(3):533-535.

30. Regnier-Rosencher E, Bizet N, Méry L. Pyoderma gangrenosum associated with renal carcinoma. *J Am Acad Dermatol*. 2011;64(6): 1208-1211.

31. Krauze E, Brzezińska-Wcisło L, Kamińska-Winciorek G, Wygledowska-Kania M, Sygula E. Pyoderma gangrenosum coexisting with acute myelogenous leukaemia. *J Eur Acad Dermatol Venereol*. 2005;19(5):589-592.

32. Staub J, Pfannschmidt N, Strohal R, et al. Successful treatment of PASH syndrome with infliximab, cyclosporine and dapsone. *J Eur Acad Dermatol Venereol*. 2015;29(11):2243-2247.

33. Wollina U, Karamfilov T. Treatment of recalcitrant ulcers in pyoderma gangrenosum with mycophenolate mofetil and autologous keratinocyte transplantation on a hyaluronic acid matrix. *J Eur Acad Dermatol Venereol*. 2000;14(3): 187-190.

34. Aytekin S, Tarlan N, Kalkanli N, Yaldiz M, Unlü G. Pyoderma gangrenosum in pregnancy. *J Eur Acad Dermatol Venereol*. 2002;16(5):546-548.

35. França AE, Salvino LK, Leite SH, et al. Pyoderma gangrenosum as first clinical manifestation of gastric adenocarcinoma. *J Eur Acad Dermatol Venereol*. 2006;20(4):440-441.

36. Mijušković ZP, Zecević RD, Pavlović MD. Pyoderma gangrenosum with spleen involvement and monoclonal IgA gammopathy. *J Eur Acad Dermatol Venereol*. 2004;18(6):697-699.

37. Alvarez-Lopez MA, Burón-Alvarez I, Villegas-Fernández C. Refractory pyoderma gangrenosum treated with platelet-rich plasma. *J Eur Acad Dermatol Venereol*. 2016;30(8):1423-1424.

38. Bellini V, Simonetti S, Lisi P. Successful treatment of severe pyoderma gangrenosum with pimecrolimus cream 1%. *J Eur Acad Dermatol Venereol*. 2008;22(1):113-115.

39. Akahoshi-Ikeda M, Yoshizawa S, Motoshita J, Furue M, Takeuchi S. A case of pyoderma gangrenosum in a patient with rheumatoid arthritis treated with abatacept. *Acta Derm Venereol*. 2016; 96(6):822-823.

40. Del Giacco SR, Firinu D, Lorrai MM, et al. Idiopathic pyoderma gangrenosum: successful resolution with infliximab therapy and pro-inflammatory cytokines assessment. *Acta Derm Venereol*. 2012;92(4):439-440.

41. Kikuchi N, Hiraiwa T, Ishikawa M, et al. Cutaneous cryptococcosis mimicking pyoderma gangrenosum: a report of four cases. *Acta Derm Venereol*. 2016;96(1):116-117.

42. Pitarch G, Torrijos A, Mahiques L, Sánchez-Carazo JL, Fortea JM. Systemic absorption of topical tacrolimus in pyoderma gangrenosum. *Acta Derm Venereol*. 2006;86(1):64-65.

43. Asahina A, Minatani Y, Tada Y, Mitsui H, Tamaki K. Successful treatment of pyoderma gangrenosum with potassium iodide. *Acta Derm Venereol*. 2006; 86(1):84-85.

44. Delgado-Jimenez Y, Pérez-Gala S, Nam-Cha S, et al. Extranodal NK/T-cell lymphoma nasal type mimicking pyoderma gangrenosum. *Acta Derm Venereol*. 2007;87(2):176-177.

45. Jasch KC, Hermes B, Scheller U, Harth W. Pyoderma gangrenosum-like primary cutaneous cryptococcosis. *Acta Derm Venereol*. 2008;88(1): 76-77.

46. Kristensen IB, Møller H, Kjaerskov MW, Yderstraede K, Møller MB, Bergmann OJ. Myeloid sarcoma developing in pre-existing pyoderma gangrenosum. *Acta Derm Venereol*. 2009;89(2): 175-177.

47. Patel F, Fitzmaurice S, Duong C, et al. Effective strategies for the management of pyoderma gangrenosum: a comprehensive review. *Acta Derm Venereol*. 2015;95(5):525-531.

48. Cummins DL, Anhalt GJ, Monahan T, Meyerle JH. Treatment of pyoderma gangrenosum with intravenous immunoglobulin. *Br J Dermatol*. 2007; 157(6):1235-1239.

49. Binus AM, Qureshi AA, Li VW, Winterfield LS. Pyoderma gangrenosum: a retrospective review of patient characteristics, comorbidities and therapy in 103 patients. *Br J Dermatol*. 2011;165(6):1244-1250.

50. Farhi D, Cosnes J, Zizi N, et al. Significance of erythema nodosum and pyoderma gangrenosum in inflammatory bowel diseases: a cohort study of 2402 patients. *Medicine (Baltimore)*. 2008;87(5): 281-293.