Perioperative management of pyoderma gangrenosum

Carter K. Haag, MD,[a] Lindsay Bacik, MD,[b] Emile Latour, MS,[c] Daniel C. Morse, MD,[d] Nicole M. Fett, MD, MSCE,[a] and Alex G. Ortega-Loayza, MD[a]
Portland, Oregon; Hershey, Pennsylvania; and Houston, Texas

Pyoderma gangrenosum (PG) classically presents with an acute inflammatory stage, characterized by rapid evolution of painful ulcerations. The pathergy associated with PG lesions complicates disease management. Although PG is commonly treated with immunosuppression, some patients have refractory noninflammatory ulcers. In this subpopulation, there are case reports of successful surgical treatment. However, there is no consensus on optimal perioperative treatment for patients with PG undergoing surgery of any kind, PG related or otherwise. Therefore, we conducted a comprehensive literature review describing perioperative management practices and risk factors that may predict response to surgical intervention. We identified 126 cases of surgical intervention in patients with active PG; among these, only 16.7% experienced postoperative disease progression. No perioperative treatments or clinical risk factors were identified as statistically significant predictors of disease recurrence. Although limited by case series design and publication bias, this study is a valuable means of hypothesis generation for this rare condition. (J Am Acad Dermatol 2020;83:369-74.)

Key words: immunosuppressants; perioperative management; postoperative treatment; prophylaxis; pyoderma gangrenosum; surgery.

Pyoderma gangrenosum (PG) is a neutrophilic dermatosis that typically presents as a small pustule, surrounded by a halo of inflammation, that extends rapidly into a painful ulceration with undermined wound edges and violaceous borders.[1,2] PG is diagnosed by excluding other similar entities caused by infections, vasculopathies, neoplasms, and various inflammatory conditions.[3] Inflammatory bowel disease (IBD), rheumatologic disorders, and hematologic malignancies are comorbid conditions frequently associated with PG.[4] The disease course of PG is characterized by an initial active, inflammatory stage, after which some people heal with suppression of the acute inflammation. However, there is a subgroup of people with PG who, after acute inflammation is controlled, are left with chronic noninflammatory ulcers. These people may benefit from surgical intervention. Pathergy, in which injury to the skin initiates a new PG lesion or exacerbates a preexisting one, is a characteristic finding of PG.[5] Due to the risk of pathergy, physicians are reluctant to perform procedures on patients with PG, and perioperative immunosuppression is often used in patients with active or inactive disease who are undergoing surgery related, or unrelated, to PG.[5] Currently, there is no consensus on perioperative treatment regimens, leaving providers to rely on past experiences, anecdotal data, and small case studies.[2] Previously documented surgical interventions for treating PG include ulcer excision, grafting of autologous cultured keratinocytes, and skin or muscle flap coverage, all of which have typically been attempted only after the inflammatory phase of PG was controlled with systemic immunosuppressive therapy.[6] Split-thickness skin grafting has also been used successfully, but only after prolonged courses of immunosuppressive therapy.[1,7]

Through a comprehensive literature review, we sought to assess for risk factors associated with disease recurrence or worsening after surgery and

From the Department of Dermatology, Oregon Health & Science University, Center for Health & Healing, Portland[a]; Department of Dermatology, Penn State University School of Medicine, Hershey[b]; Knight Cancer Institute, Oregon Health & Science University, Portland[c]; and Department of Dermatology, McGovern School of Medicine at the University of Texas Health Sciences Center, Houston.[d]

Funding sources: None.
Conflicts of interest: None disclosed.
IRB approval status: Not applicable.

Accepted for publication January 3, 2020.
Reprints not available from the authors.

Correspondence to: Alex G. Ortega-Loayza, MD, Department of Dermatology, Oregon Health & Science University, Center for Health & Healing, 3303 SW Bond Ave, Portland, OR 97239. E-mail: ortegalo@ohsu.edu.

Published online January 9, 2020.
0190-9622/$36.00

https://doi.org/10.1016/j.jaad.2020.01.002

to evaluate disease management practices used in the perioperative period.

METHODS

We performed a literature search of English language publications using the PubMed/MEDLINE database from inception until April 2018. The database search was performed to identify articles describing the perioperative immunosuppressive regimens used in patients with PG, using *pyoderma gangrenosum*, *surgery*, *preoperative*, *postoperative*, and *perioperative management* as Medical Subject Headings terms and keywords. The bibliographies of all selected articles were examined to further identify relevant articles. Citations of retrieved articles were analyzed to extract publications not identified in the database search. Inclusion criteria included all types of PG; pediatric and adult patients; and patients undergoing operations related to, and not related to, the treatment of PG. *Active PG* was defined as patients with current PG ulcers or currently taking immunosuppressive medication for the prevention of new ulcers. *Inactive PG* was defined as patients with a past history of PG ulcers that have healed and who are no longer taking immunosuppressive medication. *Recurrence* was defined as the expansion in diameter of preexisting PG ulcers, the appearance of new PG ulcers at the surgical site or at other anatomic locations, or the recurrence of a PG ulcer treated with surgery. We excluded articles describing the development of PG after surgery (postsurgical PG), those published in a language other than English, and those that did not provide detailed information about a patient's perioperative treatment regimen. All cases were reviewed by at least 2 authors to ensure the accuracy of diagnosis.

Descriptive statistics were used to summarize the demographic and clinical characteristics of the study sample. Means and standard deviations were calculated for continuous variables; medians and interquartile ranges (IQRs) were used when data were skewed. Frequencies and percentages were used for categorical variables. To compare group differences, *t* tests and Wilcoxon's rank sum tests were used for continuous data, and chi-square tests and Fisher's exact tests were used for categorical data. Analyses were performed using R (R Core Team, Vienna, Austria). $P < .05$ was considered statistically significant.

CAPSULE SUMMARY

- There is no consensus regarding perioperative medical management for patients with pyoderma gangrenosum (PG) undergoing surgery related, or unrelated, to their PG ulcers.
- There was no statistically significant perioperative regimen that was most efficacious for preventing progression of disease after surgery; however, only 16.7% of patients progressed after surgery.

RESULTS

A total of 126 cases from 81 publications were included in the study (Table I). Of the 126 cases, 21 patients (16.7%) experienced recurrence of PG ulcers after surgery. In comparing the recurrence and nonrecurrence groups, the average age of patients was 52.0 years and 50.6 years, respectively ($P = .762$). There was a predominance of women in both groups (76.2% vs 68.6%, $P = .607$). Common comorbid diseases, including IBD, rheumatoid arthritis, and malignancy, were present in 38.1% of patients (8/21) in the recurrence group, compared with 39.0% in the nonrecurrence group ($P = .415$). In the recurrence group, the median duration of PG before clinical presentation was 7.0 months (IQR, 1.1-36.0), compared with 2.0 months (IQR, 0.4-7.0) in the nonrecurrence group ($P = .105$). Median ulcer area was 121.0 cm^2 (IQR, 14.5-177 cm^2) and 72.0 cm^2 (IQR, 30.0-130.0 cm^2) in the recurrence and nonrecurrence groups, respectively ($P = .678$). Ulcers were most often found on the extremities in both groups (61.9% recurrence vs 63.8% nonrecurrence; $P = .399$).

The majority of the patients who did experience disease recurrence had active disease at the time of surgery, at 86.7% (13/15). However, most patients with active disease at the time surgery did not experience progression of their disease: 81.7% (76/93) of patients with active disease at the time of surgery did not experience recurrence ($P = .329$). There were 6 patients with recurrence and 15 without recurrence whose disease status was not known at the time of surgery. The overwhelming majority (91.3%) of patients received immunosuppression in the perioperative period. Of those who did not receive immunosuppression, hyperbaric oxygen was used in 4 of 11 cases (36.4%). In comparing perioperative immunosuppressive therapy between the recurrence and nonrecurrence groups, we found no statistically significant difference in the proportion treated with preoperative (90.5% vs 95.2%; $P = .330$) or postoperative (90.5% vs 92.4%; $P = .672$) immunosuppression. There were 2 patients

Abbreviations used:

IBD: inflammatory bowel disease
IQR: interquartile range
PG: pyoderma gangrenosum

in the recurrence group and 9 in the nonrecurrence group who did not receive either preoperative or postoperative immunosuppression.

The data contained multitudes of various preoperative and postoperative treatment regimens for patients with PG; we grouped the most commonly used medications into 6 categories: systemic corticosteroids, systemic cyclosporine, combination therapies (2 or more medications, often including corticosteroids and/or cyclosporine), other less-frequently used treatment regimens such as methotrexate and azathioprine, no treatment at all, and undescribed regimens. None of the categories of medications reached statistical significance when comparing the recurrence versus nonrecurrence groups. evaluating preoperative treatment regimens were evaluated, the lowest percentage of recurrence occurred in patients taking no medications at all, at 10.0% (1/10), followed by corticosteroid monotherapy, at 11.4% (5/44). Patients using combination treatment regimens before surgery, such as corticosteroids and cyclosporine, experienced recurrence at the highest rate, at 20.7% (12/58). Conversely, when considering postoperative treatment regimens, the lowest rates of recurrence among those described were seen with patients taking combination therapies, at 9.7% (3/31). The highest rate of recurrence among postoperative treatments was seen with patients taking no immunosuppressive medications at all, at 31.0% (9/29), which could also be influenced by initial disease mismanagement.

DISCUSSION

The utility and effectiveness of surgical therapy for patients with PG, whether to treat PG or for non–PG-related indications, is a controversial issue. Central to the debate is the threat of pathergy, which is estimated to be present in 20% to 30% of cases.[8] Due to pathergy, the conventional wisdom is to avoid any traumatic events, such as surgery, to the skin of patients with PG. However, the decision to perform procedures in patients with PG is complex. In certain circumstances, skin grafting of PG ulcerations may be used to reduce the morbidity associated with open wounds. Closure of open wounds by skin grafting is used to prevent secondary infections.[7] Similarly, there are successful reports of treating PG by using gentle debridement, free flap transfers, and split-thickness skin grafting.[4] One of our primary objectives was to evaluate the risk factors associated with disease recurrence or worsening after procedures in patients with PG.

In our review, we found that only 21 of 126 patients (16.7%) with active or inactive PG experienced recurrence or worsening of their ulcers after surgical intervention. This number may be lower than that seen in practice because of publication bias. Almost no 2 regimens were alike when accounting for medication(s) used, dose of medication(s), and duration of treatment (Table II). The most common medications used were systemic corticosteroids, systemic cyclosporine, and combination regimens, often including 1 or both of corticosteroids and cyclosporine. We found no perioperative immunosuppressive regimen to be superior to any other. For example, patients receiving no immunosuppressive medications in the preoperative period had the lowest rate of recurrence at 10.0% (1/10), and patients receiving no immunosuppression in the postoperative period experienced recurrence at the highest rate, at 31.0% (9/29). Hyperbaric oxygen has been used as a potential treatment for refractory PG ulcers in an effort to improve tissue perfusion and accelerate wound healing without inhibiting the function of immune cells such as neutrophils, fibroblasts, and macrophages.[9] It was used in 10.3% (13/126) of the cases we reviewed, and in 4 of those cases, it was used without adjuvant immunosuppression with reported successful treatment without recurrence. We were limited in our ability to draw conclusions comparing treatment regimens because of the lack of validated outcomes measures, small number of patients who had disease recurrence, and wide variety of treatment regimens.

When we considered duration of perioperative immunosuppression, we found no evidence for extending treatment for longer than 30 days before or after surgery. However, this may be attributable to the natural severity of the disease, with more mild disease being predisposed to successful treatment and shorter immunosuppression course, rather than the efficacy of the immunosuppression itself. We did not find any evidence that any particular type of surgical intervention, such as split-thickness skin grafts or free flap transfers, was correlated with increased disease recurrence. Interestingly, our estimated recurrence rate of 16.7% among surgically treated patients is similar to that described in another retrospective review, in which 15.1% of patients with PG experienced postoperative recurrence.[10] Of the 16.7% of patients who experienced recurrence after surgery, 90.5% (19/21) of the operations were for treating PG ulcers or PG-related complications.[10]

Table I. Comparison of patient demographics and disease characteristics

Measure	All patients	Recurrence	No recurrence	*P* value
Number of patients, n (%)	126 (100.0)	21 (16.7)	105 (83.3)	
Age, y, mean (SD)	50.86 (18.74)	52.00 (16.48)	50.63 (19.24)	.762
Sex, n (%)				
Female	88 (69.8)	16 (76.2)	72 (68.6)	.607
Male	38 (30.2)	5 (23.8)	33 (31.4)	
PG comorbidities, n (%)				
Autoimmune/inflammatory	27 (21.4)	3 (14.3)	24 (22.9)	.415
Infection	2 (1.6)	1 (4.8)	1 (1.0)	
Malignancy	20 (15.9)	4 (19.0)	16 (15.2)	
None	77 (61.1)	13 (61.9)	64 (61.0)	
Previous episode(s) of PG,* n (%)				
Yes	30 (23.8)	7 (33.3)	23 (21.9)	.271
No	96 (76.2)	14 (66.7)	82 (78.1)	
Duration of PG until presentation for surgery, months, median (IQR)	2.00 (0.45-8.00)	7.00 (1.05-36.00)	2.00 (0.42-7.00)	.105
Current location of PG, n (%)				
Extremities	80 (63.5)	13 (61.9)	67 (63.8)	.699
Trunk	33 (26.2)	5 (23.8)	28 (26.7)	
Both	6 (4.8)	2 (9.5)	4 (3.8)	
None	7 (5.6)	1 (4.8)	6 (5.7)	
Size of ulcer, cm^2, median (IQR)	72.00 (29.25-150.00)	121.00 (14.50-177.00)	72.00 (30.00-130.00)	.280
Active PG at time of surgery, n (%)				
Yes	89 (70.6)	13 (61.9)	76 (72.4)	.329
No	16 (12.7)	2 (10.0)	17 (15.7)	
Not available	21 (16.7)	6 (30.0)	15 (13.9)	
Preoperative treatment regimen, n (%)				
Yes	119 (94.4)	19 (90.5)	100 (95.2)	.330
No	7 (5.6)	2 (9.5)	5 (4.8)	
Duration of preoperative immunosuppressive regimen, days, n (%)				
≤30	41 (32.5)	6 (28.6)	35 (33.3)	.214
>30	25 (19.8)	7 (33.3)	18 (17.1)	
Not available	60 (47.6)	8 (38.1)	52 (49.5)	
Indication for operation, n (%)				
Non−PG-related surgery	9 (7.1)	1 (4.8)	8 (7.6)	1.000
PG-related complication	112 (88.9)	19 (90.5)	93 (88.6)	
None	5 (4.0)	1 (4.8)	4 (3.8)	
Operation, n (%)				
Skin graft	80 (63.5)	13 (61.9)	67 (63.8)	.298
Skin graft combination	22 (17.5)	5 (23.8)	17 (16.2)	
Flap	6 (4.8)	1 (4.8)	5 (4.8)	
Wound treatment	12 (9.9)	0 (0.0)	12 (11.4)	
Other	6 (4.8)	2 (9.5)	4 (3.8)	
Postoperative treatment regimen, n (%)				
Yes	116 (92.1)	19 (90.5)	97 (92.4)	.672
No	10 (7.9)	2 (9.5)	8 (7.6)	
Duration of postoperative regimen, days, n (%)				
≤30	13 (10.3)	0 (0.0)	13 (12.4)	.544
>30	31 (24.6)	3 (14.3)	28 (26.7)	
Not available	82 (65.1)	18 (85.7)	64 (61.0)	
Last follow-up, months, median (IQR)	11.00 (5.75-12.00)	1.65 (1.48-1.82)	12.00 (6.00-12.00)	.035
Mortality (%)				
Yes	2 (1.6)	2 (9.5)	0 (0.0)	.037
No	100 (79.4)	18 (85.7)	82 (78.1)	
Not available	24 (19.0)	1 (4.8)	23 (21.9)	

IQR, Interquartile range; *PG*, pyoderma gangrenosum.
*Cases of postsurgical PG were excluded from this review.

Table II. Comparison of perioperative immunosuppressive treatment regimens

	Preoperative treatment regimen (P = .495)			Postoperative treatment regimen (P = .236)		
Type of therapy	n	Recurrence, n (%)	No recurrence, n (%)	n	Recurrence, n (%)	No recurrence, n (%)
Cyclosporine	7	1 (14.3)	6 (85.7)	8	2 (25.0)	6 (75.0)
Corticosteroids	44	5 (11.4)	39 (88.6)	26	4 (15.4)	22 (84.6)
Combination therapy*	58	12 (20.7)	46 (79.3)	31	3 (9.7)	28 (90.3)
Other	5	1 (20.0)	4 (80.0)	10	1 (10.0)	9 (90.0)
None	10	1 (10.0)	9 (90.0)	29	9 (31.0)	20 (69.0)
Unspecified	2	1 (50.0)	1 (50.0)	22	2 (9.1)	20 (90.9)
Total	126	21 (16.7)	105 (83.3)	126	21 (16.7)	105 (83.3)

*Combination therapy refers to patients placed on multiple medications for the treatment of PG (eg, cyclosporine and corticosteroids).

However, the STOPGAP trial (Study of Treatments fOr Pyoderma GAngrenosum Patients) found that 30% of patients treated with cyclosporine and 28% of patients treated with prednisone experienced recurrence after initially healing. Therefore, the recurrences we observed may not be directly attributable to the surgical intervention itself but, rather, the natural history of the disease.[11] Overall, very few patients experienced recurrence in the postoperative period, and we found no statistically significant risk factors associated with recurrence. A recent clinical review of postoperative PG has suggested that patients who require additional surgery or debridement after the diagnosis of postoperative PG should be treated with immunosuppression in the perioperative period.[12] The rate of PG recurrence after surgical procedures was less than the reported rate of recurrence without surgical intervention. None of the perioperative treatment regimens were independently associated with recurrence, including no treatment at all. However, conclusions were again limited by sample size.

Surgical interventions were not included in a previously proposed general PG treatment algorithm.[13] It is possible that patients with PG who do not heal with immunosuppression alone may benefit from surgical treatment of their ulcers. Future research should additionally be directed toward examining the factors contributing to nonhealing ulcers in patients with inactive disease, such as significant limb edema, medical therapies that inhibit healing, superimposed infection, and inadequate wound care. Our literature review indicates that prospective trials are needed to assess the risks and benefits of surgery in patients with PG who do not heal with immunosuppression alone and to determine the optimal perioperative immunosuppressive regimen.

One of the strengths of our study is that, to our knowledge, this is one of the largest compilations of perioperative treatment regimens for patients with PG, a rare disease for which dogma exists to avoid surgical intervention. The retrospective nature of the study limits our ability to draw conclusions about the efficacy or necessity of perioperative immunosuppression in PG. An additional limitation of the study is that our definition of *active PG* includes patients who are actively taking immunosuppressive medications for the prevention of new PG ulcers; however, some patients with a history of PG could be taking immunosuppressive medications for comorbid diseases, such as IBD, leading to patients being incorrectly labeled as having active PG. Furthermore, we did not have data on 21 of 126 patients regarding whether they had active PG at the time of surgery. Our study is also limited because the majority of the data is composed of case reports and case series and by publication bias, which can be skewed both for and against the operative treatment of PG.

CONCLUSION

The perioperative treatment of PG is a clinical challenge, largely attributable to PG's potential for pathergy. Consensus among the medical community for the ideal medical therapy and duration of treatment is lacking. In our retrospective review, we were unable to find any statistically significant data supporting any 1 particular treatment as the most efficacious in the perioperative setting for preventing recurrence of PG after surgical intervention. We were also unable to observe any statistically significant risk factors for disease recurrence or worsening. Almost all of the surgeries were performed to treat PG, and recurrence of PG occurred in 16.7% of the cases. Given the rarity of PG, large, multicenter, prospective, randomized studies are needed to determine the optimal perioperative treatment regimen for preventing recurrence of PG after surgical intervention.

REFERENCES

1. Niezgoda JA, Cabigas EB, Allen HK, Simanonok JP, Kindwall EP, Krumenauer J. Managing pyoderma gangrenosum: a

synergistic approach combining surgical debridement, vacuum-assisted closure, and hyperbaric oxygen therapy. *Plast Reconstr Surg*. 2006;117(2):24e-28e.

2. 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.
3. Braswell SF, Kostopoulos TC, Ortega-Loayza AG. Pathophysiology of pyoderma gangrenosum (PG): an updated review. *J Am Acad Dermatol*. 2015;73(4):691-698.
4. Ahronowitz I, Harp J, Shinkai K. Etiology and management of pyoderma gangrenosum: a comprehensive review. *Am J Clin Dermatol*. 2012;13(3):191-211.
5. Campbell C, Callen J. Misdiagnosed periocular pyoderma gangrenosum requiring ectropion repair with development of second lesion of pyoderma gangrenosum at graft site. *JAMA Dermatol*. 2016;152(4):491-492.
6. Cabalag MS, Wasiak J, Lim SW, Raiola FB. Inpatient management of pyoderma gangrenosum: treatments, outcomes, and clinical implications. *Ann Plast Surg*. 2015;74(3):354-360.
7. Pichler M, Larcher L, Holzer M, et al. Surgical treatment of pyoderma gangrenosum with negative pressure wound therapy and split thickness skin grafting under adequate immunosuppression is a valuable treatment option: case series of 15 patients. *J Am Acad Dermatol*. 2016;74(4):760-765.
8. Ma G, Jones G, MacKay G. Pyoderma gangrenosum: a great marauder. *Ann Plast Surg*. 2002;48(5):546-552. discussion 552-3.
9. Longobardi P, Hoxha K, Bennett MH. Is there a role for hyperbaric oxygen therapy in the treatment of refractory wounds of rare etiology? *Diving Hyperb Med*. 2019;49:216-224.
10. Xia FD, Liu K, Lockwood S, et al. Risk of developing pyoderma gangrenosum after procedures in patients with a known history of pyoderma gangrenosum-a retrospective analysis. *J Am Acad Dermatol*. 2017;78(2):310-314.e1.
11. 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;350:1-8.
12. Tolkachjov SN, Fahy AS, Cerci FB, Wetter DA, Cha SS, Camilleri MJ. Postoperative pyoderma gangrenosum: a clinical review of published cases. *Mayo Clinic Proc*. 2016;91:1267-1279.
13. Alavi A, French LE, Davis MD, Brassard A, Kirsner RS. Pyoderma gangrenosum: an update on pathophysiology, diagnosis and treatment. *Am J Clin Dermatol*. 2017;18(3):355-372.