CLINICAL MANAGEMENT

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Pyoderma Gangrenosum: A Critical Appraisal

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GENERAL PURPOSE:

To provide information about pyoderma gangrenosum (PG), including pathophysiology, diagnostic criteria, and treatment.

TARGET AUDIENCE:

This continuing education activity is intended for physicians, physician assistants, nurse practitioners, and nurses with an interest in skin and wound care.

LEARNING OBJECTIVES/OUTCOMES:

After participating in this educational activity, the participant should be better able to:

1. Recognize the pathophysiology of PG.
2. Select the diagnostic criteria for PG.
3. Identify the treatments available for PG.

ABSTRACT

Pyoderma gangrenosum (PG) is an uncommon cutaneous disease, presenting with recurrent painful ulcerations most commonly on the lower extremities. The diagnosis is made according to a typical presentation, skin lesion morphology, skin biopsy, histopathology, and the exclusion of other etiologies. Classically, PG presents with painful ulcers with well-defined violaceous borders; other variants including bullous, pustular, and vegetative/granulomatous can also occur. Treatment of PG involves a combination of topical and systemic anti-inflammatory and immunosuppressive medications, wound care, antimicrobial agents for secondary infections, and treatment of the underlying etiology. This article is a continuing education review of the literature with a focus on the clinical application of the pathophysiology, diagnosis, and treatment of this challenging disease.

KEYWORDS: cutaneous disease, inflammatory bowel disease, neutrophilic dermatosis, pyoderma gangrenosum, ulcer

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INTRODUCTION

Pyoderma gangrenosum (PG) is an uncommon ulcerative cutaneous disease with a unique clinical presentation. It belongs to the neutrophilic dermatoses group of inflammatory dermatoses and is frequently associated with other systemic diseases. Despite the original unaltered term, *pyoderma gangerenosum*, this disease has no infectious etiology and no tissue-related vascular gangrene. Pyoderma gangrenosum usually occurs between 11 and 89 years of age, with a published case series reporting a mean age between 50 and 63 years (Table 1).[1–6] Fewer than 5% of PG cases occur in children and infants. Associated systemic diseases have been documented in 33% to 75% of patients.[1–6] Comorbidities most commonly associated with PG include inflammatory bowel disease (IBD), rheumatoid arthritis, other inflammatory or autoimmune conditions, hematologic malignancy, and solid tumors.[7–9]

The skin biopsy of the edge of a PG lesion can result in nonspecific histopathology, especially when the disease is partially treated or minimally inflamed. The histopathologic presentation depends on the phase of the lesion sampled and the location of the biopsy. Generally, acute lesions have a dense neutrophilic infiltrate with or without very localized vasculitis changes. In Binus and colleagues'[6] retrospective series of 103 patients, only 7% had a classic biopsy documented. This diagnosis is one of exclusion, requiring clinicopathologic correlation.[7–9] A biopsy can help to rule out other diagnoses including primary vasculitis, other inflammatory conditions, infections, and malignancy. A biopsy of a subacute lesion of PG often demonstrates a nonspecific mixed inflammatory infiltrate with the diagnosis made clinically, especially if a patient has a common associated systemic condition such as IBD, rheumatoid/seronegative arthritis, or hematopoietic malignancy.

The favored PG pathogenic hypothesis is autoimmune with defects in cell-mediated immunity, neutrophil and monocyte function, and humoral immunity. In addition, a patient's genetic background can lead to aberrant activation of innate-immune complexes called inflammasomes. The activated immune system leads to increased levels of dermal cytokines and subsequent contribution to neutrophilic tissue infiltration. Pyoderma gangrenosum also can be induced by medications such as granulocyte colony-stimulating factor, isotretinoin, propylthiouracil, and sunitinib. In a recently published article, cocaine was found to be the most common agent to trigger a PG reaction.[10]

The management of PG is challenging, and a decision regarding the appropriate therapy depends on the location, number, size of the lesion(s), the course of the disease (indolent vs aggressive), and other factors, including associated morbidity. Depending on the extent and type of lesion, the treatment can be topical, intralesional, systemic anti-inflammatory (corticosteroids), or immunosuppressive (cyclosporine). Targeted therapies including anti–tumor necrosis factor (TNF) α biologic agents have been used in the past few years, but newer targeted therapies may revolutionize the future management of PG.

METHODS

Information for this review was gathered from textbooks; PubMed, EMBASE, MEDLINE literature searches; and expert opinion. The PubMed, EMBASE, and MEDLINE searches were performed using search words including "pyoderma gangrenosum" together with additional keywords such as "pathophysiology," "management," and "therapy."

The search included articles in English published between 1980 and 2017. A total of 2179 articles were found, including 504 review articles, 161 articles about management, 120 articles about pathophysiology, and 48 clinical trials. After narrowing the search terms to pathophysiology and management, only 30 articles were relevant and selected for inclusion.

RESULTS

Pathophysiology

The pathophysiology of PG is yet to be fully elucidated, but it is most likely a complex reaction pattern with convergent pathways. Some of the factors contributing to the clinical manifestations of PG include neutrophil dysfunction, genetic mutations, and abnormal inflammatory responses.

Table 1.

SUMMARY OF 6 PYODERMA GANGRENOSUM CASE SERIES

Reference Case Series	Von den Driesch et al[1] (1997)	Hasselmann et al[2] (2007)	Saracino et al[3] (2011)	Binus et al[6] (2011)	Pereira et al[4] (2013)	Ye MJ (2014)[5]
No. of patients	44	18	26	103	24	23
Females	30 (68%)	14 (78%)	17 (65%)	78 (76%)	19 (79%)	16 (70%)
Males	14 (32%)	4 (22%)	9 (35%)	25 (24%)	5 (21%)	7 (30%)
Mean age, y	50 (11–80)	53 (26–78)			58 (SD, 25)	63 (30–89)
Idiopathic	20 (45%)	12 (67%)		27 (26%)	6 (25%)	12 (52%)
Associations	24 (55%)	6 (33%)	15 (58%)	76 (74%)	18 (75%)	11 (48%)
Inflammatory bowel disease	14 (32%)	2 (11%)	4 (15%)	35 (35%)	7 (29%)	
Other inflammatory		Rheumatoid arthritis, diabetes mellitus, 2 (11%)	Rheumatoid arthritis, 5 (19%)	Seronegative arthritis, 20 (19%)	3 (12%)	
Hematologic abnormalities/ malignancies	10 (23%)	Monoclonal gammopathies 2 (11%)		21 (20%)	6 (25%)	
Solid tumors			Additional associations: psoriasis, 11%; hepatitis, 9%	2 (8%)		
Site: legs	Predilection			17 (74%)	13 (57%)	
Ulcer type				15 (63%)	18 (78%)	
Bullous				2 (8%)	2 (9%)	
Pustular					4 (17%)	1 (4%)
Vegetative/granulomatous					1 (4%)	2 (9%)
Lesions						
Single	23 (52%)				15 (63%)	
Multiple	21 (48%)				9 (37%)	
Mortality	8/42 follow-up = 19%	1 (6%) (short follow-up)	27%	10%		5 (22%)

Numbers have been rounded to the nearest whole number.

The presence of clonal T-cell expansion has been reported in PG lesions, supporting the possibility of an aberrant T-cell response.[11] Inflammasomes are multiprotein oligomers often expressed in myeloid cells and keratinocytes. They may be involved in the recruitment or activation of polymorphonuclear neutrophils, as seen in cases associated with a mutation in the gene *PSTPIP1* (proline-serine-threonine phosphatase-interacting protein 1) on chromosome 15. A mutation in *JAK2* (Janus kinase 2), a nonreceptor tyrosine kinase involved in signaling via several cytokines, has also recently been identified in patients with PG.[12,13] Elevated levels of inflammatory mediators have been detected in lesions of PG, suggesting a pathologic inflammatory process. T cells and macrophages likely play a key role in the PG disease pathogenesis via abnormal cytokine signaling.[11]

Interleukin 23 (IL-23), a cytokine that plays an important role in driving IL-17–mediated and neutrophil-rich inflammation, is up-regulated at the gene expression and protein level in PG lesions. This suggests pathogenic similarities with other inflammatory diseases, including psoriasis.[14]

Clinical Forms of PG and Its Variants

Four morphologic PG variants are known:

1. ulcerative
2. vesicular-bullous (atypical)
3. pustular
4. superficial granulomatous/vegetative.

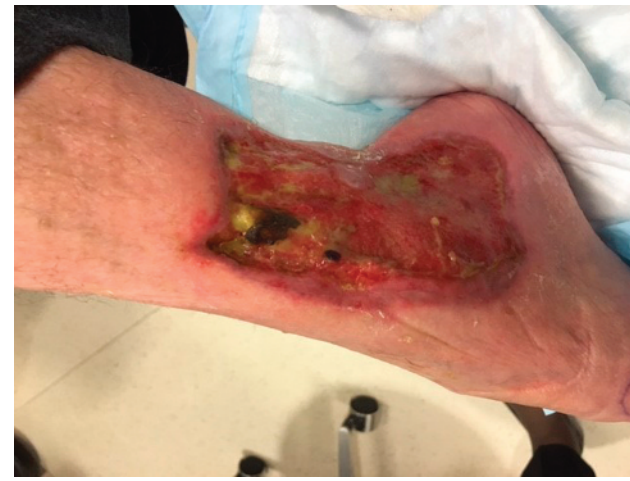
Postsurgical PG and peristomal PG usually present with an ulcerative morphology. Each PG variant has different clinical presentations and systemic associations (see Supplemental Digital Content 1, http://links.lww.com/NSW/A10, and Figures 1, 2, and 3).

The vesicular-bullous variant presents on the face and the upper extremities, especially the dorsal hands. Clinical presentation overlaps with the superficial bullous variant of the neutrophilic dermatosis Sweet syndrome (often with fever and arthralgias) that can occur most often in the setting of infections, drug use, or acute myelogenous leukemia.

The pustular type consists of multiple, small, sterile pustules. These pustules usually regress without scarring, but can evolve into classic PG. This form is most commonly reported in patients with IBD, but a similar eruption may be seen in patients with Behçet disease or as an inflammatory bowel–associated dermatosis.

The superficial granulomatous or vegetative type is a rare, usually more benign variant that favors the trunk and often follows trauma (eg, postsurgery). There is a superficial erosion or ulceration with heaped-up, often necrotic, margins. Microscopic examination of a skin biopsy will reveal less intense neutrophilic infiltrate with a more characteristic suppurative and granulomatous histology. It is clinically unlikely to be associated with an underlying disease and responds to less aggressive therapy.

Figure 1.
PYODERMA GANGRENOSUM WITH UNDERMINED BORDER AND SOME NECROTIC TISSUE IN ULCER BED



Courtesy of Dr Afsaneh Alavi.

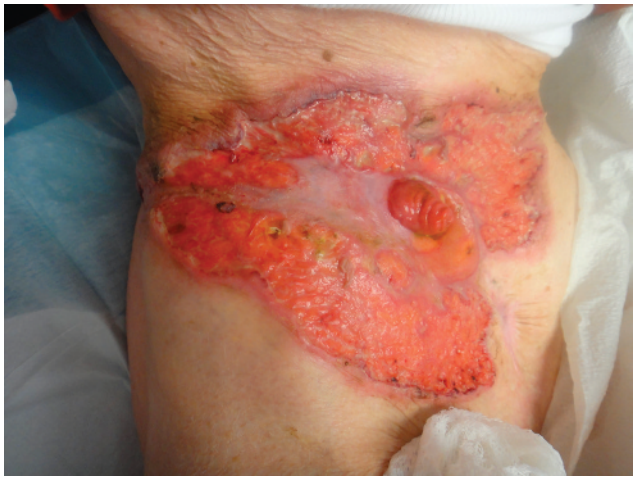
Clinical variants have been described based on the clinical presentation or the location of the lesion. Extra mucocutaneous sterile neutrophilic infiltrate has been reported in the bones, lung, liver, pancreas, spleen, kidneys, and central nervous system of patients with PG.[15,16]

Pyoderma Gangrenosum and Associations

Pyoderma gangrenosum is a common extracutaneous manifestation of IBD, more commonly associated with ulcerative colitis (5%–12%) than Crohn disease (1%–2%). Between 50% and 75% of patients with PG have an antecedent, coincident, or subsequent associated disease or condition. In a systematic literature review, DeFilippis et al[17] reviewed 208 articles describing 823 cases of PG. Thus far, the correlation of the appearance of PG with IBD activity is still controversial,[18-20] although individual patients may have PG associated with IBD activity. In addition, PG does not always clear upon treatment of the underlying bowel disease, and response to surgical resection of the abnormal bowel is unpredictable.[20]

The other common associated disorders include arthritic and hematologic disorders. In a retrospective study[6] of 103 patients with PG (74% with an associated systemic disease, including IBD [35%]), 20% had hematologic disorders, 19% had seronegative arthritis, and 26% were idiopathic.

Figure 2.
MORE EXTENSIVE BUT SUPERFICIAL ULCERATION

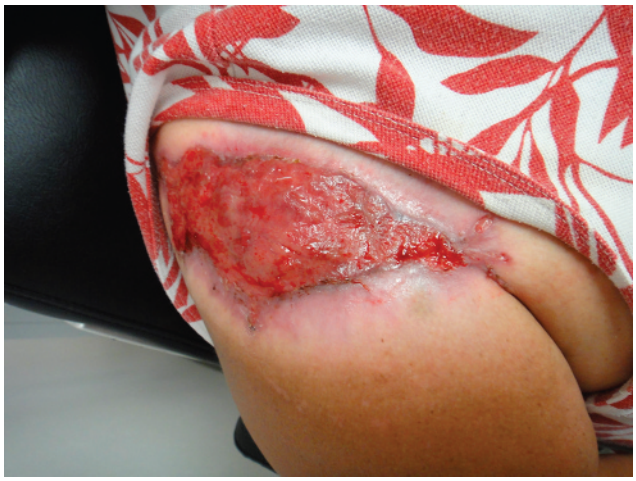


Courtesy of Dr Afsaneh Alavi.

Pyoderma gangrenosum plus syndromes: PG has been described clinically with other inflammatory disorders, including syndrome combinations with

- PASH: PG, acne, and suppurative hidradenitis
- PAPASH: PG, acne, pyogenic arthritis, and suppurative hidradenitis
- PsPASH: Psoriatic arthritis, PG, acne, and suppurative hidradenitis
- PAC: PG, acne, and ulcerative colitis
- PAPA: PG, acne, and pyogenic arthritis
- PASS: PG, acne, and spondyloarthritis

Figure 3.
POSTSURGICAL PYODERMA GANGRENOSUM



Courtesy of Dr Afsaneh Alavi.

The rarity of these syndromes complicates the establishment of evidence-based treatment guidelines. They all share a common pathogenesis involving a dysregulated innate immune system with abnormal IL-1 signaling leading to sterile neutrophilic inflammation. Treatment can be challenging because of a lack of response to standard treatment modalities.[13,21,22]

Diagnosis

The diagnosis of PG is clinical and requires the exclusion of other disorders in the differential diagnosis. The histopathology is nonspecific for this disease, and it serves to rule out other pathologic findings. Nevertheless, the classic histologic presentation is neutrophil-rich cell infiltrate in the dermis, but this is limited to early lesions. Pyoderma gangrenosum also does not have a specific laboratory workup. The differential diagnosis should include not only unique infections such as deep fungus infection (especially North American blastomycosis) and mycobacterial infections, but also other noninfectious etiologies such as bromoderma or iododerma.

(The Table Supplemental Digital Content 1, http://links.lww.com/NSW/A10) lists relevant workup and differential diagnoses providers should consider. The main emphasis should be on obtaining a thorough medical history and meticulous physical examination to enhance the clinical investigation and diagnosis. However, there is no internationally accepted diagnostic criterion for PG. In 2004, Su et al[23] proposed diagnostic criteria where both major criteria and at least 2 minor criteria (out of 4) are required to establish the diagnosis. One of the major criteria is the exclusion of other causes of cutaneous ulceration (Table 2).

The pain associated with PG can be consistent with more than 1 type of wound; however, there are 2 types of ulcers that may cause excruciating pain and are confined to the lower extremities, including arterial ulcers and Martorell (hypertensive

Table 2.
PROPOSED DIAGNOSTIC CRITERIA FOR PYODERMA GANGRENOSUM[22]

Major Criteria
1. Rapid progression of a painful, necrolytic, cutaneous ulcer with an irregular, violaceous border
2. Exclusion of other causes of cutaneous ulceration
Minor Criteria
1. History suggestive of pathergy or clinical finding of cribriform scarring
2. Systemic diseases associated with pyoderma gangrenosum
3. Histopathologic findings compatible with pyoderma gangrenosum
4. Rapid response to corticosteroids

Table 3.
DIAGNOSTIC ALGORITHM FOR PYODERMA GANGRENOSUM

Complete History and Physical Examination, Skin Biopsy		
Pyoderma Gangrenosum Workup Guided by History		
Main Differential Diagnosis Categories	**Main Differential Diagnosis Examples**	**Workup**
Infection	Deep fungal infection: blastomycosis, sporotrichosis	Cultures, special stains, chest radiograph
	Protozoa: leishmaniasis	
	Bacterial: ecthyma	
	Viral: herpes simplex	
Vasculitis and autoimmune diseases	Behçet disease	Blood work, coagulopathy panel, urinalysis
	Vasculitis	ANA, anti-DNA, ENA, rheumatoid factor, C3, C4
	Cryoglobulinemia	Direct immunofluorescence (skin biopsy)
	Antiphospholipid syndrome	
	Lupus (lupus-associated neutrophilic dermatoses)	
Neutrophilic dermatoses	Sweet syndrome	Mainly a clinical diagnosis (and histology)
		ASOT, CRP, CBC
		Check for possible drug etiology
Vascular disorders	Martorell ulcer	Deep elliptical biopsy, Doppler study, ABI or angiography, venous Duplex
	Arterial ulcer	
	Venous ulcer	
Exogenous	Factitious	History, serum bromide, and iodide
	Brown recluse spider bite	
	Bromoderma	

Abbreviations: ANA, antinuclear antibody; ABI, ankle brachial index; ASOT, aspartate aminotransferase; C3, C4, complement factors 3, 4; CBC, complement blood count; CRP, C-reactive protein; ENA, extractable nuclear antigen.

ischemic) ulcers. Arterial ulcers present in the shins (usually in pressure-dependent areas) and are deep, punched-out ulcers with a fibrous base. Clinically weaker or absent pulses are noticed. Martorell ulcers are typically located on the lateral-dorsal side of the shins and are morphologically shallower necrotic ulcers; pulses are usually palpable and normal.[24–26]

Management

The main goal of therapy is to reduce the inflammatory process of PG that leads to ulceration. The choice of treatment depends on various factors including the number and size of the lesions, their location, the presence of underlying disease, and patient preference and comorbidities. Although treatment of the underlying disease is essential, a direct relationship between the severity of associated disease and PG is debatable.

Treatment also depends on the course of the disease. Roughly, PG can be divided into an aggressive type with a rapid course and the indolent form with a more protracted and slower, chronic course. Often, the latter only requires localized therapy. Systemic therapy includes high-dose corticosteroids as first-line therapy, while cyclosporine and TNF-α inhibitors have proved useful as second- and third-line therapies. For patients with limited disease, topical and intralesional corticosteroids may give sufficient results without the necessity of systemic therapy.[27] Other topical agents include topical tacrolimus (which proved useful in a small sample prospective study[28]); other reported treatments include sodium cromoglycate, nicotine, and topical dapsone (based on case reports or small case series).[29] Alavi et al[30] recently suggested an approach for treatment based on patient course, as shown in Table 3.

Other important aspects of treatment are pain control and local wound care. Pain management is an essential part of managing patients with PG. It should be addressed initially with oral administration of acetaminophen and nonsteroidal anti-inflammatory drugs for nociceptive pain (gnawing, aching, tender, and/or throbbing pain), then as necessary mild opioids such as codeine, then strong opioids such as morphine, until the patient is free of pain.[31] Initial treatment of neuropathic pain (burning, stinging, shooting, or stabbing) can be managed with gabapentin and pregabalin, along with nortriptyline at night to facilitate sleep.

Optimal wound care includes cleansing and preventing secondary infections and the appropriate utilization of antibacterial agents in the presence of localized infection, because the prevention of deep, surrounding infection is more important than tissue toxicity from the antiseptic agents.[30] Maintaining a moist wound environment is a basic principle of wound therapy. Conservative debridement (enzymatic, autolytic, or blunt surgical) to remove nonviable tissue should be performed with caution, as PG is both induced and aggravated by pathergy (minimal trauma leads to extension of the lesions). The pathergy skin test is a hypersensitivity reaction to a skin prick and can be elicited by poking the skin with a needle or a pin and is considered a specific presentation in neutrophilic dermatoses.[32]

Systemic corticosteroids are still considered to be the first-line therapy for severe, progressive disease.[33] The treatment can be administered orally (0.5–1.0 mg/kg per day) or intravenously (100 mg/d). Rapid response should be expected.[34]

Cyclosporine (2.5–5.0 mg/kg per day) is frequently used as second-line treatment and may be effective as a steroid-sparing agent and is especially useful in cases resistant to corticosteroids.

A recently published randomized controlled study[35] compared oral prednisolone (0.75 mg/kg per day) with cyclosporine (4 mg/kg per day) to a maximum dose of 75 mg and 400 mg/d, respectively, on 121 patients with PG. Both groups demonstrated the same outcome, with fewer than half of patients in either group completely healing. Other immunosuppressive medications including methotrexate, azathioprine, mycophenolate mofetil, and sulfasalazine have been suggested as clinical alternatives for PG, but have not been the subject of controlled studies.[36]

Future treatment of PG may include biologic agents. High levels of TNF-α associated with neutrophilic infiltration characterize PG as well as other inflammatory processes,[21,37] so targeted biologic therapies such as anti–TNF-α medications may therefore expand the therapeutic options. The TNF-α antagonists (etanercept, adalimumab, infliximab) have mostly been studied in case reports and small case series treating PG. One randomized controlled study performed on infliximab showed benefit for this medication in 70% of patients; however, this was a small study, completed with just 30 patients.[38] The anti–IL-12/IL-23 ustekinumab is the only IL-23 inhibitor reported to improve PG.[39,40] A patient with psoriasis treated with adalimumab who developed PG was successfully treated with ustekinumab.[39]

Interleukin 1β, a potential proinflammatory cytokine, was demonstrated to be overexpressed in lesional skin of patients with PG, which is the rationale for a potential role of IL-1 antagonists in the management of PG.[41] Canakinumab, a human anti–IL-1β monoclonal antibody, demonstrated benefit in a recently published article on 5 patients with corticosteroid-refractory PG.[42] Anakinra, a recombinant, on-glycosylated form of IL-1 receptor antagonist used to treat RA and cryopyrinopathies (rare inherited autoinflammatory disorders that are caused by mutations in *CIAS1* [cold-induced autoinflammatory syndrome 1] gene encoding the cryopyrin protein), elicited low therapeutic efficacy in 3 studies.[43–45]

Other new targeted therapies, including anti–IL-6 (tocilizumab), were successful as described in a case report on a patient with rheumatoid arthritis and PG.[46] Additional agents including anti–IL-17 medications (eg, secukinumab, ixekizumab) may be good choices for future investigation (Table 4).

CONCLUSIONS

Pyoderma gangrenosum is a neutrophilic dermatosis. Diagnosis is made based on the characteristic clinical picture and the exclusion of other diseases. In up to two-thirds of cases, PG is associated with an underlying disease, and therapy should aim to treat both PG and the associated condition. Autoinflammatory diseases are clinically characterized by recurrent episodes of sterile inflammation in the affected organs, without high titers of circulating autoantibodies and autoreactive T cells. These conditions are associated with many genetically determined alterations of the innate immune response, inducing an overproduction of active IL-1β that can lead, via the release of several proinflammatory cytokines and chemokines, to neutrophil-mediated inflammation.

Treatment of PG should involve a combination of anti-inflammatory (oral, intralesional, topical steroids) with immunosuppressive (oral cyclosporine) medications as well as antibiotics for secondary infections, topical medications (topical tacrolimus, pimecrolimus), and wound care (conservative debridement of active lesions to prevent pathergy, topical anti-inflammatories/antimicrobials, and moisture balance).

Further patient studies are necessary to establish universally accepted diagnostic criteria for PG and elucidate the exact pathophysiology and optimal treatment of this disease.

Table 4.
THERAPEUTIC APPROACH TO PYODERMA GANGRENOSUM[28]

Approach	Management
General measures	Control underlying disease
	Avoid trauma
	Pain management
	Proper local wound care
	Control of secondary infection
	Minimize edema (compression therapy)
	Optimize nutrition
	Smoking cessation
	Glycemic control
Limited disease	Topical therapy
	Potent topical corticosteroids
	Intralesional corticosteroids
	Topical tacrolimus, pimecrolimus
	Topical sodium cromoglycate
	Topical dapsone
	Topical nicotine
	5-aminosalicylic acid
Aggressive disease (systemic therapy)	Corticosteroids (0.1–1.0 mg/kg OD)
	Cyclosporine (2.5–5.0 mg/kg OD)
	Tacrolimus (0.1–0.2 mg/kg OD)
	Thalidomide (50–150 mg QHS)
	Colchicine (0.6–1.2 mg OD)
	Dapsone (100 mg OD)
	Sulfasalazine (0.5–1.0 g TID)
	Azathioprine (50–100 mg BID)
	Methotrexate (2.5–25 mg weekly)
	Mycophenolate mofetil (1.0–1.5 g BID)
	Chlorambucil (4.6 mg OD)
	Intravenous immunoglobulin (2.0–3.0 g/kg)
	Minocycline (100 mg OD)
Aggressive disease (targeted therapy)	Anti–tumor necrosis factor
	Infliximab
	Adalimumab
	Etanercept
	Anti–interleukin 1
	Anakinra
	Canakinumab
	Gevokizumab
	Anti–interleukins 12 and 23
	Ustekinumab

Abbreviations: BID, twice daily; OD, once daily; QHS, every night; TID, 3 times daily.

PRACTICE PEARLS

- Pyoderma gangrenosum is an ulcerative skin disease with unique clinical presentations.
- The classic ulcerative variant usually presents on the legs with a deep erythematous painful ulcer and undermined borders, although there are other forms: pustular, bullous, and vegetative/granulomatous.
- Diagnosis of PG is made based on a classic clinical presentation and exclusion of other causes.
- It is associated with underlying etiologies; IBD is the most common. Arthritis (rheumatoid, seronegative) and myeloproliferative disorders need to be identified or ruled out.
- Treatment should address underlying disorders and specifically be based on anti-inflammatory/immunosuppressive medications.

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