Accepted Manuscript

New validated diagnostic criteria for pyoderma gangrenosum

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## PII: S0190-9622(18)33084-6

DOI: https://doi.org/10.1016/j.jaad.2018.08.068

Reference: YMJD 13017

To appear in: Journal of the American Academy of Dermatology

Received Date: 22 August 2018

Accepted Date: 24 August 2018

Please cite this article as: Maverakis E, Le ST, Callen J, Wollina U, Marzano AV, Wallach D, Schadt C, Martinez-Alvardao YC, Cheng MY, Ma C, Merleev A, Ormerod A, Craig F, Jockenhofer F, Dissemond J, Salva K, Williams HC, Fiorentino D, New validated diagnostic criteria for pyoderma gangrenosum, *Journal of the American Academy of Dermatology* (2019), doi: https://doi.org/10.1016/j.jaad.2018.08.068.

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## Article Type: Letter: Notes and Comments

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Word Count: 399/500 Figure Count: 0 Table Count: 0 Authorship Disclosure: No relevant financial or nonfinancial relationships to disclose. *To the Editor:* We read with interest the review on neutrophilic dermatoses by Ashchyan et al<sup>1</sup> and believe it will be of significant value to the dermatologic community. To supplement their review, there are two additional viewpoints that we would like to highlight, specifically regarding the diagnosis and treatment of pyoderma gangrenosum (PG).

Ashchyan et al<sup>1</sup> state that PG remains a "diagnosis of exclusion,"<sup>2</sup> a definition that is difficult to justify, as it is impractical to have a medical diagnosis that requires one to rule out all other possible diagnoses. In fact, the lack of clear diagnostic criteria for PG may be one reason why it has been reported that many cases initially diagnosed as PG ultimately can be reclassified as an alternative diagnosis.<sup>3</sup>

Pertinent to this topic, two PG diagnostic criteria have been recently published.<sup>4,5</sup> The new criteria were independently developed in parallel by separate groups following different approaches.<sup>5</sup> The first of the two studies utilized a score-based approach in which criteria weight was determined by observed prevalence amongst PG patients.<sup>4</sup> The second study based their criteria on a Delphi exercise, which was then mathematically refined and validated.<sup>5</sup> Hopefully, these diagnostic models will be of benefit in the clinical and research settings. Both models attempt to de-emphasize the need to exhaustively exclude other causes of ulceration and instead focus more on the pathologic features of PG. Of course, when suspected, relevant causes of ulceration should still be excluded.

Secondly, Ashchyan et al also highlighted as a "key point" that the criterion standard therapy for PG is systemic corticosteroids. Although corticosteroids and cyclosporine have been the most well characterized agents in the literature, we would caution against designating any PG therapy as a "criterion standard".<sup>6</sup> To date, there have only been two randomized controlled clinical trials in PG.<sup>7,8</sup> While Ashchyan et al do describe the STOP-GAP trial in their discussion of treatments, the finding that the prednisolone and cyclosporine treatment arms had similar overall healing rates, 47% at six months, was not addressed. In addition, the STOP-GAP study demonstrated that serious adverse reactions, such as infections, were more common in the prednisolone group.<sup>7</sup> Based on the available data, selection of a systemic immunosuppressant should be tailored to each individual patient based on medication adverse event profiles, PG severity, and medical comorbidities, especially in light of the fact that approximately 55% of PG occurs in association with underlying systemic disease.<sup>9</sup>

- 1. Ashchyan HJ, Nelson CA, Stephen S, James WD, Micheletti RG, Rosenbach M. Neutrophilic dermatoses. Part II. Pyoderma gangrenosum and other bowel and arthritis associated neutrophilic dermatoses. *J Am Acad Dermatol*. April 2018. doi:10.1016/j.jaad.2017.11.063
- 2. Su WPD, Davis MDP, Weenig RH, Powell FC, Perry HO. Pyoderma gangrenosum: clinicopathologic correlation and proposed diagnostic criteria. *Int J Dermatol.* 2004;43(11):790-800. doi:10.1111/j.1365-4632.2004.02128.x
- 3. Weenig RH, Davis MDP, Dahl PR, Su WPD. Skin Ulcers Misdiagnosed as Pyoderma Gangrenosum. *N Engl J Med*. 2002;347(18):1412-1418. doi:10.1056/NEJMoa013383
- 4. Jockenhöfer F, Wollina U, Salva KA, Benson S, Dissemond J. The PARACELSUS score: a novel diagnostic tool for pyoderma gangrenosum. *Br J Dermatol*. May 2018. doi:10.1111/bjd.16401
- 5. Maverakis E, Ma C, Shinkai K, et al. Diagnostic Criteria of Ulcerative Pyoderma Gangrenosum. *JAMA Dermatology*. 2018;154(4):461. doi:10.1001/jamadermatol.2017.5980
- 6. Partridge ACR, Bai JW, Rosen CF, Walsh SR, Gulliver WP, Fleming P. Effectiveness of systemic treatments for pyoderma gangrenosum: a systematic review of observational studies and clinical trials. *Br J Dermatol*. June 2018. doi:10.1111/bjd.16485
- 7. Ormerod AD, Thomas KS, Craig FE, et al. Comparison of the two most commonly used treatments for pyoderma gangrenosum: results of the STOP GAP randomised controlled trial. *BMJ*. 2015;350:h2958. doi:10.1136/BMJ.H2958
- 8. Brooklyn TN, Dunnill MGS, Shetty A, et al. Infliximab for the treatment of pyoderma gangrenosum: a randomised, double blind, placebo controlled trial. *Gut*. 2006;55(4):505-509. doi:10.1136/gut.2005.074815
- 9. 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. doi:10.1111/j.1365-2133.2011.10565.x