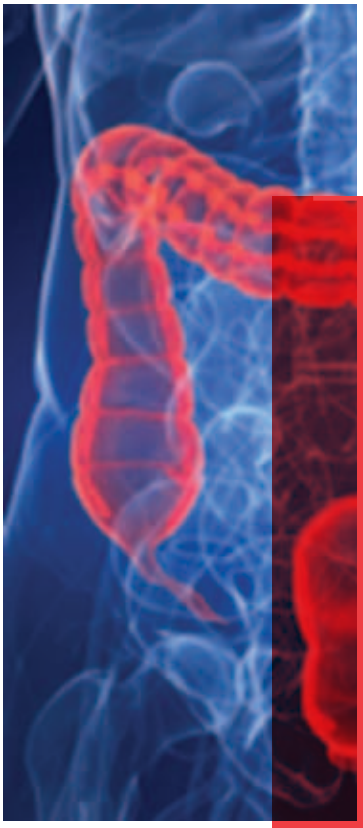
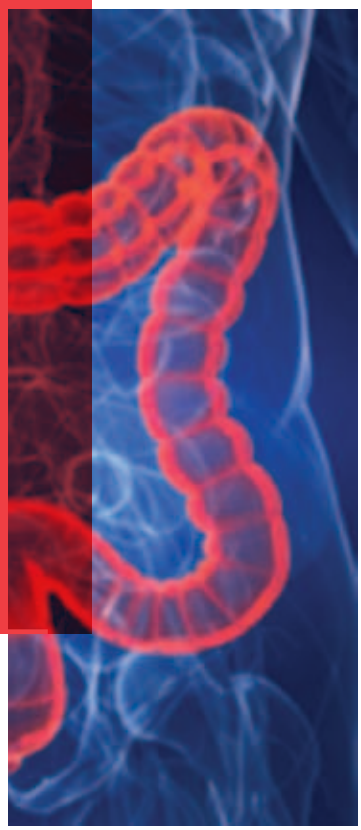


The DERMATOLOGY of INFLAMMATORY BOWEL DISEASE

A Primer for Gastroenterologists



Brought to you by Mentoring in IBD®

CO-AUTHORS: **Mary E. Sherlock**, MB BCh BAO MRPCI FRCPC **Brendan P. Halloran**, MD BSc FRCPC
CO-EDITORS: **Scott R.A. Walsh**, MD PhD FRCPC DABD **Richard N. Fedorak**, MD FRCPC FRCP (London)

UNIVERSITY OF ALBERTA

CO-AUTHORS

Mary E. Sherlock, MB BCh BAO MRPCI FRCPC
Clinical Research Fellow
Division of Gastroenterology, Hepatology & Nutrition
The Hospital for Sick Children
Toronto, ON

Brendan P. Halloran, MD BSc FRCPC
Inflammatory Bowel Disease Fellow
Division of Gastroenterology
University of Alberta
Edmonton, AB

CO-EDITORS

Scott R.A. Walsh, MD PhD FRCPC DABD
Assistant Professor, Division of Dermatology
Sunnybrook Health Sciences Centre
University of Toronto
Toronto, ON

Richard N. Fedorak, MD FRCPC FRCP (London)
Professor of Medicine, Division of Gastroenterology
University of Alberta
Edmonton, AB

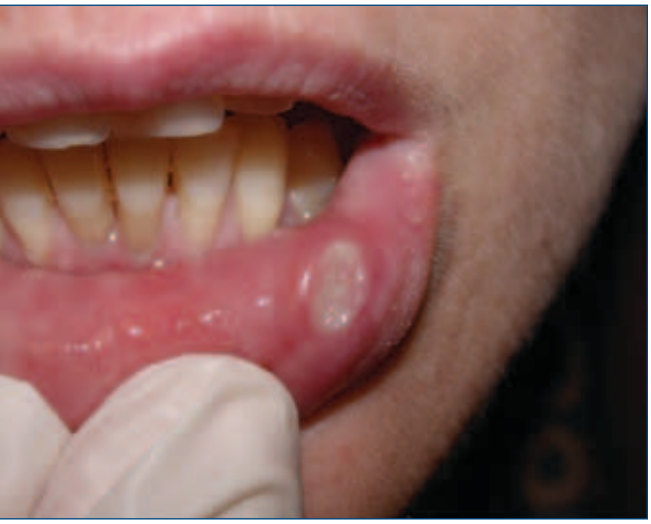
INTRODUCTION

Cutaneous eruptions are relatively common in patients with inflammatory bowel disease (IBD). These dermatologic manifestations may be an extraintestinal manifestation of the underlying disease process, an associated condition, or a complication of therapy. Approximately 10 to 20% of IBD patients develop dermatologic manifestations.

This primer presents a variety of dermatologic manifestations gastroenterologists may encounter in patients with IBD, describes clinical and histologic features, and suggests treatment strategies.

CONTENTS

APHTHOUS STOMATITIS



Relation to IBD

- A common manifestation of IBD which is seen in 4 to 20% of patients

Clinical appearance and presentation

- Painful, shallow, round ulcers with central fibrinous membrane and erythematous halo that may interfere with eating, speaking and swallowing
- Oral cavity eruptions on non-keratinized, free-moving mucosal surfaces (not on hard palate, attached gingival mucosa or dorsum of tongue)
- *Simple aphthosis:* <3 oral aphthous ulcerations; lesions typically last 5 to 7 days
- *Complex aphthosis* (if Behçet's criteria not met): >3, almost constant, oral aphthae

Histology

- *Not typically biopsied, as no pathognomonic findings*
- Fibropurulent pseudomembrane in ulcer base
- Spongiotic changes at the marginal epithelium with lymphocytosis
- Neutrophils and chronic inflammatory infiltrate (histiocytes and lymphocytes) in superficial stroma
- Perivascular chronic inflammatory infiltrates in deeper submucosa

Differential diagnosis

- Recurrent aphthous stomatitis
- Oral herpes simplex virus (HSV), coxsackie virus, human immunodeficiency virus (HIV)
- Traumatic ulcers, gluten-sensitive enteropathy, hematinic deficiency (iron, folate, zinc, B_1, B_2, B_6, B_{12}) cyclic neutropenia, Behçet's syndrome, syphilis

Diagnosis

- No vesicular component (in contrast with coxsackie virus or HSV where vesicles can be seen)
- Consider Behçet's syndrome and other causes of secondary aphthae
- Swab for HSV if diagnosis is in doubt

Treatment

Treatment approaches are listed below.

Topical therapy			
Drug class	**Agent**	**Application**	**Availability**
Local anesthetic	Lidocaine viscous suspension, 2%	Swish and spit BID to QID x 4–8 weeks	100-mL bottle
Corticosteroid	Triamcinolone acetonide, 0.1%, dental paste	TID x 4–8 weeks	5-g and 7.5-g tubes
	Dexamethasone, 0.5 mg/5 mL, suspension	Swish and spit, TID x 4–8 weeks	240-mL and 500-mL bottles
	Clobetasol powder, 0.05%, in orabase	BID x 4–8 weeks	15 g and 30 g
Antiallergic	Amlexanox, 5%	QID until healed, about 10 days	3-g tube

Systemic therapy			
Drug class	**Agent**	**Dose**	**Notes**
Antibiotic	Dapsone	25–100 mg/day PO x 3–6 months	Perform G6PD testing Do not use in patients with G6PD deficiency, due to hemolysis Start at 25 mg/day; increase dose weekly by 25 mg to 100 mg/day if tolerated Monitor complete blood count (CBC), liver enzymes, creatinine Methemoglobinemia may occur at doses >200 mg/day
Anti-inflammatory	Colchicine	0.6 mg PO, BID to TID, as tolerated, x 3–6-month trial	
5-ASA	Sulfasalazine	1 g PO BID x 3–6-month trial	Supplement folate 1 mg/day, especially in young females
Corticosteroids	Prednisone	30 mg/day PO x 2 weeks	Taper dose by 5 mg/week until off Total 8-week course
Hemorrheologic	Pentoxyfilline	400 mg PO BID to TID x 3–6-month trial	
Immunomodulator	Thalidomide	50–150 mg/day PO x 3-month trial	

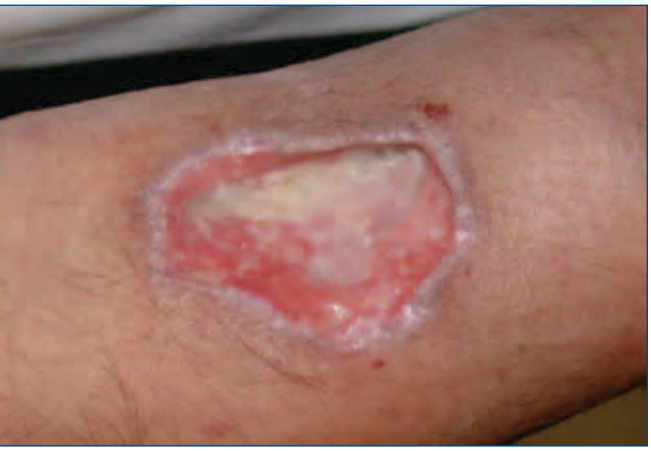
References

Eisenberg E. Diagnosis and treatment of recurrent aphthous stomatitis. *Oral Maxillofacial Surg Clin N Am* 2003;15:111-22.

Letsinger JA, McCarty MA, Jorizzo JL. Complex aphthosis: a large case series with evaluation algorithm and therapeutic ladder from topicals to thalidomide. *J Am Acad Dermatol* 2005;52(3 Pt 1):500-8.

Trost L, McDonnell J. Important cutaneous manifestations of inflammatory bowel disease. *Postgrad Med J* 2005;81:580-5.

PYODERMA GANGRENOSUM



Relation to IBD

- 1 to 5% of IBD patients: one of the most problematic extraintestinal manifestations of IBD
- Pyoderma activity is often independent of intestinal inflammation

Clinical appearance and presentation

- The most frequent lesion is an ulcer with a well-defined, elevated, violaceous border, often beginning as a pustule with an erythematous halo
- Lesions may be single or occur in clusters, often with rapid progression; pathergy may occur
- Lesions often very painful and complicated by infection
- Healing with cribriform scarring
- Systemic features, such as pyrexia and myalgia, may be present

Histology

- Performing a biopsy may make the pyoderma worse and should be avoided if possible
- No pathognomonic histologic features
- Typically, sterile abscesses with abundant neutrophilic infiltrate, hemorrhagic and necrotic areas, and thromboses within small vessels

Differential diagnosis

- Sweet's syndrome, neutrophilic dermatosis, vasculitis (Wegener's granulomatosis, systemic lupus erythematosus [SLE], rheumatoid arthritis [RA]), infectious or vascular insufficiency ulcers
- Approximately 50% of cases are associated with systemic conditions such as: IBD, malignancy, Behçet's syndrome, viral infection (hepatitis C virus [HCV], HIV), monoclonal gammopathy, RA

Diagnosis

- Clinical, no specific diagnostic test
- Negative culture and biopsy with heavy neutrophilic infiltrate ± vasculitis are supportive findings

Treatment

General management includes analgesia and wound care, prevention of secondary infection, and treatment of any associated systemic disease. Topical therapy is useful for mild lesions, and intralesional therapy may be used for isolated lesions. Prednisone is appropriate for moderate disease. Biologics are rapidly becoming the first-line treatment for severe IBD-associated pyoderma, but a variety of other therapies are also used. The range of treatment approaches is listed below.

Topical therapy: useful for mild lesions			
Drug class	**Agent**	**Application**	**Availability**
Corticosteroid	Clobetasol propionate, 0.05%, unguent	QD to BID to ulcer until healed	50-g tubes
Calcineurin inhibitor	Tacrolimus, 0.1%, unguent	BID to ulcer until healed	30-g and 60-g tubes
Antiallergic	Sodium cromoglycate, 1%, ophthalmic solution	QD to ulcer until healed	5-mL and 10-mL bottles

Intralesional therapy: useful for isolated lesions			
Drug class	**Agent**	**Dose**	**Preparation**
Corticosteroid	Triamcinolone acetonide, 40 mg/mL	20–40 mg q 4–6 weeks into active border of lesion	5-mL vials Dilute with preserved saline to desired concentration Hold off on further injections if atrophy present

Systemic therapy: moderate disease			
Drug class	**Agent**	**Dose**	**Notes**
Corticosteroid	Prednisone	1 mg/kg/day PO x 3–6-month course	Maximum daily dose 60 mg Taper when ulcer has started to heal: typically reduce daily dose by 5 mg weekly

Systemic therapy: severe disease			
Drug class	**Agent**	**Dose**	**Notes**
TNF-α inhibitor	Infliximab **(first-line therapy)**	5 mg/kg IV q 8 weeks x 6-month trial	Loading dose: 5 mg/kg at weeks 0, 2, and 6 Maintenance dose: 5 mg/kg q 8 weeks Loss of response: Increase dose to 10 mg/kg q 8 weeks *or* Shorten interval to q 4 weeks
Antibiotic	Dapsone	100 mg/day PO x 3–6-month trial	Perform G6PD testing Do not use in patients with G6PD deficiency, due to hemolysis Start at 50 mg/day; increase dose weekly by 50 mg up to 150 mg/day if tolerated Monitor CBC, liver enzymes, creatinine Methemoglobinemia may occur at doses >200 mg/day
Corticosteroid	Methylprednisolone	20 mg IV q 12h	Switch to prednisone with taper once response achieved
	Prednisone	1 mg/kg/day PO x 3–6-months	Maximum daily dose 60 mg Taper once improvement: typically reduce daily dose by 5 mg weekly
Immunomodulator	Azathioprine	2.5 mg/kg PO QD x 3–6-month trial	Start at 50 mg/day Increase 50 mg q 2 weeks to target dose Normal thiopurine methyltransferase (TPMT) genotype/activity: start at target dose Monitor CBC, ALT weekly x 4 weeks, then monthly
	Methotrexate	25 mg SQ, IM, or PO weekly x 3-month trial	May decrease to 15 mg weekly for maintenance Monitor CBC, ALT monthly Supplement folate 1 mg daily Methotrexate is teratogenic
Immunosuppressive	Mycophenolic acid sodium	CellCept, 1 g PO BID, *or* Myfortic, 720 mg PO BID x 6-month trial	Monitor CBC, hepatic enzymes, creatinine, urinalysis, q 2 weeks x 3 weeks, then monthly
Immunoglobulin	Immunoglobulin (various brands, e.g., Gammagard, Gamunex, etc.)	1 g/kg/day IV x 2 days Then 1 g/kg once 1 month later Then 1 g/kg monthly x 6 months	Order through transfusion units
Calcineurin inhibitor	Cyclosporine	3–5 mg/kg/day PO x 3–6 months	Dose is maintenance, non-rescue, bridging to immunomodulator Monitor cyclosporine trough levels: 150–300 ng/mL Monitor CBC, creatinine, BUN, urinalysis, Mg, electrolytes, uric acid, cholesterol Neurotoxicity Hypertension and diabetes *Pneumocystis jiroveci* pneumonia prophylaxis required

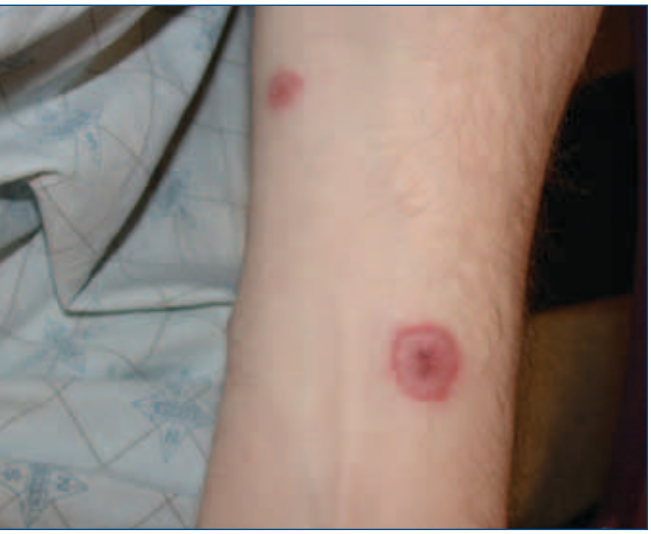
References

Miller J, Yentzer BA, Clark A, Jorizzo JL, Feldman SR. Pyoderma gangrenosum: a review and update on new therapies. *J Am Acad Dermatol* 2010;62:646-54.

Prajapati V, Man J, Brassard A. Pyoderma gangrenosum: common pitfalls in management and a stepwise, evidence-based, therapeutic approach. *J Cutan Med Surg* 2009;13(Suppl 1): S2-11.

Reguiai Z, Grange F. The role of anti-tumor necrosis factor-alpha therapy in pyoderma gangrenosum associated with inflammatory bowel disease. *Am J Clin Dermatol* 2007;8:67-77.

SWEET'S SYNDROME



Relation to IBD

- Rare, acute, febrile neutrophilic dermatosis; may be associated with IBD

Clinical appearance and presentation

- Painful erythematous papules, nodules, and plaques asymmetrically distributed on head, neck, arms, and trunk; may form pseudovesicular lesions or pustules; may ulcerate
- Three clinicopathologic groups:
  - *Classic:* four times as frequent in females as males; 30 to 50% associated with upper respiratory tract infection (URTI), IBD, pregnancy
  - *Malignancy associated:* acute myeloid leukemia (AML) most common
  - *Drug induced:* granulocyte colony-stimulating factor (G-CSF), minocycline, trimethoprim-sulfamethoxazole
- Abrupt onset of painful cutaneous neutrophilic infiltrates with pyrexia ± organ involvement
- Neutrophilic inflammation of the eyes, bones, muscles, lungs, aorta, liver, and intestines has been reported
- Neutrophil count, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) may be elevated

Histology

- Dense mature neutrophilic dermal infiltration with edema; no evidence of vasculitis

Differential diagnosis

- Vasculitis
- Infection: pyoderma, fungal, mycobacterium
- Malignancy: lymphoma and leukemia cutis
- Inflammatory: neutrophilic dermatosis of the dorsal hand, pyoderma gangrenosum

Diagnosis

- Two major and two minor criteria required for diagnosis
- *Major criteria*
  - Sudden onset painful cutaneous lesions
  - Typical biopsy

Diagnosis *(cont'd)*

- *Minor criteria*
  - Preceding fever, infection, IBD, pregnancy
  - Accompanying fever, arthralgia, malignancy, conjunctivitis
  - Leukocytosis, neutrophilia, elevated ESR or CRP
  - Steroid or potassium iodide responsive, antibiotic non responsive
- Malignancy workup should be initiated: full history and physical (including thyroid, digital rectal examination, breast, testicular, pelvic), complete blood count (CBC), peripheral smear, serum protein electrophoresis, urine protein electrophoresis, calcium, lactate dehydrogenase (LDH), ESR, CRP ± chest x-ray, fecal occult blood test, urinalysis, and culture

Treatment

Treatment approaches are summarized below.

Topical therapy: useful for mild lesions			
Drug class	**Agent**	**Application**	**Availability**
Corticosteroid	Clobetasol propionate, 0.05%, unguent	QD to BID x 4–6 weeks	50-g tubes Usually under occlusion q hs
Calcineurin inhibitor	Tacrolimus, 0.1%, unguent	QD to BID x 8 weeks	30-g and 60-g tubes Usually under occlusion q hs

Intralesional therapy: useful for painful lesions			
Drug class	**Agent**	**Dose**	**Preparation**
Corticosteroid	Triamcinolone acetonide, 10 mg/mL	5–10 mg q 4–6 weeks x 3 injections	5-mL vials Dilute with preserved saline to desired concentration Hold off on further injections if atrophy develops

Systemic therapy			
Drug class	**Agent**	**Dose**	**Notes**
Antibiotic	Dapsone	50–100 mg PO BID x 6-month trial	Perform G6PD testing Do not use in patients with G6PD deficiency, due to hemolysis Start at 50 mg/day; increase dose to 100 mg/day after 1 week if tolerated Monitor CBC, liver enzymes, creatinine Methemoglobinemia may occur at doses >200 mg/day
Corticosteroid	Prednisone	1 mg/kg/day PO	Maximum daily dose 60 mg Taper once defervescence occurs: usually reduce by 5 mg weekly over 8–12 weeks
5-ASA	Sulfasalazine	1 g PO BID x 3-month trial	Supplement folate 1 mg daily, especially in young females
Anti-inflammatory	Colchicine	0.6 mg PO, BID to TID, as tolerated x 3-month trial	
	Saturated solution of potassium iodide (SSKI)	Start with 5 drops TID PO Increase to 10 drops TID as tolerated x 3-month trial	Write prescription as follows: Potassium iodide, SSKI Give in milk or juice Each drop contains 67 mg potassium iodide Monitor thyroid for Wolf-Chaikoff or Jod-Basedow effect

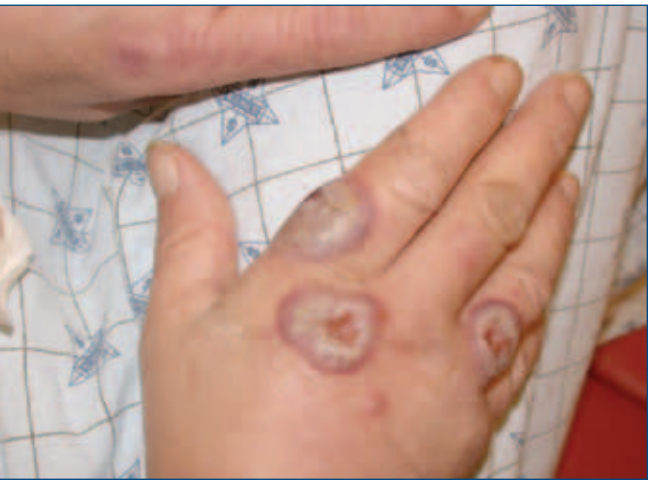
References

Boh EE, al-Smadi RM. Cutaneous manifestations of gastrointestinal diseases. *Dermatol Clin* 2002;20:533-46.

Cohen PR. Sweet's syndrome–a comprehensive review of an acute febrile neutrophilic dermatosis. *Orphanet J Rare Dis* 2007;2:34.

Su WP, Liu HN. Diagnostic criteria for Sweet's syndrome. *Cutis* 1986;37:167-74.

NEUTROPHILIC DERMATOSIS OF THE DORSAL HAND



Relation to IBD

- 15% of patients have underlying IBD; other associations include malignancy, streptococcus infection, Raynaud's disease

Clinical appearance and presentation

- Clinically indistinguishable from atypical pyoderma gangrenosum
- Painful violaceous nodules and plaques, may form pustules and/or ulcerate
- Lesions generally restricted to dorsal hands
- May have elevated temperature, ESR, CRP, and white blood cell (WBC) count

Histology

- Histologically indistinguishable from atypical pyoderma gangrenosum
- Dense neutrophilic infiltration of dermis, possibly with evidence of leukocytoclastic vasculitis

Differential diagnosis

- Sweet's syndrome, pyoderma gangrenosum, vasculitis; infection, such as blastomycosis or mycobacterial infection

Diagnosis

- Clinical presentation with typical biopsy, in the absence of infection
- Rapid response to prednisone often seen

Treatment

Treatment is essentially the same as for pyoderma gangrenosum and Sweet's syndrome (see *pyoderma gangrenosum*, page 4, and *Sweet's syndrome*, page 6). Provide moist wound care for all lesions. Treatment approaches are summarized below.

Topical therapy			
Drug class	**Agent**	**Application**	**Availability**
Corticosteroid	Clobetasol propionate, 0.05%, unguent	BID x 4–8 weeks	50-g tubes

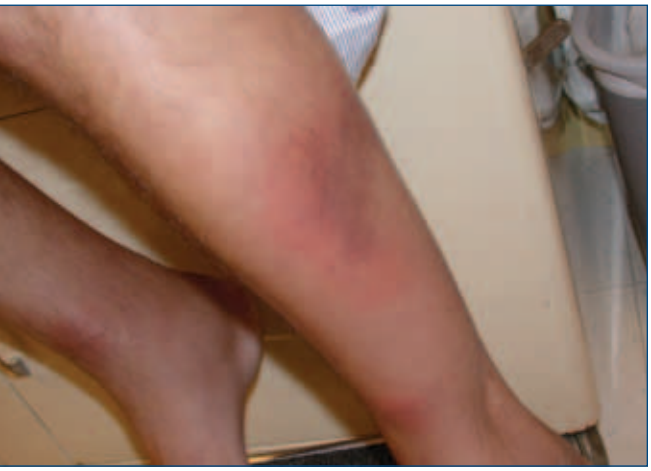
Systemic therapy			
Drug class	**Agent**	**Dose**	**Notes**
Antibiotic	Dapsone	50–100 mg/day PO x 3–6-month trial	Perform G6PD testing Do not use in patients with G6PD deficiency, due to hemolysis Start at 50 mg/day; increase dose to 100 mg/day if tolerated Monitor CBC, liver enzymes, creatinine Methemoglobinemia may occur at doses >200 mg/day
Corticosteroid	Prednisone	1 mg/kg/day PO	Maximum daily dose 60 mg Taper once improvement: usually reduce dose by 5 mg weekly over 8–12 weeks
5-ASA	Sulfasalazine	1 g PO BID x 3-month trial	Supplement folate 1 mg daily, especially in young females
Anti-inflammatory	Colchicine	0.6 mg PO, BID–TID, as tolerated x 3-month trial	
	Saturated solution of potassium iodide (SSKI)	Start with 5 drops TID PO Increase to 10 drops TID as tolerated x 3-month trial	Write prescription as follows: Potassium iodide, SSKI Give in milk or juice Each drop contains 67 mg potassium iodide Monitor thyroid for Wolf-Chaikoff or Jod-Basedow effect
Immunosuppressive	Mycophenolic acid sodium	CellCept, 1 g PO BID, *or* Myfortic, 720 mg PO BID x 6-month trial	Monitor CBC, hepatic enzymes, creatinine, urinalysis, q 2 weeks x 3, then monthly

References

Larsen HK, Danielsen AG, Krustrup D, Weismann K. Neutrophil dermatosis of the dorsal hands. *J Eur Acad Dermatol Venereol* 2005;19:634-7.

Walling HW, Snipes CJ, Gerami P, Piette WW. The relationship between neutrophilic dermatosis of the dorsal hands and Sweet's syndrome: report of 9 cases and comparison to atypical pyoderma gangrenosum. *Arch Dermatol* 2006;142:57-63.

ERYTHEMA NODOSUM



IBD associations

- Most common cause of inflammatory nodules on leg, likely due to delayed hypersensitivity response to immune complexes
- Most common skin manifestation of IBD, seen in 10% of IBD patients
- Parallels disease activity but not severity

Clinical appearance and presentation

- Sudden onset, often associated with fever, synovitis, and arthritis
- Multiple bilaterally symmetrical erythematous, warm, painful nodules
- Round or oval lesions, 2 to 10 cm in diameter
- Initially reddish brown, eventually developing blue colour
- Usually on shins, but can be found on calves, trunk, and face
- Typically no ulceration or scarring

Histology

- Not usually biopsied
- If lesions are atypical or ulcerating, use incisional biopsy
- Subcutaneous septae infiltrated with neutrophils, lymphocytes, and histiocytes, without associated vasculitis

Differential diagnosis

- Systemic infection: streptococcus, tuberculosis (TB), yersinia, salmonella, coccidioides
- Sarcoidosis, Sweet's syndrome, connective tissue disease, IBD, Behçet's syndrome, lymphoma, pregnancy
- Drug reaction: oral contraceptives, penicillin, sulfa

Diagnosis

- Biopsy is usually not required; consistent history and physical examination provides diagnosis

Treatment

First-line therapy is conservative and consists of rest, compression, elevation ± nonsteroidal anti-inflammatory drugs (NSAIDs) cautiously, as NSAID therapy may provoke an IBD flare. This treatment resolves most cases in 6 weeks. Other treatment options are listed below.

Systemic therapy: second-line therapy			
Drug class	**Agent**	**Dose**	**Notes**
Corticosteroid	Prednisone	0.5 mg/kg/day PO x 3–4 weeks	Maximum daily dose 40 mg Taper by 5 mg q 3–5 days until off over 6–8 weeks
Antibiotic	Dapsone	50–100 mg/day PO x 3-month trial	Perform G6PD testing Do not use in patients with G6PD deficiency, due to hemolysis Start at 50 mg/day; increase dose to 100 mg/day after 1 week if tolerated Monitor CBC, liver enzymes, creatinine Methemoglobinemia may occur at doses >200 mg/day
Immunomodulator	Hydroxychloroquine	<6.5 mg/kg/day PO, divided BID, x 3–6-month trial	Tablet (200 mg) cannot be broken Based on weight, dosing may be Monday to Friday, Monday to Saturday, or daily
5-ASA	Sulfasalazine	1–1.5 g PO BID x 3-month trial	Supplement folate 1 mg daily, especially in young females
Anti-inflammatory	Saturated solution of potassium iodide (SSKI)	Start with 5 drops TID PO Increase to 10 drops TID as tolerated, x 3-month trial	Write prescription as follows: Potassium iodide, SSKI Give in milk or juice Each drop contains 67 mg potassium iodide Monitor thyroid for Wolf-Chaikoff or Jod-Basedow effect

Systemic therapy: third-line therapy			
Drug class	**Agent**	**Dose**	**Notes**
TNF-α inhibitor	Infliximab	5 mg/kg IV q 8 weeks	Loading dose: 5 mg/kg at weeks 0, 2, and 6 Usually responds by 3 infusions Maintenance dose: 5 mg/kg q 8 weeks Loss of response: Increase dose to 10 mg/kg q 8 weeks *or* Shorten interval to q 4 weeks
	Adalimumab	40 mg SC q 2 weeks	Loading dose: 160 mg week 0, 80 mg week 2 Maintenance dose: 40 mg q 2 weeks Usually responds by 4–6 injections Loss of response: shorten interval to weekly

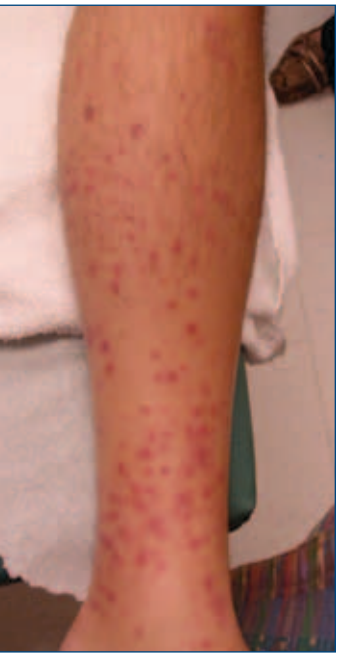
References

Calabrese L. Cutaneous vasculitis, hypersensitivity vasculitis, erythema nodosum, and pyoderma gangrenosum. *Curr Opin Rheumatol* 1991;3:23-7.

Feliciani C, De Simone C, Amerio P. Dermatological signs during inflammatory bowel disease. *Eur Rev Med Pharmacol Sci* 2009;13(Suppl 1): 15-21.

Trost LB, McDonnell JK. Important cutaneous manifestations of inflammatory bowel disease. *Postgrad Med J* 2005;81:580-5.

LEUCOCYTOCLASTIC VASCULITIS



Relation to IBD

- Inflammation of post-capillary venules, believed to result from immune complex formation
- Seen with both ulcerative colitis (UC) and Crohn's disease (CD), more common with UC

Clinical appearance and presentation

- Typically presents with palpable purpura or infiltrated erythema on legs and dependent areas
- Other presentations include nodular erythema, livedo reticularis, or ulceration
- Systemic symptoms, such as pyrexia, malaise, arthralgia, and arthritis are common

Histology

- Initial neutrophilic infiltrate followed by macrophages and lymphocytes
- Direct immunofluorescence demonstrates IgG, IgA or IgM ± C3 (surrounding or within the vessel wall)

Differential diagnosis

- Henoch-Schönlein purpura, urticarial vasculitis, Sweet's syndrome, neutrophilic dermatosis
- Often associated with systemic conditions:
  - Autoimmune disorders: Sjögren's disease, RA, SLE

Differential diagnosis *(cont'd)*

  - Anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitides: Churg-Strauss syndrome, Wegener's granulomatosis
  - Infection: hepatitis B virus (HBV), HCV, streptococcus, staphylococcus
  - Other associations: cryoglobulinemia, cryofibrinogenemia, lymphoproliferative disorders, myeloproliferative disorders
  - Drug-induced vasculitis: thiazide diuretics and trimethoprim-sulfamethoxazole are most common drug causes

Diagnosis

- Skin biopsy essential
- Workup for associated systemic disorders may be indicated
- Essential to rule out renal involvement

Treatment

Aggressive treatment of the underlying disease is critical for effective treatment of secondary vasculitis. Limb elevation, analgesia, and compression stockings are recommended for all patients. Topical therapy may be effective for disease limited to the skin. Systemic therapy is used for extensive or generalized disease, such as renal or neurologic involvement.

Topical therapy: disease limited to the skin			
Drug class	**Agent**	**Application**	**Availability**
Corticosteroid	Clobetasol propionate, 0.05%, unguent	QD x 4 weeks	50-g tubes
	Fluocinonide, 0.05%, unguent	BID x 4–6 weeks	60-g tubes
	Betamethasone dipropionate, 0.05%, unguent	BID x 4–6 weeks	50-g tubes

Systemic therapy: limited disease			
Drug class	**Agent**	**Dose**	**Notes**
Antibiotic	Dapsone	25–100 mg/day PO x 3-month trial	Perform G6PD testing Do not use in patients with G6PD deficiency, due to hemolysis Start at 25 mg/day; increase dose to 50 mg/day after 1 week if tolerated Monitor CBC, liver enzymes, creatinine Methemoglobinemia may occur at doses >200 mg/day
Anti-inflammatory	Colchicine	0.6 mg PO, BID–TID, as tolerated, x 3-month trial	

Systemic therapy: first-line therapy for systemic disease Begin with methylprednisolone or with prednisone, and then, after tapering prednisone, trial dapsone, sulfasalazine, or hydroxychloroquine			
Drug class	**Agent**	**Dose**	**Notes**
Corticosteroid	Methylprednisolone	1 g IV daily x 3 days	Switch to prednisone with taper once response achieved
	Prednisone	1–1.5 mg/kg/day PO, up to 3 weeks	Taper by 5 mg q 3–5 days until off over 6–8 weeks
Antibiotic	Dapsone	25–100 mg/day PO x 3-month trial	Perform G6PD testing Do not use in patients with G6PD deficiency, due to hemolysis Start at 25 mg/day; increase dose by 25 mg weekly if tolerated Monitor CBC, liver enzymes, creatinine Methemoglobinemia may occur at doses >200 mg/day
5-ASA	Sulfasalazine	1 g PO BID x 3-month trial	Supplement folate 1 mg daily, especially in young females
Immunomodulator	Hydroxychloroquine	<6.5 mg/kg/day PO divided BID x 3–6-month trial	Tablet (200 mg) cannot be broken Based on weight, dosing may be Monday to Friday, Monday to Saturday, or daily

Systemic therapy: second-line therapy for systemic disease			
Drug class	**Agent**	**Dose**	**Notes**
Immunomodulator	Azathioprine	2.5 mg/kg/day PO x 3–6-month trial	Start at 50 mg/day Increase 50 mg q 2 weeks to target dose Normal TPMT genotype/activity: start at target dose Monitor CBC, ALT weekly x 4 weeks, then monthly
	Methotrexate	25 mg SQ, IM, or PO weekly x 3-month trial	May decrease to 15 mg weekly for maintenance Monitor CBC, ALT monthly Supplement folate 1 mg daily Methotrexate is teratogenic
Immunosuppressive	Mycophenolic acid sodium	CellCept, 1 g PO BID, *or* Myfortic, 720 mg PO BID x 6-month trial	Monitor CBC, hepatic enzymes, creatinine, urinalysis, q 2 weeks x 3 weeks, then monthly
Disease-modifying anti-rheumatic drug	Leflunomide	20 mg/day PO x 3-month trial	Loading dose: 100 mg/day PO x 3 days Maintenance dose: 10–20 mg/day PO Monitor CBC, hepatic enzymes, creatinine, q 2 weeks x 3, then monthly
Alkylating agent	Cyclophosphamide	1–1.25 mg/kg/day PO in AM x 3–4-month trial	2–3 L fluid consumption during day to prevent hemorrhagic cystitis from acrolein products Monitor CBC, liver enzymes, creatinine, urinalysis q 2 weeks *Pneumocystis jiroveci* pneumonia prophylaxis required

Systemic therapy: third-line therapy			
Drug class	**Agent**	**Dose**	**Notes**
	Plasmapheresis		Done q 2–4 weeks in transfusion unit
Immunoglobulin	Immunoglobulin (various brands, e.g., Gammagard, Gamunex, etc.)	1 g/kg/day IV x 2 days Then 1 g/kg once 1 month later Then 1 g/kg monthly x 6-month trial	Order from transfusion unit
TNF-α inhibitor	Infliximab	5 mg/kg IV q 8 weeks	Loading dose: 5 mg/kg at weeks 0, 2, and 6 Maintenance dose: 5 mg/kg q 8 weeks Responds by 2–4 infusions Loss of response: Increase dose to 10 mg/kg q 8 weeks *or* Shorten interval to q 4 weeks
Monoclonal CD20 antibody	Rituximab	1000 mg IV, days 1 and 15	Pre-medicate 15–30 minutes before infusion with acetaminophen 650 mg, diphenhydramine 50 mg, and methylprednisolone 100 mg IV Consider second course in 6 months if CD20 count increasing on flow cytometry

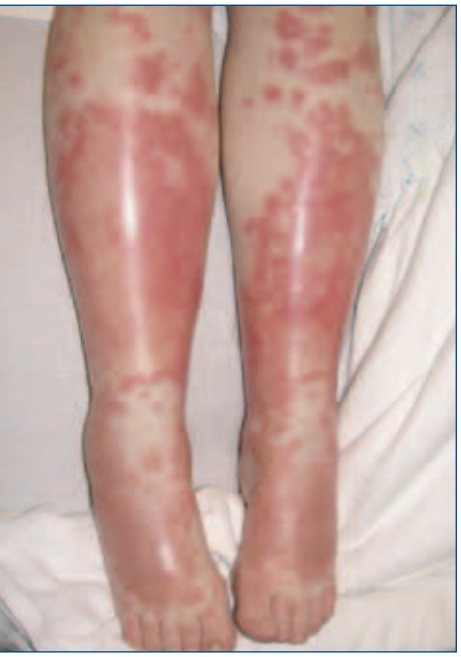
References

Akbulut S, Ozaslan E, Topal F, Albayrak L, Kayhan B, Efe C. Ulcerative colitis presenting as leukocytoclastic vasculitis of skin. *World J Gastroenterol* 2008;14:2448-50.

Carlson JA, Chen KR. Cutaneous vasculitis update: small vessel neutrophilic vasculitis syndromes. *Am J Dermatopathol* 2006;28:486-506.

Chen KR, Carlson JA. Clinical approach to cutaneous vasculitis. *Am J Clin Dermatol* 2008;9:71-92.

SNEDDEN-WILKINSON DISEASE



Relation to IBD

- Extremely rare in IBD, cases limited to small number of case reports

Clinical appearance and presentation

- Rare, relapsing, pustular eruption most commonly seen in middle-aged females
- Distribution symmetric, flexures most frequently involved
- Small flaccid pustules on normal or mildly erythematous skin rapidly coalesce into annular or serpiginous patterns, then rupture followed by scaling, crusting, light hyperpigmentation
- Also known as subcorneal pustular dermatosis

Histology

- *Light microscopy*
  - Subcorneal pustules on normal epidermis, with migrating neutrophils and associated spongiosis
- *Immunofluorescence*
  - Generally negative vs. IgA pemphigus, which has positive IgA intercellular immunofluorescence

Differential diagnosis

- Pustular psoriasis, dermatitis herpetiformis, impetigo, IgA pemphigus, pemphigus foliaceus
- Systemic associations: lymphoproliferative disorders, especially multiple myeloma, IgA or IgG monoclonal gammopathies, pyoderma gangrenosum, SLE, RA

Diagnosis

- Characteristic clinical presentation and histopathology

Treatment

The range of treatment approaches is summarized below.

Topical therapy: may help in localized disease			
Drug class	**Agent**	**Application**	**Availability**
Corticosteroid	Clobetasol propionate, 0.05%, unguent	BID x 4–8 weeks	50-g tubes Use for trunk
	Halobetasol, 0.05%, unguent	BID x 4–8 weeks	50-g tubes Use for trunk
	Hydrocortisone valerate, 0.2%, cream	BID x 4–8 weeks	60-g tubes Use for skin folds

Systemic therapy: first-line therapy			
Drug class	**Agent**	**Dose**	**Notes**
Antibiotic	Dapsone	50–200 mg/day PO x 3-month trial	Perform G6PD testing Do not use in patients with G6PD deficiency, due to hemolysis Start at 50 mg/day; increase weekly by 50 mg to 200 mg/day if tolerated Resolution may take 4 weeks Reduce dose to lowest maintenance dose once lesions resolved Long-term prophylaxis at lowest maintenance dose may be necessary Monitor CBC, liver enzymes, creatinine Methemoglobinemia may occur at doses >200 mg/day

Systemic therapy: second-line therapy			
Drug class	**Agent**	**Dose**	**Notes**
Corticosteroid	Prednisone	40 mg/day PO x 4–6 weeks	± dapsone (see above) Taper 5 mg/week down to 20 mg then 2.5 mg/week until off
Retinoid	Isotretinoin	0.5–1 mg/kg/day, divided BID x 15–20 weeks	Maximum 120 mg/kg total dose Monitor CBC, ALT, AST, creatinine, lipids, monthly x 3 months Teratogenic: 2 forms of birth control mandatory Monitor β-human chorionic gonadotropin monthly Implicated in IBD without much evidence Associated with benign intracranial hypertension (pseudotumor cerebri)
TNF-α inhibitor	Infliximab	5 mg/kg IV q 8 weeks	Loading dose: 5 mg/kg at weeks 0, 2, and 6 Maintenance dose: 5 mg/kg q 8 weeks Usually responds by 3–4 infusions Loss of response: Increase dose to 10 mg/kg q 8 weeks *or* Shorten interval to q 4 weeks

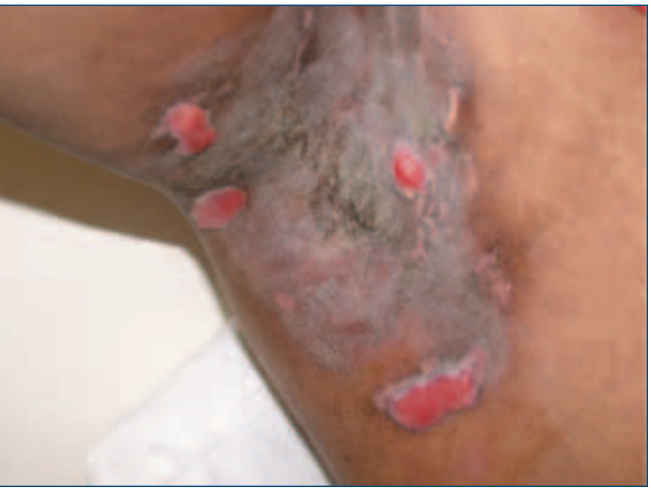
References

Cohen PR. Neutrophilic dermatoses: a review of current treatment options. *Am J Clin Dermatol* 2009;10:301-12.

Reed J, Wilkinson J. Subcorneal pustular dermatosis. *Clin Dermatol* 2000;18:301-13.

Vazquez J, Almagro M, del Pozo J, Fonseca E. Neutrophilic pustulosis and ulcerative colitis. *J Eur Acad Dermatol Venereol* 2003;17:77-9.

HIDRADENITIS SUPPURATIVA



Relation to IBD

- The prevalence of CD in patients with hidradenitis suppurativa has been reported to be as high as 40%
- All have an affected perineum plus extensive extraperineal involvement
- Unknown whether CD is a potential trigger

Clinical appearance and presentation

- A chronic, recurrent, inflammatory, occlusive disease of the hair follicle, also known as acne inversa (previously Verneuil's disease)
- Lesions present in the intertriginous areas: axillae, groin, neck, and inframammary area
- Classical: early 20s, F>M, up to 40% have family history
- Progressive lesions:
  - *Primary lesions:* erythematous, pruritic, indurated papules and nodules ± pustules and painful abscesses; may initially resolve fully
  - *Secondary lesions:* erythematous draining sinus tracts with granulation tissue and hypertrophic scarring as primary lesions become chronic, coalescent and interlinked
  - *Tertiary lesions:* aberrant healing producing subcutaneous networks of thick, ropy, fibrous tracts, which may decrease range of motion

Histology

- Infundibular follicular occlusion with subsequent follicular dilation, rupture, and apocrine gland stasis
- Dermal perifolliculitis and squamous epithelial-lined cysts
- Abscess formation and destruction of the pilosebaceous unit with sinus tract formation and extensive granulomatous and suppurative inflammatory infiltrate and fibrosis

Differential diagnosis

- Bacterial infection: abscess, carbuncles, furuncles, TB, granuloma inguinale, lymphogranuloma venereum, noduloulcerative syphilis
- Fungal infection: blastomycosis, nocardidiosis
- Cysts: epidermoid, pilonidal
- CD: fistulae

Diagnosis

- Age, location and clinical course are critical to diagnosis
- Must meet all criteria:
  - *Typical lesions:* primary painful, deep nodules or abscesses plus secondary draining sinuses, bridged scars, grouped open comedones ('tombstone comedones')
  - *Typical topography:* intertriginous skin of axillae, groin, genitals, perineal region, buttock, and mammary folds
  - *Chronicity or recurrence*

Treatment

The range of treatment approaches is summarized below. In addition to pharmacotherapy, laser removal of all hairs within intertriginous regions using a long-pulsed Nd-YAG laser may be useful. Surgical therapy consists of de-roofing abscesses, marsupializing sinus tracts, excising affected skin, and skin grafting.

Topical therapy			
Drug class	**Agent**	**Application**	**Availability**
Antibiotic	Clindamycin, 1–2%, in isopropyl alcohol	BID x 8–12 weeks	60-mL bottles

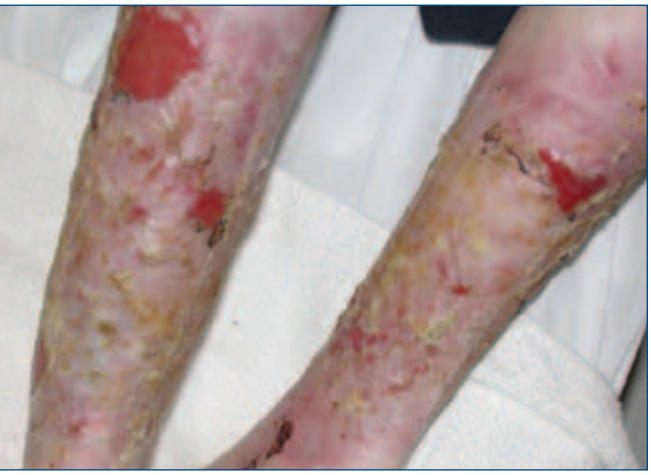
Systemic therapy			
Drug class	**Agent**	**Dose**	**Notes**
Antibiotic **(often in combination)**	Metronidazole	500 mg PO BID x 8 weeks	Warn patient about potential disulfiram reaction with alcohol Peripheral neuropathy
	Tetracycline	500 mg PO BID x 3–6 months	250-mg capsules Take on empty stomach Avoid calcium 2 hours before to 4 hours after dose
	Clindamycin	300 mg PO BID x 8 weeks	
	Rifampicin	600 mg/day PO QD x 8 weeks	
	Trimethoprim-sulfamethoxazole DS	800/160 mg/day PO x 3–6 months	
	Dapsone	50–200 mg/day PO x 3-month trial	Perform G6PD testing Do not use in patients with G6PD deficiency, due to hemolysis Start at 50 mg/day; increase weekly by 50 mg to 200 mg/day if tolerated Monitor CBC, liver enzymes, creatinine Methemoglobinemia may occur at doses >200 mg/day
Retinoid	Isotretinoin	0.5–1 mg/kg/day, divided BID, x 3-month trial	Maximum 120 mg/kg total dose Typical treatment duration 15–20 weeks Monitor CBC, ALT, AST, creatinine, lipids monthly x 3 months Teratogenic: 2 forms of birth control mandatory Monitor β-human chorionic gonadotropin monthly Implicated in IBD without much evidence Associated with benign intracranial hypertension (pseudotumor cerebri)
Anti-androgen	Spironolactone	50–100 mg PO qhs x 6-month trial	Consider electrolyte testing after 1 week in elderly patients
	Finasteride	5 mg/day PO x 6-month trial	Teratogenic No blood work required
	Cyproterone acetate	50 mg/day PO x 6-month trial	
	Flutamide	250 mg/day PO x 3-month trial	Monitor CBC, liver enzymes, creatinine monthly x 3 months
TNF-α inhibitor	Infliximab	5 mg/kg IV q 8 weeks x 3–4-infusions trial Permanent in responders	Loading dose: 5 mg/kg at weeks 0, 2, and 6 Maintenance dose: 5 mg/kg q 8 weeks Loss of response: Increase dose to 10 mg/kg q 8 weeks *or* Shorten interval to q 4 weeks
	Adalimumab	40 mg SC q 2 weeks x 3-month trial Permanent in responders	Loading dose: 160 mg week 0, 80 mg week 2 Maintenance dose: 40 mg q 2 weeks Loss of response: Shorten interval to weekly

References

Alikhan A, Lynch PJ, Eisen DB. Hidradenitis suppurativa: a comprehensive review. *J Am Acad Dermatol* 2009;60:539-61.

Danby FW, Margesson LJ. Hidradenitis suppurativa. *Dermatol Clin* 2010; 28:779-93.

EPIDERMOLYSIS BULLOSA ACQUISITA



Relation to IBD

- A rare autoimmune disorder with antibodies to type VII collagen, associated more often with CD than UC

Clinical appearance and presentation

- Extreme fragility of the skin with blistering ± mucus membrane involvement
- Lesions preferentially occur at trauma sites, such as extensor surfaces of limbs, frequently heal with scarring

Histology

- *Light microscopy:* blistering in subepidermal region ± variable leukocyte infiltrate
- *Direct immunofluorescence:* linear deposits of IgG ± C3 at the dermoepidermal junction

Differential diagnosis

- Bullous disorders: pemphigus, bullous pemphigoid, linear IgA disease, bullous lupus erythematosus

Diagnosis

- Clinical, histologic, and immunofluorescence features are suggestive but non-diagnostic
- Diagnosis based on presence of antibodies to type VII collagen (immuoblot analysis or enzyme-linked immunosorbent assay [ELISA])

Treatment

Epidermolysis bullosa acquisita is often refractory to treatment. Ensuring adequate nutrition and meticulous wound care with aggressive treatment of infection are important, along with avoiding hard foods and trauma where possible. **Topical therapy has no role in treatment.** Treatment options are summarized below.

Systemic therapy: mild disease Prednisone is recommended ± dapsone or colchicine			
Drug class	**Agent**	**Dose**	**Notes**
Corticosteroid	Prednisone	0.5–1 mg/kg/day PO x 2–3 months then slow taper	± dapsone or colchicine Taper over 3–6 months
Antibiotic	Dapsone	100–200/mg/day PO x 6-month trial	Perform G6PD testing Do not use in patients with G6PD deficiency, due to hemolysis Start at 50 mg/day; increase dose weekly by 50 mg/day if tolerated Monitor CBC, liver enzymes, creatinine Methemoglobinemia may occur at doses >200 mg/day
Anti-inflammatory	Colchicine	0.6 mg PO, BID to TID, as tolerated, x 3-month trial	

Systemic therapy: moderate to severe disease Prednisone is used in combination with one of the following: dapsone, colchicine, azathioprine, intravenous immunoglobulin, cyclophosphamide, or rituximab			
Drug class	**Agent**	**Dose**	**Notes**
Corticosteroid	Prednisone	1–1.5 mg/kg/day PO x 1–3 months	Combine with dapsone, colchicine, azathioprine, intravenous immunoglobulin, cyclophosphamide, or rituximab (may be long term) Taper over 3–6 months
Immunomodulator	Azathioprine	2.5 mg/kg/day PO x 6-month trial	Start at 50 mg/day Increase 50 mg q 2 weeks to target dose Normal TPMT genotype: start at 50 mg BID Monitor CBC, ALT weekly x 4 weeks, then monthly
Alkylating agent	Cyclophosphamide	1–1.25 mg/kg/day PO in AM x 6-month trial	2–3 L fluid consumption during day to prevent hemorrhagic cystitis from acrolein products Monitor CBC, liver enzymes, creatinine, urinalysis q 2 weeks *Pneumocystis jiroveci* pneumonia prophylaxis required
Immunoglobulin	Immunoglobulin (various brands, e.g., Gammagard, Gamunex, etc.)	1 g/kg/day IV x 2 days Then 1 g/kg once 1 month later Then 1 g/kg monthly x 6-month trial	Order through transfusion unit
Monoclonal CD20 antibody	Rituximab	1000 mg IV, days 1 and 15	Pre-medicate 15–30 minutes before infusion with acetaminophen 650 mg, diphenhydramine 50 mg, and methylprednisolone 100 mg IV Consider second course in 6 months if CD20 count increasing on flow cytometry

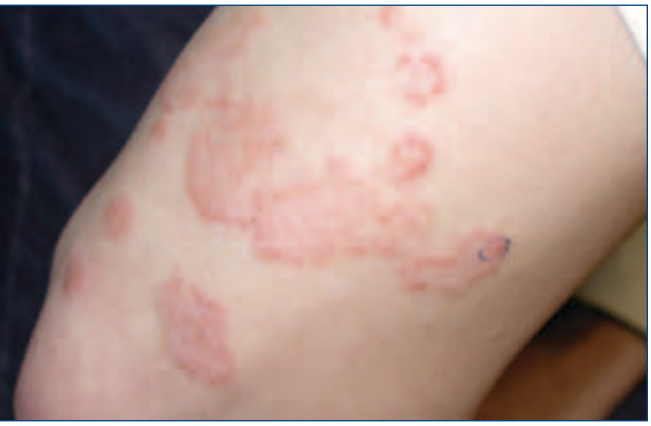
References

Hundorfean G, Neurath MF, Sitaru C. Autoimmunity against type VII collagen in inflammatory bowel disease. *J Cell Mol Med* 2010;14:2393-403.

Ishii N, Hamada T, Dainichi T, Karashima T, Nakama T, Yasumoto S, *et al.* Epidermolysis bullosa acquisita: what's new? *J Dermatol* 2010;37:220-30.

Yeh SW, Ahmed B, Sami N, Razzaque Ahmed A. Blistering disorders: diagnosis and treatment. *Dermatol Ther* 2003;16:214-23.

LINEAR IgA DISEASE



Relation to IBD

- Rare autoimmune blistering disorder described in association with CD, more common with UC

Clinical appearance and presentation

- Pruritic urticarial plaques with central clearing, clusters of annular papules, vesicles and bullae
- Often on extensor surfaces, surrounded by normal skin
- Oral ulceration and conjunctivitis may be seen
- 'String of pearls' sign may be present: new blisters occurring at edges of previous blisters
- In pediatric patients, known as chronic bullous disease of childhood

Histology

- *Light microscopy:* subepidermal bullae, neutrophilic accumulation along basement membrane and tips of dermal papillae
- *Direct immunofluorescence:* linear IgA ± IgG and C3 deposits along basement membrane

Differential diagnosis

- Dermatitis herpetiformis, bullous pemphigoid, bullous impetigo
- Association with medications (i.e., lithium, vancomycin, diclofenac), malignancies, autoimmune and connective tissues disorders

Diagnosis

- Skin biopsy with linear IgA deposits diagnostic: may be negative early in disease course
- Nonspecific histopathology: similar in bullous lupus erythematosus, bullous pemphigoid, mucosal membrane pemphigoid

Treatment

Treatment approaches are listed below.

Topical therapy			
Drug class	**Agent**	**Application**	**Availability**
Corticosteroid	Clobetasol propionate, 0.05%, unguent	BID x 6–8 weeks	50-g tubes

Systemic therapy: first line			
Drug class	**Agent**	**Dose**	**Notes**
Antibiotic	Dapsone	25–50 mg/day PO x 3–6-month trial	Perform G6PD testing Do not use in patients with G6PD deficiency, due to hemolysis Start at 25 mg/day; increase dose by 25 mg/day after 1 week if tolerated Monitor CBC, liver enzymes, creatinine Methemoglobinemia may occur at doses >200 mg/day

Systemic therapy: second line			
Drug class	**Agent**	**Dose**	**Notes**
5-ASA	Sulfasalazine	1 g PO BID x 3-month trial	Supplement folate 1 mg daily, especially young females
Anti-inflammatory	Colchicine	0.6 mg PO, BID–TID, as tolerated, x 3-month trial	

Systemic therapy: third line Use prednisone in combination with azathioprine, mycophenolic acid, leflunomide, or cyclophosphamide			
Drug class	**Agent**	**Dose**	**Notes**
Corticosteroid	Prednisone	0.5–1 mg/kg/day PO x 4–6 weeks	Combine with azathioprine, mycophenolic acid, leflunomide, or cyclophosphamide Taper by 5 mg q 2 weeks over 2–6 months
Immunomodulator	Azathioprine	2.5 mg/kg/day PO x 3–6-month trial	Start at 50 mg/day Increase 50 mg q 2 weeks to target dose Normal TPMT genotype/activity: start at target dose Monitor CBC, ALT weekly x 4 weeks, then monthly
Immunosuppressive	Mycophenolic acid sodium	CellCept, 1 g PO BID, *or* Myfortic, 720 mg PO BID x 6-month trial	Monitor CBC, hepatic enzymes, creatinine, urinalysis, q 2 weeks x 3 weeks, then monthly
Disease-modifying anti-rheumatic drug	Leflunomide	20 mg/day PO x 3-month trial	Loading dose: 100 mg/day PO x 3 days Maintenance dose: 10–20 mg/day PO Monitor CBC, hepatic enzymes, creatinine, q 2 weeks x 3, then monthly
Alkylating agent	Cyclophosphamide	1–1.25 mg/kg/day PO in AM x 6-month trial	2–3 L fluid consumption during day to prevent hemorrhagic cystitis from acrolein products Monitor CBC, liver enzymes, creatinine, urinalysis q 2 weeks *Pneumocystis jiroveci* pneumonia prophylaxis required

Systemic therapy: other agents			
Drug class	**Agent**	**Dose**	**Notes**
Antibiotic	Cloxacillin	500 mg PO QID x 6-week trial	
	Erythromycin	250–500 mg PO QID x 3-month trial	
Immunoglobulin	Immunoglobulin (various brands, e.g., Gammagard, Gamunex, etc.)	1 g/kg/day IV x 2 days Then 1 g/kg once 1 month later Then 1 g/kg monthly x 6-month trial	Order through transfusion unit
Monoclonal CD20 antibody	Rituximab	1000 mg IV, days 1 and 15	Pre-medicate 15–30 minutes before infusion with acetaminophen 650 mg, diphenhydramine 50 mg, and methylprednisolone 100 mg IV Consider second course in 6 months if CD20 count increasing on flow cytometry

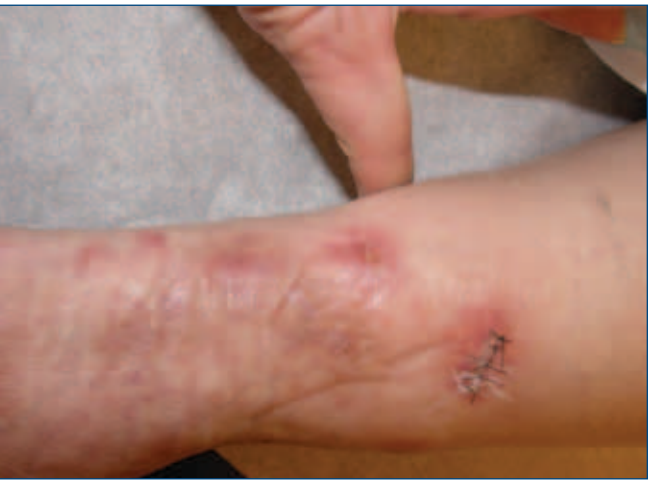
References

Bickle K, Roark TR, Hsu S. Autoimmune bullous dermatoses: a review. *Am Fam Physician* 2002;65:1861-70.

Lara-Corrales I, Pope E. Autoimmune blistering diseases in children. *Semin Cutan Med Surg* 2010;29:85-91.

Paige DG, Leonard JN, Wojnarowska F, Fry L. Linear IgA disease and ulcerative colitis. *Br J Dermatol* 1997;136:779-82.

METASTATIC CROHN'S DISEASE



Relation to IBD

- This is a very rare cutaneous manifestation of IBD
- 80% of adults diagnosed with metastatic CD have previously diagnosed CD; in contrast, only 15% of pediatric patients have previously diagnosed CD, although all develop it subsequently
- High rate of concurrent perianal disease
- Bowel resection does not affect course
- Presentation in pediatric IBD patients is extremely rare

Clinical appearance and presentation

- Non-caseating, cutaneous granulomas separated from gastrointestinal tract by normal tissue (i.e., not associated with enterocutaneous fistula)
- *Single or multiple lesions:* may have a perivascular distribution, generally asymptomatic but sometimes tender
- *Non-genital:* red-brown papules, nodules or erythematous plaques ± ulceration especially in intertriginous areas (more common in adult patients)
- *Genital:* swelling ± erythema and ulceration (more common in pediatric patients)

Histology

- Discrete, non-caseating granuloma with multinucleated giant cells in the superficial and deep dermis and adipose tissue with perivascular or perifollicular neutrophilia

Differential diagnosis

- May mimic large number of dermatoses: TB, sarcoidosis, Wegener's granulomatosis, Behçet's syndrome, foreign body reactions, hidradenitis suppurativa, sexually transmitted infection (STI)

Diagnosis

- Skin biopsy diagnostic with negative cultures
- Tissue biopsy: Periodic-acid schiff (PAS) stain, Ziehl-Neelsen (ZN) stain, Gram stain
- Chest x-ray
- TB testing
- STI workup if genital lesions present

Treatment

- No established guidelines or widely accepted therapies exist, although treatment with a tumour necrosis factor-α (TNF-α) inhibitor may be highly effective. Treatment options are summarized below. Surgical therapy constitutes the last-line treatment and may include curettage, excision, and skin grafting.

Topical therapy			
Drug class	**Agent**	**Application**	**Availability**
Corticosteroid	Clobetasol propionate, 0.05%, unguent	BID x 4 weeks	50-g tube
Calcineurin inhibitor	Tacrolimus, 0.1%, unguent	BID x 8 weeks	30-g and 60-g tubes
	Pimecrolimus, 1%, cream	BID x 8 weeks	30-g and 60-g tubes

Intralesional therapy			
Drug class	**Agent**	**Dose**	**Preparation**
Corticosteroid	Triamcinolone acetonide, 40 mg/mL	5–20 mg q 4–6 weeks x 2–3 injections maximum	5-mL vials Dilute with preserved saline to desired concentration Hold off on further injections if atrophy develops

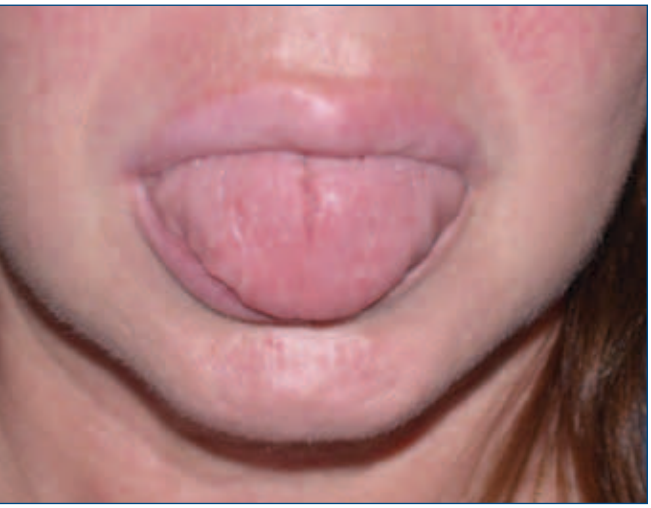
Systemic therapy			
Drug class	**Agent**	**Dose**	**Notes**
Antibiotic	Metronidazole	500 mg PO BID x 8 weeks	Warn patient about potential disulfiram reaction with alcohol Peripheral neuropathy
	Tetracycline	250–500 mg PO BID x 12 weeks	Take on empty stomach Avoid calcium 2 hours before to 4 hours after dose
	Dapsone	100 mg/day PO x 3–6 months	Perform G6PD testing Do not use in patients with G6PD deficiency, due to hemolysis Start at 50 mg/day; increase dose 50 mg after 1 week Taper when condition resolves (generally 3–6 months in responders) Monitor CBC, liver enzymes, creatinine Methemoglobinemia may occur at doses >200 mg/day
5-ASA	Sulfasalazine	4–6 g/day PO x 6 months	Start at 1 g BID; increase to 1.5 g PO QID if necessary Supplement folate 1 mg daily, especially in young females
	Mesalamine	2–5 g/day PO	Dosing depends on brand and tablet strength, including 400 mg, 500 mg, 800 mg, and 1200 mg
Corticosteroid	Prednisone	40 mg/day PO x 16-week total course	Start at 40 mg x 4 weeks Taper dose by 5 mg/week down to 20 mg Then taper by 2.5 mg/week until off
Immunomodulator	Azathioprine	2.5 mg/kg/day PO x minimum 6–12 months	Start at 50 mg/day Increase 50 mg q 2 weeks to target dose Normal TPMT genotype/activity: start at target dose Monitor CBC, ALT weekly x 4 weeks, then monthly
	6-mercaptopurine	1.5 mg/kg/day PO x minimum 6–12 months	Initiate at 25 mg/day Increase 25 mg q 2 weeks to target dose Normal TPMT genotype/activity: start at target dose Monitor CBC, ALT weekly x 4, then monthly
	Methotrexate	25 mg SQ, IM, or PO weekly x minimum 3 months	May decrease to 15 mg weekly for maintenance Monitor CBC, ALT monthly Supplement folate 1 mg daily Methotrexate is teratogenic
TNF-α inhibitor	Infliximab	5 mg/kg IV q 8 weeks	Loading dose: 5 mg/kg at weeks 0, 2, and 6 Maintenance dose: 5 mg/kg q 8 weeks Response usually seen after 2–4 doses Loss of response: Increase dose to 10 mg/kg q 8 weeks *or* Shorten interval to q 4 weeks
	Adalimumab	40 mg SC q 2 weeks	Loading dose: 160 mg week 0, 80 mg week 2 Maintenance dose: 40 mg q 2 weeks Response usually seen after 4–5 injections Loss of response: shorten interval to weekly
Calcineurin inhibitor	Cyclosporine	3–5 mg/kg/day PO	Dose is maintenance, non-rescue, bridging to immunomodulator Monitor cyclosporine trough levels: 150–300 ng/mL Response usually seen at 4–8 weeks; then taper to maintenance dose Monitor CBC, creatinine, BUN, urinalysis, Mg, electrolytes, uric acid, cholesterol Neurotoxicity Hypertension and diabetes *Pneumocystis jiroveci* pneumonia prophylaxis required

References

Keiler S, Tyson P, Tamburro J. Metastatic cutaneous Crohn's disease in children: case report and review of the literature. *Pediatr Dermatol* 2009;26:604-9.

Palamaras I, El-Jabbour J, Pietropaolo N, Thomson P, Mann S, Robles W, Stevens HP. Metastatic Crohn's disease: a review. *J Eur Acad Dermatol Venereol* 2008;22:1033-43. Epub 2008 Jun 19.

OROFACIAL GRANULOMATOSIS



Relation to IBD

- The presence of oral granulomatous inflammation frequently precedes diagnosis of CD; if CD already diagnosed, described as *'oral CD'*
- Prevalence >40% in Irish pediatric CD population, much lower in North American CD populations
- Not seen in UC

Clinical appearance and presentation

- Also known as cheilitis granulomatosa when only lip swelling is present (classic presentation)
- Other features: fissuring of lips and tongue, cobblestone buccal mucosa, swollen tongue, oral ulcerations, tender and hypertrophied gums
- Melkersson-Rosenthal syndrome: triad of orofacial swelling, recurrent facial nerve paralysis, and tongue fissuring (lingua plicata)

Histology

- Non-caseating granulomata and lymphedema

Differential diagnosis

- Sarcoidosis, TB
- Delayed hypersensitivity may be involved in the pathogenesis, due to allergy to dental material or additives, such as benzoates or gallates (present in some processed foods, cosmetics, and pharmaceuticals)
- Infection and immunologic processes may also be involved in the pathogenesis

Diagnosis

- Clinical, plus demonstration of granulomata on oral biopsy
- Consider having patients examined by physician or dentist with expertise in the oral manifestations of CD

Treatment

Treatment is often challenging and needs to be individualized to each patient. A trial of a gallate-, cinnamon- and benzoate-free diet may be helpful (gallates are E310 series preservatives found in vegetable oils). Treatment options are summarized below.

Topical therapy			
Drug class	**Agent**	**Application**	**Availability**
Corticosteroid	Prednisolone, 1 mg/mL, mouthwash	5 cc swish and spit BID x 8–12 weeks	120 mL bottle
	Betamethasone dipropionate, 0.05%, unguent	BID x 4–8 weeks	15-g and 50-g tubes
Calcineurin inhibitor	Tacrolimus, 0.1%, unguent	BID x 12 weeks	30-g and 60-g tubes

Intralesional therapy			
Drug class	**Agent**	**Dose**	**Preparation**
Corticosteroid	Triamcinolone acetonide, 10 mg/mL	2.5–5 mg q 4–6 weeks x 3 injections	5-mL vials Dilute with preserved saline to desired concentration Hold off on further injections if atrophy develops

Systemic therapy			
Drug class	**Agent**	**Dose**	**Notes**
Corticosteroid	Prednisone	40 mg PO q AM x 4 weeks	Taper dose by 5 mg/week down to 20 mg Then taper by 2.5 mg/week until off
Immunomodulator	Azathioprine	2.5 mg/kg/day PO x 6–12 months	Start at 50 mg/day Increase 50 mg q 2 weeks to target dose Normal TPMT genotype/activity: start at target dose Monitor CBC, ALT weekly x 4 weeks, then monthly
	Methotrexate	25 mg SQ, IM, or PO weekly x 3–6 months	May decrease to 15 mg weekly for maintenance Monitor CBC, ALT monthly Supplement folate 1 mg daily Methotrexate is teratogenic
	Hydroxychloroquine	<6.5 mg/kg/day, divided BID x 6–12 months	Tablet (200 mg) cannot be broken Based on weight, dosing may be Monday to Friday, Monday to Saturday, or daily
TNF-α inhibitor **Consider for severe cases**	Infliximab	5 mg/kg IV q 8 weeks	Loading dose: 5 mg/kg at weeks 0, 2, and 6 Maintenance dose: 5 mg/kg q 8 weeks Response usually seen by 3–4 infusions Loss of response: Increase dose to 10 mg/kg q 8 weeks *or* Shorten interval to q 4 weeks
	Adalimumab	40 mg SC q 2 weeks	Loading dose: 160 mg week 0, 80 mg week 2 Maintenance dose: 40 mg q 2 weeks Response usually seen by 4–6 injections Loss of response: shorten interval to weekly

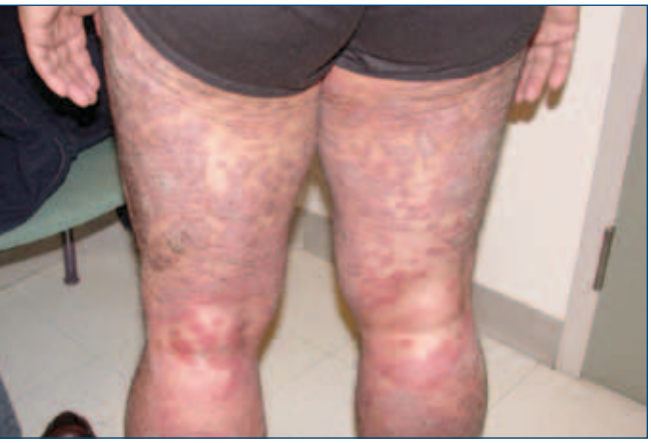
References

Grave B, McCullough M, Wiesenfeld D. Orofacial granulomatosis – a 20-year review. *Oral Dis* 2009;15:46-51.

Harty S, Fleming P, Rowland M, Crushell E, McDermott M, Drumm B, *et al.* A prospective study of the oral manifestations of Crohn's disease. *Clin Gastroenterol Hepatol* 2005;3:886-91.

Rowland M, Fleming P, Bourke B. Looking in the mouth for Crohn's disease. *Inflamm Bowel Dis* 2010;16:332-7.

PSORIASIS



Relation to IBD

- Prevalence 2% in general population; up to 10% in CD
- Psoriasis patients also have a prevalence of IBD higher than the general population
- Has been described to occur with TNF-α inhibitor therapy

Clinical appearance and presentation

- Variable presentations of chronic inflammatory skin disorder
  - *Plaque psoriasis:* most common, with surface scaling on well demarcated erythematous plaques, predilection for extensor surfaces and scalp
  - *Guttate psoriasis:* less common, diffuse rain-drop-sized papules and plaques, may follow streptococcal infection
  - *Pustular psoriasis:* rare, disseminated areas of erythema and pustules or limited to palms and soles (*palmo-plantar pustulosis*)
- Nail involvement is common
- Arthritis may be seen in up to 30% of cases

Histology

- Plaques are characterized by epidermal keratinocyte hyperproliferation, hyperkeratosis, parakeratosis, associated with abnormally dilated and increased numbers of dermal vessels with leukocyte infiltration of dermis and epidermis, contributing to microabscess formation

Differential diagnosis

- Seborrheic dermatitis, fungal infection, nummular eczema, lichen planus and lichen simplex chronicus, squamous cell carcinoma *in situ*, cutaneous T cell lymphoma, cutaneous lupus erythematosus, secondary syphilis

Diagnosis

- Usually clinical; skin biopsy reserved for refractory or atypical cases

Treatment

The **first-line therapy** of localized psoriasis is based on topical corticosteroid preparations of various potency and formulation, such as creams, ointments, gels, lotions, and shampoos, which are used alone or combined with other topical agents. The potency of the corticosteroid selected is determined by psoriasis location and severity. **Low-potency** agents are used for the face and intertriginous areas and for infants. **High-potency** corticosteroids should not be used longer than 2 to 4 weeks, due to the risk of systemic side effects. Taper after a clinical response is achieved. Continue treatment until lesions have resolved. Resume treatment for new lesions.

Topical therapy: localized disease			
Drug class	**Agent**	**Application**	**Availability**
Corticosteroid **Low potency**	Hydrocortisone, 1%	BID until lesions resolve	50-g tubes
	Hydrocortisone valerate, 0.2%, cream or unguent	BID until lesions resolve	60-g tubes
Corticosteroid **High potency** **Limit treatment to 2–4 weeks**	Fluocinonide, 0.05%, unguent, gel, or cream	BID until lesions resolve: maximum 4 weeks	60-g tubes
	Clobetasol propionate, 0.05%, cream, unguent, or lotion	QD until lesions resolve: maximum 4 weeks	50-g tubes
Keratoplastic	Coal tars (liquor carbonis detergens [LCD 3–10%]) compounded in topical corticosteroid, such as hydrocortisone, 1%, cream	QHS until lesion resolution	200-g jar
Keratolytic	Salicylic acid (SA), compounded at 2–5% in a topical corticosteroid such as fluocinonide, 0.05%, cream	QHS until lesion resolution	120-g jar

Topical therapy: localized disease (cont'd)			
Drug class	**Agent**	**Application**	**Availability**
Vitamin D analogues	Calcipotriol cream	BID until lesion resolution	60- and 120-g tubes
Retinoid	Tazarotene, 0.05%, gel	QD until lesion resolution	30-g tubes
Antipsoriatic	Anthralin, 1%, in white petrolatum	QHS to lesions	100-g jar
Combinations	LCD,10%, + SA, 5%, in fluocinonide, 0.05%, unguent	QHS until lesion resolution	180 g-tube

Systemic therapy: used for systemic or severe disease

Dermatologist consultation is recommended for the management of severe disease. Phototherapy (UVA + psoralen + UVB) given several times a week for up to 30 treatments may be useful.

Drug class	Agent	Dose	Notes
Immunomodulator	Methotrexate	7.5–25 mg SQ, IM, or PO weekly x 3-month trial	May decrease to 15 mg weekly for maintenance Monitor CBC, AST, albumin monthly Supplement folate 1 mg daily Methotrexate is teratogenic
Retinoids	Acitretin	0.25–0.75 mg/kg/day PO x 6-month trial	10 and 25 mg capsules Monitor CBC, ALT, AST, creatinine, lipids, monthly x 3 months Teratogenic: 2 forms of birth control mandatory Monitor β-human chorionic gonadotropin monthly Implicated in IBD without much evidence Associated with benign intracranial hypertension (pseudotumor cerebri) Birth control must be used for 2 years after a course of acitretin
Calcineurin inhibitor	Cyclosporine	3–5 mg/kg/day PO x 3-month trial	Monitor cyclosporine trough levels: 150–300 ng/mL Monitor CBC, creatinine, BUN, urinalysis, Mg, electrolytes, uric acid, cholesterol Neurotoxicity Hypertension and diabetes *Pneumocystis jiroveci* pneumonia prophylaxis required
TNF-α inhibitor	Infliximab	5 mg/kg IV q 8 weeks x 3-month trial	Loading dose: 5 mg/kg at weeks 0, 2, and 6 Maintenance dose: 5 mg/kg q 8 weeks Loss of response: Increase dose to 10 mg/kg q 8 weeks *or* Shorten interval to q 4 weeks
	Adalimumab	40 mg SC q 2 weeks x 3-month trial	Loading dose: 160 mg week 0, 80 mg week 2 Maintenance dose: 40 mg q 2 weeks Loss of response: shorten interval to weekly
	Etanercept	50 mg SC weekly x 3-month trial	Loading dose: 50 mg twice weekly x 3 months
Immunosuppressant (CD2 inhibitor)	Alefacept	15 mg IM weekly x 12 weeks	Monitor CD4+ lymphocytes at initiation and q 2 weeks CD4+ count >400 to start drug Hold drug if CD4+ count <250
Monoclonal antibody (IL-12, IL-23) **Severe or recalcitrant disease**	Ustekinumab	45 mg SC q 12 weeks x 16-week trial (<100 kg)	Loading dose: 45 mg SC at weeks 0 and 4 Maintenance dose: 45 mg q 12 weeks Use 90 mg for patients >100 kg Shorten interval to q 8 weeks for minimal responders

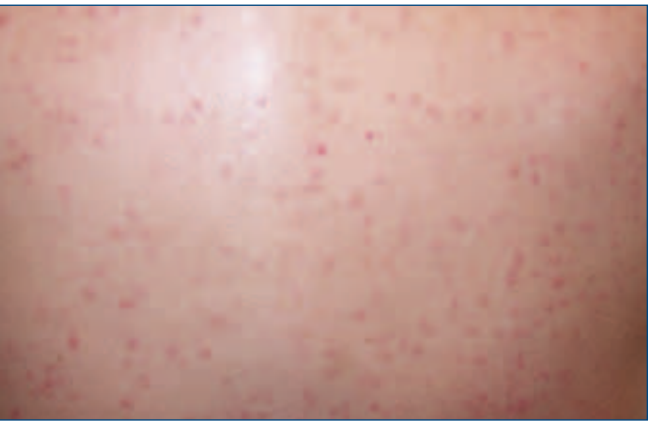
References

Menter A, Korman NJ, Elmets CA, Feldman SR, Gelfand JM, Gordon KB, *et al.* Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 3. Guidelines of care for the management and treatment of psoriasis with topical therapies. *J Am Acad Dermatol* 2009;60:643-59.

Menter A, Korman NJ, Elmets CA, Feldman SR, Gelfand JM, Gordon KB, *et al.* Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 4. Guidelines of care for the management and treatment of psoriasis with traditional systemic agents. *J Am Acad Dermatol* 2009;61:451-85.

Schon MP, Boehncke WH. Psoriasis. *N Engl J Med* 2005;352:1899-912.

GLUCOCORTICOID-INDUCED ACNE



Relation to IBD

- Steroid folliculitis occurs following the administration of glucocorticoids or corticotropin
- Has also been described with immunosuppression and TNF-α inhibitors

Clinical appearance and presentation

- Monomorphous erythematous mildly pruritic papules and pustules, commonly on trunk, shoulders, upper arms, often with facial sparing
- Comedones rarely seen
- Abrupt onset of eruption in patients receiving systemic glucocorticoids
- May be accompanied by acanthosis nigricans, hirsutism, alopecia, hyperpigmentation, and cushingoid features

Histology

- Focal folliculitis with neutrophilic infiltrates

Differential diagnosis

- Acne vulgaris, rosacea, folliculitis, pityrosporum folliculitis, drug hypersensitivity syndrome
- Other drugs associated with acneiform eruptions: cyclosporine; isoniazid; vitamins B_2, B_6 and B_{12}; lithium; phenytoin; halogens; epidermal growth factor receptor (EGFR) inhibitors

Diagnosis

- Usually clinical: recent glucocorticoid administration, characteristic appearance and distribution

Treatment

The first step in management of glucocorticoid acne is discontinuation of corticosteroid therapy, if possible. A variety of topical and systemic medications, which are summarized below, can be used for treatment.

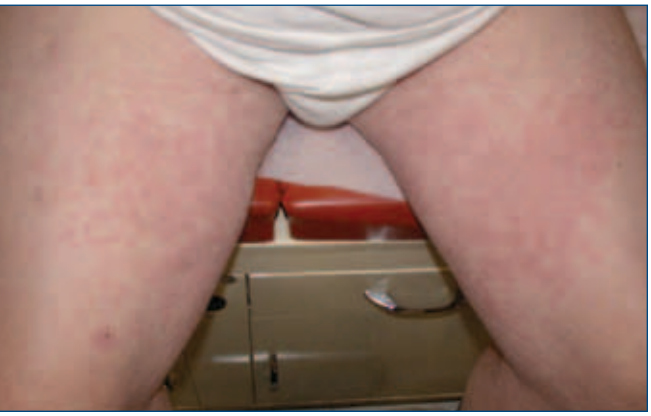
Topical therapy			
Drug class	**Agent**	**Application**	**Availability**
Antibiotic	Benzoyl peroxide, 2–5%, wash	Daily x 3-month trial; treat until resolution	Many products
	Clindamycin pledgets	BID x 3-month trial; treat until resolution	Box
	Erythromycin, 1–3%, compounded in vehicle, such as Cetaphil lotion	BID x 3-month trial; treat until resolution	45-g tube
Antibiotic combination	Clindoxyl gel	BID x 3-month trial; treat until resolution	45-g tube
	Benzaclin gel	BID x 3-month trial; treat until resolution	50-g tube
Retinoid	Adapalene, 0.3%, cream	QD x 3-month trial; treat until resolution	60-g tube

Systemic therapy			
Drug class	**Agent**	**Dose**	**Notes**
Antibiotic **Anti-inflammatory**	Tetracycline	500 mg PO BID x 3-month trial	250-mg capsules Take on empty stomach Avoid calcium 2 hours before to 4 hours after dose
	Erythromycin	500 BID x 3-month trial	
	Trimethoprim-sulfamethoxazole DS	800/160 mg/day PO x 3-month trial	
Retinoid	Isotretinoin	0.5–1 mg/kg/day, divided BID x 16–26 weeks typical duration	Maximum 120 mg/kg total dose Monitor CBC, ALT, AST, creatinine, lipids, monthly x 3 months Teratogenic: 2 forms of birth control mandatory Monitor β-human chorionic gonadotropin monthly Implicated in IBD without much evidence Associated with benign intracranial hypertension (pseudotumor cerebri)

Reference

Lolis MS, Bowe WP, Shalita AR. Acne and systemic disease. *Med Clin North Am* 2009;93:1161-81.

DRUG HYPERSENSITIVITY SYNDROME



Relation to IBD

- Serious idiosyncratic medication reaction, described in association with a wide variety of medications, including the IBD medications sulfasalazine and azathioprine, possibly related to abnormal drug metabolism and viral reactivation

Clinical appearance and presentation

- Usually malaise with pyrexia, rash, lymphadenopathy
- Initial rash is typically an urticarial, maculopapular eruption, possibly with vesicles, bullae, purpura, and target lesions, followed by exfoliative dermatitis with extensive skin peeling
- Leukocytosis with atypical lymphocytosis and increased transaminase levels
- Eosinophilia usually present: referred to as drug reaction with eosinophilia and systemic symptoms (DRESS); if eosinophilia absent, drug hypersensitivity syndrome is more appropriate
- Systemic features can involve any organ system and be severe or life-threatening
- Pneumonitis, hepatitis, renal and neurologic disturbance may be seen

Differential diagnosis

- Systemic infection, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)

Diagnosis

- Diagnosis relies on clinical recognition
- Described in association with a wide variety of medications, including anti-epileptic drugs, allopurinol, and IBD medications
- RegiSCAR is an international research group prospectively studying severe cutaneous reactions
  - RegiSCAR defines 'potential' cases of drug-induced hypersensitivity if 3 of the following 4 criteria are present:
    - Fever >38°C, lymphadenopathy at ≥2 sites
    - ≥1 internal organ involved
    - Acute skin rash
    - Hematologic abnormalities: lymphocytosis or lymphopenia, eosinophilia, thrombocytopenia
  - Other criteria: need for hospitalization, suspicion of drug reaction

Treatment

Immediate discontinuation of the responsible medication is the first step in treating a suspected drug hypersensitivity reaction. **The patient should never be rechallenged with the medication.** The incidence of autoimmunity, particularly autoimmune thyroiditis, is increased after a drug hypersensitivity episode. Long-term monitoring for the development of autoimmunity, which may be asymptomatic in the early stages, is recommended. **Topical therapy has no role in the treatment of drug hypersensitivity.**

Systemic therapy: first line			
Drug class	**Agent**	**Dose**	**Notes**
Corticosteroid	Methylprednisolone	20–30 mg IV q 12	Switch to prednisone with slow taper once response achieved Consider ICU admission
	Prednisone	0.5–1 mg/kg/day PO in AM x 4 weeks	Taper by 5 mg each week over 3 months total

Systemic therapy: second line			
Drug class	**Agent**	**Dose**	**Notes**
Corticosteroid	Methylprednisolone	20 mg/kg IV x 3 days pulsed	Switch to prednisone with taper once response achieved
	Prednisone	0.5–1 mg/kg/day PO in AM x 4 weeks	Taper by 5 mg each week over 3 months total
Immunoglobulin	Immunoglobulin (various brands, e.g., Gammagard, Gamunex, etc.)	1 g/kg/day IV x 2 days Then 1 g/kg once 1 month later Then 1 g/kg monthly x 6-month trial	Order through the transfusion unit
	Plasmapheresis		Order through transfusion unit

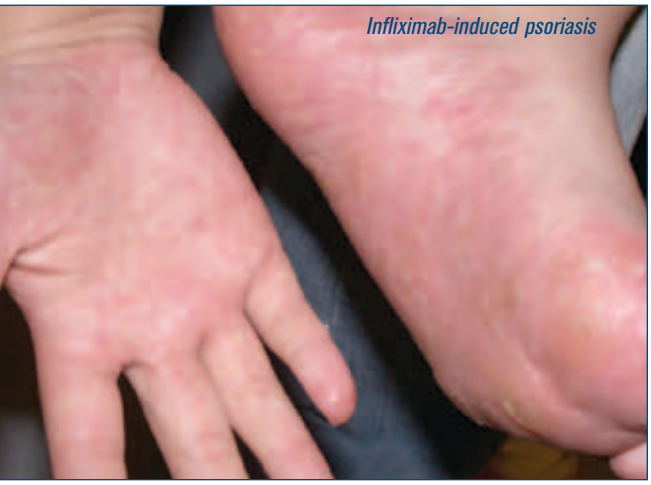
References

Kardaun SH, Sidoroff A, Valeyrie-Allanore L, Halevy S, Davidovici BB, Mockenhaupt M, *et al.* Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist? *Br J Dermatol* 2007;156:609-11.

Shiohara T, Inaoka M, Kano Y. Drug-induced hypersensitivity syndrome (DIHS): a reaction induced by a complex interplay among herpes viruses and antiviral and antidrug immune responses. *Allergol Int* 2006;55:1-8.

Walsh SA, Creamer D. Drug reaction with eosinophilia and systemic symptoms (DRESS): a clinical update and review of current thinking. *Clin Exp Dermatol* 2011;36:6-11.

TNF-α INHIBITOR-ASSOCIATED RASHES



Infliximab-induced psoriasis

Relation to IBD

- TNF-α inhibitors are associated with a range of dermatologic adverse reactions
- Eruptions are described in up to 20% of IBD patients treated with infliximab
- Most common significant rashes: psoriatic/psoriasiform eruptions, psoriatic palmoplantar pustulosis
- Rare cutaneous reactions: Stevens-Johnson syndrome, toxic epidermal necrolysis, diffuse acne

Infusion reactions

- Acute or delayed
  - *Acute reactions*
    - Mild to severe (anaphylaxis)
    - Skin manifestations include erythema, urticaria
    - Management based on severity
  - *Delayed hypersensitivity*
    - May occur up to 2 weeks after an infusion, often associated with elevated human anti-chimeric antibodies (HACA)
    - Symptoms include malaise, arthralgia, pyrexia, urticaria, pruritus, lymphadenopathy, and angioedema
- Treatment
  - *Acute reactions:*
    - Mild: slow infusion rate, premedicate with:
      - Acetaminophen, 500–1000 mg PO daily 7 consecutive days before and after infusion
      - Hydrocortisone, 100–200 mg IV prior to infusion
      - Diphenhydramine, 25–50 mg IV prior to infusion
    - More severe: stop infusion
    - Anaphylaxis: treat immediately
  - *Delayed hypersensitivity:*
    - Further use of infliximab is contraindicated for severe reactions
    - For less severe reactions, it may be possible to continue TNF-α inhibitors therapy along with premedication (see *acetaminophen*, *hydrocortisone*, and *diphenhydramine* above)

Injection-site reactions

- Adalimumab: mild tenderness, swelling, and erythema, associated with local trauma or hypersensitivity
- Management is supportive, with ice compresses, analgesia, and topical steroids if necessary

Topical therapy			
Drug class	**Agent**	**Application**	**Availability**
Corticosteroid	Hydrocortisone valerate, 0.2%, unguent or cream	BID until resolution	60-g tube Use for face or skin folds
	Fluocinonide, 0.05%, cream or unguent	BID until resolution	60-g tube Use for lesions on body
Emollient	Many products, such as Eucerin, Impruv, Cetaphil, Aveeno, etc.	BID until resolution	Various

Skin infections

- Data on prevalence of skin infections sparse, but it is important to exercise vigilance
- Rates of varicella zoster, herpes simplex, and bacterial and fungal infections may be increased

Treat the associated infection and consider withholding the TNF-α inhibitor. Consultation with an infectious disease specialist may be appropriate.

Eczematous rashes

- Reported with all TNF-α inhibitors
- Can occur anywhere, including scalp, flexures, trunk, and face
- Most rashes respond to emollient and topical steroid therapy
- Severe unresponsive rashes may benefit from switching or discontinuing TNF-α inhibitor

Topical therapy			
Drug class	**Agent**	**Application**	**Availability**
Corticosteroid	Hydrocortisone valerate, 0.2%, unguent or cream	BID until resolution	60-g tube Use for face or skin folds
	Fluocinonide, 0.05%, cream or unguent	BID until resolution	60-g tube Use for lesions on body
Emollient	Many products, such as Eucerin, Impruv, Cetaphil, Aveeno, etc.	BID until resolution	Various

Psoriasis and psoriasiform exanthemata

- Lesions may be any type of psoriasis
- New-onset or worsening psoriasis has been reported during TNF-α inhibitor treatment in up to 10% of patients with CD and in patients with rheumatologic disorders
- This finding is paradoxical, as TNF-α inhibitors are effective in psoriasis
- Duration of TNF-α inhibitor exposure before rash onset is variable
- Lesions may occur anywhere on the body, but a predilection exists for the scalp, palms, and soles
- It is important to rule out infection, as the appearance is similar
- Therapy:
  - Topical may be effective without discontinuing TNF-α inhibitor
  - Combination with methotrexate may be needed
  - Severe, unresponsive disease may warrant discontinuation of TNF-α inhibitor

Topical therapy			
Drug class	**Agent**	**Application**	**Availability**
Corticosteroid	Hydrocortisone valerate, 0.2%, unguent or cream	BID until resolution	60-g tube Use for face or skin folds
	Fluocinonide, 0.05%, cream or unguent	BID until resolution	60-g tube Use for lesions on body

Systemic therapy: may need to combine methotrexate with topical			
Drug class	**Agent**	**Dose**	**Notes**
Immunomodulator	Methotrexate	25 mg SQ, IM, or PO weekly x 3-month trial	May decrease to 15 mg weekly for maintenance Monitor CBC, AST, albumin monthly Supplement folate 1 mg daily Methotrexate is teratogenic

References

Borras-Blasco J, Navarro-Ruiz A, Borras C, Castera E. Adverse cutaneous reactions induced by TNF-alpha antagonist therapy. *South Med J* 2009;102:1133-40.

Collamer AN, Battafarano DF. Psoriatic skin lesions induced by tumor necrosis factor antagonist therapy: clinical features and possible immunopathogenesis. *Semin Arthritis Rheum* 2010;40:233-40.

Fidder H, Schnitzler F, Ferrante M, Noman M, Katsanos K, Segaert S, *et al.* Long-term safety of infliximab for the treatment of inflammatory bowel disease: a single-centre cohort study. *Gut* 2009;58:501-8.

Kerbleski JF, Gottlieb AB. Dermatological complications and safety of anti-TNF treatments. *Gut* 2009;58:1033-9.

Ko JM, Gottlieb AB, Kerbleski JF. Induction and exacerbation of psoriasis with TNF-blockade therapy: a review and analysis of 127 cases. *J Dermatolog Treat* 2009;20:100-8.

Rahier JF, Buche S, Peyrin-Biroulet L, Bouhnik Y, Duclos B, Louis E, *et al.* Severe skin lesions cause patients with inflammatory bowel disease to discontinue anti-tumor necrosis factor therapy. *Clin Gastroenterol Hepatol* 2010;12:1048-55. Epub 2010 Aug 20.

Sandborn WJ, Hanauer SB. Infliximab in the treatment of Crohn's disease: a user's guide for clinicians. *Am J Gastro* 2002;97:2962-72.

Mentoring in IBD XI Curriculum is made possible by unrestricted educational grants from:

Janssen · Abbott A Promise for Life · Shire · AXCAN PHARMA · FERRING PHARMACEUTICALS · WARNER CHILCOTT

CATRILE & Associates Ltd.

Published by Catrile & Associates Ltd.
1B-391 Berkeley Street, Toronto, Ontario M5A 2X8

Printed in Canada.