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REVIEW

Pyoderma Gangrenosum and Inflammatory Bowel Disease: Recent Insights into Epidemiology, Pathogenesis, and Therapeutic Approaches

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Abstract: Pyoderma gangrenosum (PG) is a rare neutrophilic dermatosis strongly associated with inflammatory bowel disease (IBD). This narrative review summarizes current knowledge on the epidemiology, clinical features, proposed mechanisms, and treatment of PG in patients with IBD. In addition to population-based, large cohort, and mechanistic studies, we reviewed 115 published case reports and case series describing patients with PG and IBD and synthesized demographic, clinical, and therapeutic trends. Most patients developed PG after an IBD diagnosis, with smaller proportions presenting simultaneously or before an IBD diagnosis. PG in IBD patients typically affects middle-aged adults and has a female predominance. Clinical features are heterogeneous, which complicates recognition and timely diagnosis. Treatment responses are also highly variable. Corticosteroids and immunosuppressants are commonly used as first-line therapies, but many patients require sequential or combined regimens. Biologics are increasingly used, reflecting efforts to target shared inflammatory pathways between PG and IBD; however, treatment approaches remain highly individualized. Mechanistic and genetic studies implicate Th17/Th1 immune dysregulation, IL-1β/IL-36 signaling, and gut-skin immune crosstalk. There is a critical need for longitudinal, controlled studies to clarify pathogenesis, predict outcomes, and guide evidence-based, standardized treatment approaches in this complex patient population.

Keywords: ulcerative colitis, crohn's disease, extraintestinal manifestations, neutrophilic dermatoses

Introduction

Pyoderma gangrenosum (PG) is a rare extraintestinal manifestation of inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), characterized by painful, rapidly progressive skin lesions. Although the exact pathogenesis of PG is unknown, it is thought to involve a combination of immune dysregulation and neutrophil dysfunction in patients with genetic susceptibility. PG is rare in the general population but occurs disproportionately in patients with immune-mediated systemic diseases, including IBD.[1]

The relationship between PG and IBD has been recognized for decades, but its complexity is incompletely understood. Estimates of PG prevalence among patients with IBD vary, and the timing of PG diagnosis in IBD patients differs between cohorts. PG in patients with IBD has a variable presentation influenced by age, sex, ethnicity, additional comorbidities, and IBD severity. As a result, the diagnosis of PG in IBD patients is challenging and is further complicated by the lack of universally accepted diagnostic criteria.[2]

Considering these difficulties, a better understanding of the epidemiology, clinical course, and mechanistic links between PG and IBD is essential to improve recognition, management, and patient outcomes. This review synthesizes data from pediatric and adult population-based studies, case reports, and mechanistic research to provide an updated overview of the associations between PG and IBD. We highlight current limitations and identify priorities for future investigations.

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Methods

A narrative literature review was performed to identify studies describing the association between PG and IBD. PubMed was searched using the following search terms: "pyoderma gangrenosum" AND "inflammatory bowel disease", "ulcerative colitis", "Crohn's disease", and "inflammatory bowel disease" AND "extraintestinal manifestation". We accepted the definitions of PG used by the study authors without applying additional diagnostic criteria. Two reviewers (KD, RZ) independently removed duplicate articles and screened all titles and abstracts in a blinded manner to determine relevance. Full-text articles were then independently reviewed to assess if they included information on the epidemiology, clinical features, treatments, or outcomes of PG in patients with IBD. Articles unavailable in English were excluded.

To summarize published case reports and series, data were compiled from 115 reports published within the last 10 years describing patients with both IBD and PG. Extracted variables included demographics, ulcer characteristics, disease course, treatments, and outcomes. Findings should be interpreted as exploratory rather than population-level estimates. A flowchart summarizing the search strategy is available as Supplemental Figure 1 and a full list of included case reports and series is available in Supplementary Table 1.

Epidemiology and Risk Factors for PG in IBD

Epidemiology studies consistently show that PG occurs disproportionately more among patients with IBD compared to the general population. Recent large cohort and registry studies have clarified the prevalence of PG in IBD and identified subgroups at the highest risk. These findings highlight the importance of recognizing PG as both a diagnostic and therapeutic challenge in patients with IBD. To provide context, Table 1 summarizes key epidemiology features of PG in adults and children.

IBD Prevalence in Adults with PG

Population-based analyses in the United States demonstrate a high prevalence of IBD among PG patients. In a cohort of 1,920 patients with PG, 34% also had a diagnosis of IBD compared to 0.9% among controls. Within this cohort, 17% had CD, 9.6% had UC, and the remaining 7.4% had unspecified or indeterminate IBD.[6] Other large US datasets report similar

Table 1 Epidemiologic Features of Pyoderma Gangrenosum in Adults and Children

Feature	Adults	Children
Age at Onset	Occurs at any age, most common between 20–50 years[3]	Mean age of onset reported between 9.6–15.6 years; presentation may vary depending on comorbidities[4,5]
Sex Distribution	Slight female predominance[3]	Slight female predominance in some series;[5] other reports show no differences by sex[4]
Common Comorbidities	IBD, inflammatory arthritis, and lymphoproliferative disorders[3]	Most commonly IBD, followed by hematologic disorders, vasculitis, immune deficiencies, juvenile idiopathic arthritis, or PAPA syndrome; >50% occur without an underlying disease[4,5]
PG Subtypes	Ulcerative (classic) most common; other subtypes include peristomal, vegetative, pustular and bullous[3]	Ulcerative (classic) most frequent; pustular lesions also common, especially on the head and buttocks.[4,5] Perianal/genital involvement is more common in infants.[3,4] Multiple lesions occur more often than single lesions[4]
Association with IBD	Along with erythema nodosum, PG is among the most common dermatologic disorders in patients with IBD[3]	IBD is the most frequently reported comorbidity in pediatric PG[4,5]
Outcomes	Variable: remission often requires systemic therapy; recurrence is frequent; mortality is higher than the general population[3]	Generally favorable outcomes, though recurrence may occur; long-term outcome data are limited.[4,5]

findings, with 16.3–26% of PG patients having IBD depending on the population studied.[7–9] In academic referral centers, 25.8% of PG patients had CD, and 15.4% had UC.[10]

Outside the United States, estimates of IBD prevalence in PG patients vary, likely reflecting regional differences in baseline IBD prevalence, but still consistently demonstrate an overrepresentation of IBD among patients with PG. In Spain, 15.7% of patients hospitalized for PG also had IBD,[11] and in Brazil, 20% of PG patients also had IBD.[12] In Germany, prevalence ranged from 7.6% among patients hospitalized for PG to 9.9% in wound care centers.[13,14] In Denmark, PG was strongly associated with IBD, with an adjusted odds ratio of 19.15 and an adjusted hazard ratio of 6.51 for developing IBD.[15] Population-based data in Israel found a 7.0% prevalence of CD and a 7.3% prevalence of UC in PG patients compared to 0.3% and 0.5% respectively in controls, corresponding to a 28-fold increase in the odds of PG with CD, and a 15-fold increase in the odds of PG with UC.[16,17] A single-center study further reported an IBD prevalence of 41.9% in PG patients.[18] In Argentina, 32% of adults with PG had co-occurring IBD.[19] Notably, the prevalence of UC in Japan was 32.2%, higher than reported in other international cohorts, while the prevalence of CD was only 1.6%, lower than elsewhere.[20]

While most studies do not specify PG subtype, one US study specifically evaluating peristomal PG found that 93% of patients had a history of IBD,[21] and an Australian study found that 41.7% of peristomal PG cases were associated with CD, and another 41.7% were associated with UC.[22]

PG Prevalence in Adults with IBD

Complementary data examining patients with IBD demonstrate an increased risk of developing PG, although the prevalence remains low. A 2020 meta-analysis integrating data from multiple cohorts found an average PG incidence of 0.6% among patients with IBD, with slightly higher risk among CD patients than those with UC.[2] Large US-based cohort studies report that less than 1% of patients with IBD develop PG. In Michigan, 44 of 6,225 (0.7%) patients with IBD were diagnosed with PG (OR 22.1; 95% CI: 11.1–44.0), and MarketScan identified 607 PG cases among 80,907 (0.8%) patients with IBD (OR 6.2; 95% CI: 5.5–7.0).[23] National Inpatient Sample analysis found 388 cases of PG per 100,000 hospitalizations for CD.[24]

Non-US populations show similarly low prevalence, but elevated relative to the general population. In the UK, 0.5% of patients with IBD also had PG with an odds ratio of 47.4 for CD and 29.24 for UC (difference not statistically significant).[25] In Korea, one study reported a PG prevalence of 0.8%,[26] while another found that, compared to the general population, the prevalence ratio of PG was 4.43 in patients with CD and 4.36 in patients with UC.[27] An Italian cohort found that in patients with IBD, the prevalence of PG was significantly higher than in the general population (0.42% vs 0.0005%).[28] Smaller regional cohorts from Pakistan, India, Brazil, Lithuania, Argentina, and the Middle East reported similar findings with PG prevalence ranging from 1.6–8% in patients with IBD.[29–35] In Germany, the prevalence of PG was notably higher at 16.3% among patients with IBD and ostomies.[36]

Pediatric Populations

Pediatric studies offer insight into the association between PG and IBD with fewer confounding effects from comorbidities that develop later in life. In the international ImproveCareNow registry of 32,497 patients with IBD aged ≤ 21 years, PG prevalence was 0.9%, with slightly higher rates in patients with CD (0.98%) compared to those with UC (0.72%).[37] Similarly, a cohort of Korean pediatric patients with IBD had a PG prevalence of 0.6%.[38] Among US pediatric patients with IBD and at least one dermatologic manifestation, PG prevalence was higher at 2.4%.[39]

Age

Age appears to strongly influence the prevalence of IBD in PG patients. Compared to age-matched controls, the relative prevalence of IBD was the highest in PG patients aged 18–44 years (aPR 56.8; 95% CI: 52.0–62.0), and decreased with age (45–64 years: aPR 31.4; and >65 years: aPR 20.9).[6] Similarly, US studies have shown that patients with PG younger than 65 years were more likely to have associated IBD,[10] and that co-occurring CD and PG were less likely among patients older than

60 years.[24] An Israeli cohort confirmed strong associations for PG with both CD and UC among patients less than 54 years, with patients who have PG and IBD presenting at younger ages than patients with PG alone.[16,17]

Sex and Ethnicity

Sex and ethnicity also modulate the risk of PG in IBD patients. A 2020 meta-analysis found that female IBD patients had a significantly increased relative risk of PG compared to male patients (RR 1.328; 95% CI: 1.161–1.520).[2] US data show that among patients with CD, PG is more common in female patients, and that Black and Hispanic patients were more likely than white patients to develop PG.[24] An Israeli cohort reported that the association between PG and UC was more prominent in female patients, but the association between PG and CD was more prominent in male patients.[16,17]

Comorbidities

Comorbidities appear to influence the risk of PG and patient outcomes. A US study of patients with CD found that PG was more likely in those with a history of diabetes, obesity, and cachexia, but less likely in patients with hypertension, dyslipidemia, systemic lupus erythematosus (SLE), or a history of neoplasm or alcohol abuse.[24] Another study reported that PG patients with co-occurring diagnoses of hematologic cancers, dyscrasias, or vasculitides experience worse hospital outcomes compared to those with IBD.[8] Similarly, an analysis of hospital admissions in Spain found that patients with co-occurring PG and IBD had a lower risk of mortality compared to PG patients without IBD.[11] Consistent with these findings, a single-center study from Israel demonstrated that IBD-associated PG had the most favorable course compared to autoimmune and connective tissue disease-associated PG, hematologic malignancy-associated PG, and idiopathic PG. A multivariate analysis revealed that IBD was independently associated with a higher likelihood of achieving remission (HR: 2.56, 95% CI: 1.49–4.35; $p < 0.001$).[18]

Disease Activity and Severity

Disease activity and severity strongly influence the risk of PG in IBD patients; however, the clinical courses do not always mirror each other. US cohorts show higher PG prevalence in patients with more severe intestinal disease,[39] elevated inflammatory markers (eg ESR, CRP), and other extraintestinal manifestations such as arthritis and uveitis. IBD remission reduced the odds of developing PG by 58%.[37] Similarly, data from Pakistan demonstrated that PG was significantly more likely to develop during periods of active IBD compared to remission (45% vs 18%, $p<0.001$).[29] Findings from a single-center cohort in Israel found that at PG presentation, most patients had severe (57.7%) or mild to moderate (28.8%) IBD activity. Remission of PG was associated with an improvement of disease activity (OR 0.17; 95% CI: 0.1–0.38; $p<0.001$), while relapse coincided with IBD flares (OR 3.23; 95% CI: 1.01–10.1; $p=0.048$).[18]

Smoking

Smoking has been proposed as a potential risk modifier, though findings are inconsistent. In a US cohort of patients with CD, PG was less likely among those who smoke.[24] Similarly, a US population-based analysis found that non-smokers with PG have nearly twice the prevalence of IBD compared to smokers.[6] An Israeli cohort also found that the association between PG and UC was stronger in non-smokers, but conversely found that the association between CD and PG was more robust among smokers.[16,17] Overall, the role of smoking in modulating risk remains unclear.

Timing of Onset

There is also a temporal dimension to the risk of developing PG in patients with IBD. Across multiple cohorts, PG most often presents after the diagnosis of IBD. In a large UK study, PG was more frequently diagnosed after an IBD diagnosis than before, with adjusted odds ratios of 12.9 for PG preceding IBD and 39.3 for PG following IBD.[25] Similarly, a Swiss cohort found that only 14.3% of patients developed PG before IBD,[34] and a population-based study from Taiwan demonstrated a significantly increased risk of PG after an IBD diagnosis compared to controls (aHR 17.79, 95% CI: 6.35–49.86).[40] In an Israeli cohort, patients with IBD had the longest latency from onset of their primary disease to developing PG (mean latency 10.3 years; SD=12.2; $p=0.01$) compared to those with hematologic or autoimmune/connective tissue disease associated PG.[18] Additional Israeli studies indicate that PG typically arises several years

after CD diagnosis, with a mean latency of 7.9 years (SD=4.4) and 81% of patients developing PG more than five years after their CD diagnosis.[16] In contrast, PG in UC patients tends to appear earlier, with 31.8% of patients developing PG within the first year after UC diagnosis, and 50% after five years.[17]

Clinical Manifestations

To better characterize features of pyoderma gangrenosum (PG) and inflammatory bowel disease (IBD), we conducted a narrative review of case reports and case series describing co-occurring PG and IBD from the last 10 years available in English on PubMed and extrapolated demographic, clinical, and treatment data (Tables 2–6). We included a total of 115 case reports and case series describing 140 patients (Supplementary Table 1). Most patients were female (58.6%), and nearly half were aged 18–40 years (49.3%). Pediatric PG was uncommon, with only four cases involving patients under

Table 2 Demographic of Patients with Co-Occurring IBD and PG Reported in the Last 10 Years. Data Are Presented as the Numbers (Percentage) of Patients

	All IBD (n=140)	UC (n=90)	CD (n=46)	Unspecified IBD (n=4)
Age				
<18	4 (2.9%)	3 (3.3%)	1 (2.2%)	0 (0.0%)
18-40	69 (49.3%)	41 (45.6%)	26 (56.5%)	2 (50%)
41-65	45 (32.1%)	30 (33.3%)	13 (28.3%)	2 (50%)
>65	21 (15.0%)	15 (16.7%)	6 (13.0%)	0 (0.0%)
Unknown	1 (0.7%)	1 (1.1%)	0 (0.0%)	0 (0.0%)
Sex				
Male	57 (40.7%)	37 (41.1%)	19 (41.3%)	1 (25.0%)
Female	82 (58.6%)	52 (57.8%)	27 (58.7%)	3 (75.0%)
Unknown	1 (0.7%)	1 (1.1%)	0 (0.0%)	0 (0.0%)
Comorbidities				
Inflammatory Arthritis	8 (5.7%)	3 (3.3%)	5 (10.9%)	0 (0.0%)
Arthritis - unspecified	5 (3.6%)	1 (1.1%)	4 (8.7%)	0 (0.0%)
Autoimmune Disease[a]	5 (3.6%)	5 (5.6%)	0 (0.0%)	0 (0.0%)
Diabetes	5 (3.6%)	4 (4.4%)	1 (2.2%)	0 (0.0%)
Obesity	4 (2.9%)	2 (2.2%)	2 (4.3%)	0 (0.0%)
Solid Cancer	4 (2.9%)	1 (1.1%)	3 (6.5%)	0 (0.0%)
Erythema nodosum	3 (2.1%)	3 (3.3%)	0 (0.0%)	0 (0.0%)
Hidradenitis Suppurativa	2 (1.4%)	1 (1.1%)	1 (2.2%)	0 (0.0%)
Inflammatory Eye Conditions[b]	2 (1.4%)	1 (1.1%)	0 (0.0%)	1 (25.0%)
PASH syndrome	2 (1.4%)	1 (1.1%)	1 (2.2%)	0 (0.0%)
Acne	1 (0.7%)	1 (1.1%)	0 (0.0%)	0 (0.0%)
Congestive Heart Failure	1 (0.7%)	1 (1.1%)	0 (0.0%)	0 (0.0%)
Deep vein thrombosis	1 (0.7%)	1 (1.1%)	0 (0.0%)	0 (0.0%)

Notes: [a]Autoimmune diseases included: alopecia areata (n=2), multiple sclerosis (MS), primary sclerosing cholangitis (PSC), and Tolosa-Hunt syndrome. [b]Inflammatory eye conditions included: uveitis and peripheral ulcerative keratitis.

Table 3 Temporal Relationship Between IBD and PG, Stratified by IBD Subtype. Data Are Presented as the Numbers (Percentage) of Patients

	All IBD (n=140)	UC (n=90)	CD (n=46)	Unspecified IBD (n=4)
Presentation				
IBD First	103 (73.6%)	70 (77.8%)	30 (65.2%)	3 (75.0%)
PG First	13 (9.3%)	7 (7.8%)	6 (13.0%)	0 (0.0%)
Simultaneous	6 (4.3%)	5 (5.6%)	0 (0.0%)	1 (25.0%)
Unknown	18 (12.9%)	8 (8.9%)	10 (21.7%)	0 (0.0%)

Table 4 Medications Patients Were Receiving at the Time of PG Onset, Stratified by IBD Subtype. Data Are Presented as the Numbers (Percentage) of Patients

	All IBD (n=103)	UC (n=70)	CD (n=30)	Unspecified IBD (n=3)
Anti-Inflammatory	29 (28.2%)	25 (35.7%)	4 (13.3%)	0 (0.0%)
Biologics	20 (19.4%)	9 (12.9%)	10 (33.3%)	1 (33.3%)
Immunosuppression	27 (26.2%)	18 (25.7%)	8 (26.7%)	1 (33.3%)
None	17 (16.5%)	13 (18.6%)	4 (13.3%)	0 (0.0%)
Unknown	34 (33.0%)	22 (31.4%)	10 (33.3%)	2 (66.7%)

Notes: Treatment categories include anti-inflammatory medications (mesalamine and sulfasalazine), biologics (infliximab, vedolizumab, adalimumab, and golimumab), and immunosuppressive medications (azathioprine, corticosteroids, and cyclosporine). Patients may have received more than one therapy; categories are not mutually exclusive, and percentages do not sum to 100%.

Table 5 Ulcer Locations in Patients with IBD and PG, Stratified by IBD Subtype. Data Are Presented as the Numbers (Percentage) of Patients

	All IBD (n=140)	UC (n=90)	CD (n=46)	Unspecified IBD (n=4)
Ulcer Location				
Lower Extremities	24 (17.1%)	61 (67.8%)	22 (47.8%)	2 (50%)
Upper Extremities	5 (3.6%)	16 (17.8%)	4 (8.7%)	1 (25%)
Head/Neck	11 (7.9%)	12 (13.3%)	10 (21.7%)	1 (25%)
Trunk/Peristomal	27 (19.3%)	34 (37.8%)	24 (52.2%)	3 (75%)
Genital	5 (3.6%)	6 (6.7%)	5 (10.9%)	0 (0.0%)
Unknown	1 (0.7%)	1 (1.1%)	1 (2.2%)	0 (0.0%)

Notes: Some patients had ulcers in multiple locations; categories are not mutually exclusive, and percentages do not sum to 100%.

Table 6 Healing Outcomes and Treatment Responses for PG in Patients with IBD, Stratified by IBD Subtype. Data Are Presented as the Numbers (Percentage) of Patients

	All IBD (n=140)	UC (n=90)	CD (n=46)	Unspecified IBD (n=4)
Complete Healing				
Yes	109 (77.9%)	75 (83.3%)	32 (69.6%)	2 (50%)
No	25 (17.9%)	13 (14.4%)	11 (23.9%)	1 (25.0%)
Unknown	6 (4.3%)	2 (2.2%)	3 (6.5%)	1 (25.0%)
Successful Treatments				
Anti-Inflammatory	16 (11.4%)	13 (14.4%)	3 (6.5%)	0 (0.0%)
Biologics	71 (50.7%)	43 (47.8%)	26 (56.5%)	2 (50%)
Immunosuppression	72 (51.4%)	47 (52.2%)	22 (47.8%)	3 (75%)
Immunomodulation	4 (2.9%)	1 (1.1%)	2 (4.3%)	1 (25%)
Oral Antibiotics	7 (5.0%)	6 (6.7%)	1 (2.2%)	0 (0.0%)
Topical Therapies	8 (5.7%)	3 (3.3%)	5 (10.9%)	0 (0.0%)
Other	10 (7.1%)	9 (10%)	1 (2.2%)	0 (0.0%)
Failed Treatments				
Anti-Inflammatory	18 (12.9%)	15 (16.7%)	2 (4.3%)	1 (25%)
Biologics	38 (27.1%)	19 (21.1%)	18 (39.1%)	1 (25%)
Immunosuppression	41 (29.3%)	27 (30.0%)	12 (32.6%)	2 (50%)
Immunomodulation	3 (2.1%)	0 (0.0%)	3 (6.5%)	0 (0.0%)
Oral Antibiotics	16 (11.4%)	13 (14.4%)	3 (6.5%)	0 (0.0%)
Topical Therapies	13 (9.3%)	8 (8.9%)	5 (10.9%)	0 (0.0%)
Other	4 (2.9%)	4 (4.4%)	0 (0.0%)	0 (0.0%)

Notes: Treatment categories include anti-inflammatory medications (mesalamine, pentoxifylline, clofazimine, apremilast, and sulfasalazine), biologics (infliximab, rituximab, vedolizumab, certolizumab, adalimumab, ustekinumab, upadacitinib, canakinumab, secukinumab, and golimumab), immunosuppressive medications (azathioprine, corticosteroids, and cyclosporine, JAK inhibitor), immunomodulating medications (dapsone, intravenous immunoglobulin), oral antibiotics, topical therapies (corticosteroids, tacrolimus), and other therapies (granulocyte–Monocyte Apheresis, intralesional corticosteroid, hyperbaric oxygen therapy, negative-pressure wound therapy). Patients may have received more than one therapy; categories are not mutually exclusive, and percentages do not sum to 100%.

18. Comorbidities were variable, including inflammatory arthritis (13/140, 9.3%), autoimmune disease (5/140, 3.6%), and erythema nodosum (3/140, 2.1%) (Table 2). Most patients developed PG after an IBD diagnosis (103/140, 73.6%), while 13 (9.3%) presented with PG before being diagnosed with IBD, and 6 (4.3%) had simultaneous onset. In 18 cases, the timing was unknown (Table 3). Among the 103 patients who developed PG after being diagnosed with IBD, the most common treatments at the time of PG onset were anti-inflammatory (28.2%) and immunosuppressive (26.2%) medications (Table 4). Ulcer morphology and location were heterogeneous, with the lower extremity most affected in patients with UC (61/90, 67.8%), and the trunk/peristomal region most affected in patients with CD (24/46, 52.2%). Forty-five patients (32.1%) had ulcers in multiple sites (Table 5).

Of the 140 patients with IBD and PG, 109 (77.9%) patients achieved complete healing of their target ulcer (Table 6). Of the patients with documented healing the median reported time to heal was 3 months (IQR 2–5.5). Biologic and immunosuppressive treatment demonstrated varying efficacy. Notably, infliximab and corticosteroids were the most frequently prescribed medications associated with healing. Adalimumab, ustekinumab, vedolizumab, cyclosporine, tofacitinib, upadacitinib, and tacrolimus were also reported to be beneficial in some patients (Table 6). Combination therapy was also beneficial in a subset of patients, of which infliximab and corticosteroids were the most common.

Treatment failures were substantial across all therapeutic classes. Corticosteroids and infliximab also accounted for the largest number of failed treatments; adalimumab, vedolizumab, ustekinumab, cyclosporine, and tacrolimus were also ineffective in a proportion of cases (Table 6). These data display the heterogeneous presentation of patients with PG and IBD and the ongoing challenges of identifying effective treatments.

Treatment Overlap

Management of PG in the context of IBD often uses therapies that address both conditions, including immunosuppressants and biologics. The STOP GAP trial, a randomized controlled trial comparing prednisolone and cyclosporine in patients with clinician diagnosed PG showed that 28 of 59 patients in the cyclosporine group and 25 of 53 patients in the prednisolone group achieved healing by six months. In this cohort, 12 patients in the cyclosporine group and 11 patients in the prednisolone group had IBD. Results indicated that IBD was not a comorbidity that should influence provider choice between cyclosporine and prednisone.[41] In UC-associated PG, a retrospective study of 20 patients found that a combination therapy of corticosteroids and 5-aminosalicylic acid resulted in a clinical response in 95% of patients.[42]

Anti-TNF treatment remains an effective therapy for IBD-associated PG. Pediatric cases have shown complete responses to infliximab and adalimumab, leading to clinical recommendations that they should be considered first-line in severe pediatric IBD-associated PG.[43] In peristomal PG, retrospective studies show high response rates with TNF-inhibitors. A retrospective study of 41 patients showed a 63% resolution rate after initiation.[44]

While the use of TNF inhibitors is prevalent in IBD-associated PG, newer biologics have shown promise. Ustekinumab, a targeted antibody against IL-12 and IL-23, has shown efficacy in treating refractory PG and IBD. A retrospective study of 44 patients with peristomal PG had 41 cases associated with inflammatory bowel disease. Two patients were treated with ustekinumab; one reported a partial response, and the other achieved a complete response.[21] Another multicenter retrospective study evaluated ustekinumab for CD-associated neutrophilic dermatoses. Efficacy of ustekinumab was assessed 16 weeks after treatment initiation. Of the seven patients who received ustekinumab with CD, four also had PG. Three of the four patients had a complete response to ustekinumab, and one had a partial response, with no serious adverse events reported.[45] Alternatively, vedolizumab, an antibody that targets the interaction between α4β7 and MAdCAM-1, may be less beneficial. After treating 71 patients with IBD, 19 subsequently developed extraintestinal manifestations, including PG.[46] JAK inhibitors are also being explored. Of 19 patients with refractory Crohn's disease, the addition of tofacitinib to ongoing biologic therapy showed complete resolution in four patients with concomitant PG, highlighting its potential treatment role.[47]

Beyond immunosuppressants and biologics, adjunctive and non-conventional therapies have also been explored in the management of PG, particularly in cases that are refractory to treatment. Cytapheresis is a treatment that depletes elevated and activated leukocytes. Among 181 patients with UC, 13 also had PG or erythema nodosum, and all had marked improvement with cytapheresis.[48] Hyperbaric oxygen therapy (HBOT) is a promising adjunctive treatment for PG and refractory Crohn's disease. A study conducted in Brazil included 29 subjects with refractory Crohn's disease. Of

these patients, four had concomitant PG, and all achieved successful healing with HBOT.[49] Another HBOT study in Brazil included 40 patients with refractory Crohn's disease, of whom six had concomitant PG, and all achieved healing.[50] Observational data also suggest that long-term probiotic use may be an adjunctive treatment to reduce cutaneous manifestations.[51]

Fecal microbiota transplantation (FMT) has been shown to induce remission and may reduce flares in patients with UC, though there is limited evidence in CD.[52] Because increased IBD severity is associated with a higher risk of developing PG, FMT may have relevance for PG as well. In a Danish cohort of 131 patients with IBD, those with extraintestinal manifestations had different fecal microbiota profiles compared to those without. Differences were found in bacterial diversity and composition, with loss of health-associated gut bacteria and enrichment of bacteria previously linked to immune-mediated diseases.[53] Although FMT has not been formally explored as a treatment for PG in patients with IBD, these findings suggest mechanistic overlap and highlight FMT as a potential treatment option for IBD patients with PG.

Genetic and Molecular Insights

Studies of genetic variation and molecular pathways have provided insight into the link between PG and IBD. A recent Mendelian-randomization (MR) analysis using large genome-wide association study (GWAS) datasets demonstrated that IBD causally increases the risk of developing PG (OR = 1.604, 95% CI 1.308–1.966, $p = 5.58 \times 10^{-6}$), with no evidence that PG causally increases risk of IBD. A two-step MR analysis identified CD4+ regulatory T cells (Tregs) as a plausible mediator, with an IBD-driven elevation of Tregs (OR = 1.063, 95% CI 1.007–1.123, p = 0.026) subsequently increasing the probability of developing PG (OR = 1.311, 95% CI 1.006–1.708, p = 0.045).[54]

Another study screened four genetic databases and identified 48 genes that overlap in IBD and its extraintestinal manifestations, including PG. Of these, 20 genes had the highest predicted involvement and are involved in immune modulation, cytokine signaling, and apoptosis (eg, *IL17A, NOD2, TNF*). Notably, *SLCO1B3* was uniquely linked to PG, UC, and CD, while *IL25* and *MON2* were shared among UC, CD, PG, and arthritis, highlighting disease-specific genetic nodes.[55]

An immunohistochemistry study demonstrated overlapping protein expression in IBD and PG. The TNFα/NFκB pathway was overexpressed in both IBD and PG, supporting the efficacy of anti-TNF agents. *STAT3* was upregulated in both active and inactive IBD and PG, supporting potential for therapeutic responses to JAK inhibition. *MAdCAM1* was upregulated in active UC, but not in CD or PG, potentially limiting the efficacy of vedolizumab (an antibody blocking the interaction between α4β7 and MAdCAM-1) in PG. Additionally, CD68 and Caspases 3/9 expression distinguished PG and erythema nodosum from psoriasis, highlighting novel potential therapeutic targets for extraintestinal manifestations of IBD.[56]

A group of rare monogenetic syndromes, including PASH (PG, acne, hidradenitis suppurativa), PAPASH (pyogenic arthritis, PG, acne, hidradenitis suppurativa), and PAPA (pyogenic arthritis, PG, acne) involve mutations in *PSTPIP1*. These mutations predict a favorable therapeutic response to IL-1 signal blocking.[57] In 2015, a case was reported of a patient with UC, PG, and acne, and their genetic testing revealed a novel mutation in *PSTPIP1*. This condition was subsequently termed PAC syndrome.[58] These syndromes provide complementary evidence that rare monogenic variation can contribute to PG susceptibility.

Pathophysiology and Mechanisms

PG is a Th17/Th1-driven neutrophilic dermatosis and a common cutaneous manifestation of IBD. It is characterized by uncontrolled neutrophil activation and migration, as well as the release of autoinflammatory cytokines, including IL-1β, IL-6, TNF-α, and IL-36.[59,60] Although the etiology of PG and its link with IBD is poorly understood, multiple mechanisms have been proposed for its pathogenesis. PG and IBD are associated with neutrophil dysregulation, cytokine-driven autoinflammation, and gut-skin immune crosstalk. These converging pro-inflammatory pathways, driven by genetic and environmental factors, culminate in uncontrolled neutrophil migration to the skin, as illustrated in Figure 1. Studies in a mouse model of PG-like neutrophilic dermatosis with concomitant intestinal inflammation show that the IL-1β-primed neutrophils can enhance neutrophil extracellular traps (NETs) formation in both the skin and the

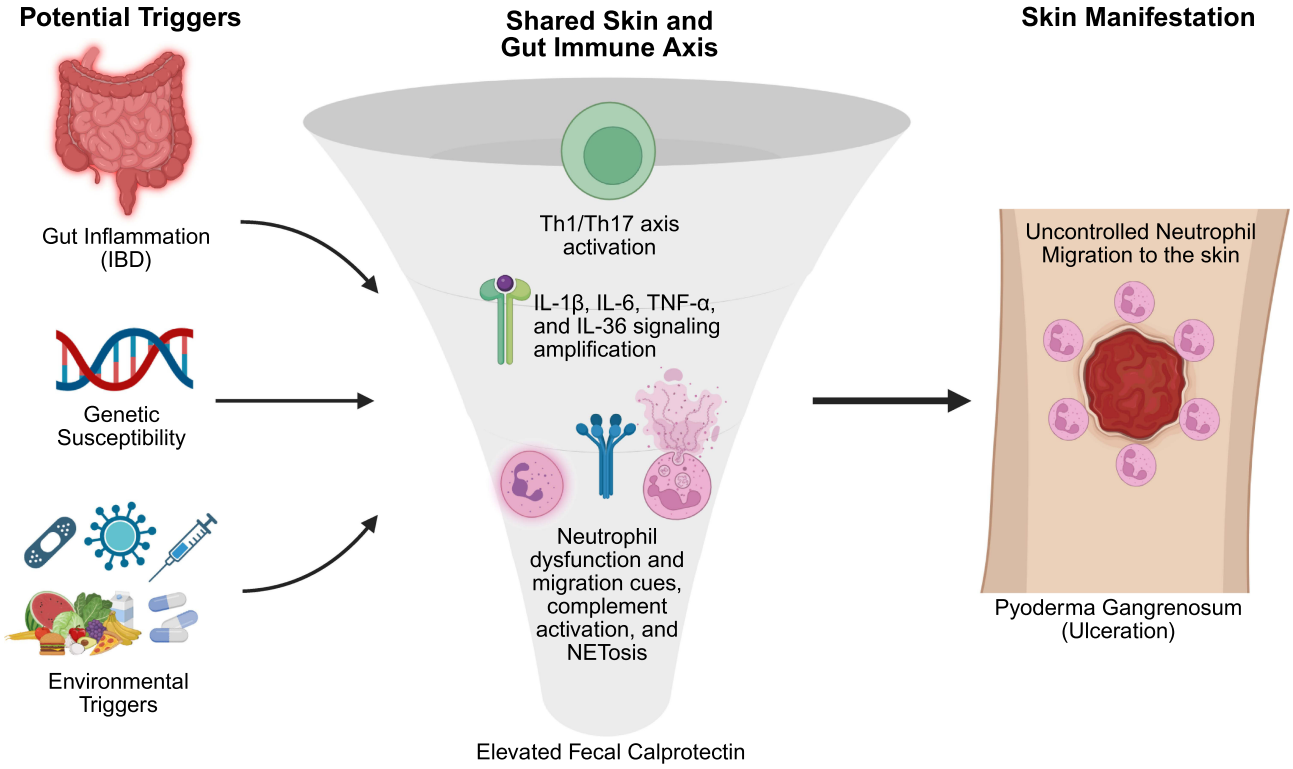

Figure 1 Convergence of Pro-Inflammatory Pathways in Pyoderma Gangrenosum. Created in BioRender. Vague, M. (2025) https://BioRender.com/sitlg8i.

intestine and activate inflammatory loops between the skin and gut.[61] These observations suggest that uncontrolled neutrophil activation and migration to sites of inflammation driven by chemokine cues could be a key pathogenic mechanism of PG.

Trauma can also trigger PG by inducing cytokine release, activating the Th17/Th-1 inflammatory cascade, and elevating levels of IL-36. IL-36 plays a pivotal role in both innate and adaptive immune responses. There are four IL-36 isoforms, of which IL-36α, IL-36β, and IL-36γ have agonist activity. Dysregulation of the IL-36 axis promotes endothelial activation through ICAM-1 and VCAM-1 to increase leukocyte infiltration. IL-36γ is abundant in keratinocytes and dermal dendritic cells. Gene expression studies of perilesional skin have revealed the activation of inflammatory pathways and the upregulation of IL-1, IL-36, IL-17, and CXCL1/8, as well as the chemokines CCL20 and CCL2. While IL-36 facilitates intestinal barrier healing in the acute stage of IBD, chronic overexpression can suppress the expansion of FoxP3-regulatory T cells. This process induces the differentiation of CD4+ T-cells to pathogenic IL-9-producing CD4+ T-cells, promoting intestinal fibrosis and potentially worsening both PG and IBD severity.[59]

Beyond intrinsic immune dysregulation pathways, environmental factors may induce PG in patients with IBD. Approximately 66% of patients with UC have reported drug sensitivity, which has been characterized by elevated IgE, IL-4, TNF-α, and IgG4 levels. A hapten-like mechanism may explain the onset of PG in UC, where overlapping antibody-binding epitopes lead to uncontrolled immune activation.[62] Case reports have also documented PG following the immune stimulation of a COVID-19 vaccination in a patient with UC, suggesting that external antigens might cause PG in patients who are genetically or immunologically predisposed.[63]

While there is no established biomarker to detect and assess PG severity, the fecal calprotectin (FC) levels may serve as an indicator for the severity of idiopathic PG. FC is a cytosolic protein widely used to monitor IBD activity and is released by neutrophils infiltrating the intestinal mucosa, an indicator of mucosal inflammation. In a retrospective cohort of 66 patients from 2000 to 2024, 21 subjects with idiopathic PG underwent fecal occult blood and FC testing. Of these, four patients developed CD. All four had positive fecal occult blood and FC tests, compared with only 3 of 17 without IBD (100% sensitivity, 82.35% specificity, PPV 57.14%, NPV 100%). Additionally, elevated FC levels (>50 µg/g) were

observed in two of the four CD cases (50% sensitivity, 100% specificity, PPV 100%, NPV 89.47%).[64] In a separate retrospective cohort study, serial FC testing performed six months before and after PG diagnosis demonstrated that higher FC levels were correlated with larger ulcer sizes and increased PG disease activity, particularly in cases associated with IBD.[65] These studies suggest that elevated FC and positive fecal occult blood tests may predict the development of CD in idiopathic PG.

Studies have suggested additional mechanisms highlighting the association of PG with IBD. The migration of α4β7+ lymphocytes to both the gut and skin explained how interventions, including colonic resection or α4β7 integrin blockade, can lead to PG improvement.[66] While anti-TNF-α inhibitors have also been used to treat PG and IBD, 20–40% of patients show a primary nonresponse.[46] These data suggest that PG likely involves overlapping yet distinct pathogenic mechanisms compared to classical IBD presentations. Conversely, some biologics may induce or exacerbate PG. The initiation of the IL-17A inhibitor secukinumab was reported to trigger the recurrence of refractory peristomal PG at an ileostomy site.[67] Additionally, patients with ostomies secondary to IBD tend to develop peristomal PG potentially due to the challenges in maintaining a proper seal of the ostomy pouch.[68]

Rare genetic syndromes, such as PAC syndrome (PG, acne, UC) caused by a mutation in *PSTPIP1*,[57] further highlight how innate immune dysregulation can contribute to the onset of PG. These results support the evaluation of fecal calprotectin and stool blood as biomarkers of neutrophil-driven inflammation and IL-1β and IL-36 signaling pathways as therapeutic targets for patients with PG and IBD.

Ongoing and Recent Clinical Trials

Several clinical trials have evaluated the use of biologic and topical therapies to treat CD and associated cutaneous manifestations, including PG. The first was a six-month open-label pilot study that tested the treatment of intravenous infliximab in adults with IBD and moderate-to-severe PG (NCT00791557). Two of the eight intended subjects were enrolled due to the timing of the study. Infusions were administered at weeks 1, 2, 14, and 22. Of the two participants, one completed the study while the other withdrew due to adverse events, including an infusion reaction, bone marrow suppression, and infection.[69]

The UNITI-1, UNITI-2, and IM-UNITI trials were randomized, double-blind, placebo-controlled Phase III trials evaluating ustekinumab in adult patients with moderately to severely active Crohn's disease. Across these trials, a subset of patients also presented with PG: 2 in UNITI-1, 4 in UNITI-2, and 2 in IM-UNITI. In the UNITI-1 trial, both patients with PG were randomized to the ustekinumab 130 mg arm, with each achieving resolution of their target lesion and a reduction in the total number of lesions.[70] In the UNITI-2 trial, one patient with PG received ustekinumab 130mg and three received ustekinumab ~6mg/kg. Resolution of the primary lesion was reported in one patient from the ~6mg/kg group.[71] In the IM-UNITI trial, one patient with PG was in the placebo group and one was in the ustekinumab 90 mg every 12-weeks arm. Both had resolution of their primary lesion and a reduction in the total number of lesions.[72] These data suggest the potential utility of ustekinumab in PG and IBD management.

A Phase II study evaluated topical tacrolimus 0.1% ointment for cutaneous CD, with treatment response assessed through a blinded photographic review (NCT01233570).[73] No results have been posted for this study. Additionally, a phase II/III multi-center, randomized, double-blind clinical trial investigated the usage of adalimumab for the induction and maintenance of remission in CD (NCT00445432).[74,75] Induction remission rates at week 4 were 33.3% (160/80mg), 17.6% (80/40mg), and 13% (placebo). At week 52, maintenance remission rates were 38.1% for adalimumab in comparison to 9.1% for placebo.[74] In these studies, PG was evaluated as part of a broader assessment rather than assessed as a specific endpoint.

lL-36 signaling has been implicated as a shared pathway between PG and IBD, making IL-36 a potential therapeutic target. However, clinical trials of spesolimab, an IL-36 inhibitor, have not demonstrated efficacy in UC or CD.[76–78] A phase II trial of spesolimab is currently recruiting for patients with PG (NCT06624670) and may help clarify the role of IL-36 inhibition in this disease.[79]

Currently, there is a great need for future clinical trial designs assessing outcomes in PG among patients with IBD.

Discussion

This review highlights the complex relationship between PG and IBD. Across multiple populations, IBD is consistently overrepresented in patients with PG (7.6–41.9%), and the prevalence of PG in IBD cohorts is elevated (0.5–8%). Consistent with the literature, the 115 reviewed case reports indicate that most patients developed PG after an IBD diagnosis (73.6%), with smaller proportions presenting simultaneously (4.3%) or before IBD diagnosis (9.3%). These findings underscore the importance of maintaining vigilance for PG in patients with an established IBD diagnosis, as well as considering IBD evaluation in patients who present with PG.

Demographic trends in the reviewed case reports also aligned with the literature, indicating that most PG cases occurred in adults aged 18–40, with a female predominance (58.6%). Clinical manifestations of PG in IBD are diverse, and ulcer locations vary by IBD subtype. Lower extremities were most affected in UC, whereas trunk and peristomal regions were more frequently affected in CD. Multi-site involvement occurred in roughly one-third of patients. This heterogeneity of disease presentation complicates recognition and can lead to delays in correct diagnosis. In the reviewed cases, comorbidities beyond IBD and PG were rarely reported, which may reflect underreporting rather than true absence.

Data in the literature describing hospital outcomes and mortality risk among patients with IBD and PG compared to other subtypes of PG are mainly derived from inpatient cohorts, which likely overrepresent severe or refractory cases. As a result, outpatient populations remain under characterized, limiting the generalizability of existing findings. Notably, in our review of IBD-associated PG cases, the median reported time to heal was 3 months (IQR 2–5.5), which is faster than reported in broader PG populations, where the median reported time to heal is typically several months and may extend up to 21.7 months in the setting of diagnostic delay.[80] This indicates that IBD-associated PG may be more treatment-responsive or detected earlier than other subtypes of PG; however, reliance on case reports and case series biases this observation.

Therapeutic responses for PG in the setting of IBD are also variable. Most patients require systemic therapy, with corticosteroids and immunosuppressants commonly used as initial treatments. However, many patients required multiple sequential or concurrent therapies, highlighting the difficulty in achieving disease control. There is increasing use of biologics, including TNF-α inhibitors, reflecting a shift toward targeting overlapping inflammatory pathways in PG and IBD and using IBD-directed therapies for PG management. Despite advances, there remains variability in treatment responses, underscoring the need for individualized treatment strategies and comparative effectiveness studies to inform therapeutic decision-making.

Mechanistic and genetic studies support biologically plausible links between PG and IBD, including Th17/Th1 immune dysregulation, IL-1β/IL-36 signaling, and gut-skin immune crosstalk. These links suggest potential for dual therapies; however, mechanistic studies remain limited. Further research is needed to clarify whether PG represents a distinct entity triggered by IBD-related immune dysregulation or whether PG and IBD are both part of a broader shared autoinflammatory spectrum.

While this review synthesizes 115 published case reports and case series representing a significant portion of the literature on the topic, there are several limitations impacting the conclusions drawn. Due to the nature of the inclusion criteria, the findings are derived from a descriptive summary rather than a formal meta-analysis, limiting statistical comparison of outcomes. The reliance on published case reports and small case series also introduces inherent reporting bias, as findings are often skewed towards atypical or severe presentations and potentially inflate therapeutic successes. Additionally, clinical data about the temporal sequence of PG and IBD onset is retrospective and susceptible to recall or reporting bias. Inconsistencies in PG diagnosis, due to the lack of a universally accepted diagnostic criterion, further complicate interpretation and add to the difficulty of comparing findings in the IBD-PG population. The summaries of treatment responses are derived from non-standardized regimens and uncontrolled studies so causality and efficacy cannot be confirmed. Mechanistically, while we discussed proposed pathways (eg, IL-1β/IL-36, Th17/Th1 dysregulation), these remain correlational and are not definitively proven as the primary pathogenic drivers. Finally, most of the available literature originates from Western cohorts so the generalizability and global applicability of these findings may be restricted.

Conclusion

Pyoderma gangrenosum is a rare but clinically significant extraintestinal manifestation of IBD with a heterogeneous clinical presentation and treatment response. This review reinforces that most PG in the setting of IBD develops after IBD diagnosis, and we note that the median healing time of 3 months in these reviewed cases appears faster than what has been described in broader PG populations. The growing use of biologics reflects a therapeutic strategy aimed at targeting the shared inflammatory pathways, yet treatment remains highly individualized, and challenging.

Despite a growing body of literature, significant deficiencies remain, largely due to the inherent limitations of descriptive data. There remains a significant need for standardized diagnostic criteria and evidence-based treatment guidelines specifically for IBD-associated PG. Future prospective, ideally multi-center, studies are needed to address reporting bias and uncontrolled data that currently define the field. These efforts are crucial for establishing definitive causality, validating mechanistic pathways, improving diagnostic accuracy, and reducing treatment delays.

Data Sharing Statement

This review is based on data extracted from previously published studies All studies used are cited in the Supplementary reference list. No new data were generated.

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Author Contributions

Katelyn Downey: Conceptualization, Data curation, Visualization, Writing – original draft, and Writing-reviewing and editing; Richard Zhang: Conceptualization, Data curation, Writing – original draft, and Writing-reviewing and editing; Alex G Ortega-Loayza: Conceptualization, Supervision, and Writing-reviewing and editing.

All authors gave final approval of this version to be published, agreed on the journal to which the article will be submitted, and agree to take responsibility and be accountable for the contents of the article.

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