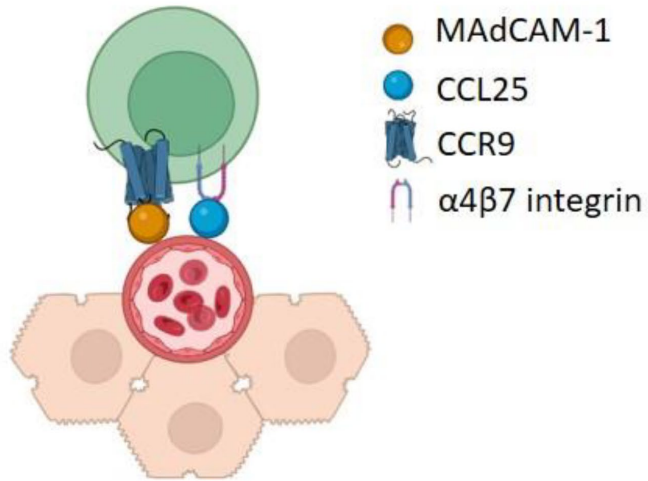
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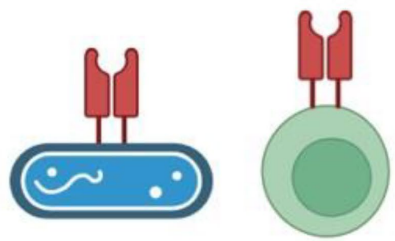
Management of Articular and Dermatologic Manifestations of IBD

Extension of immune responses from the intestine

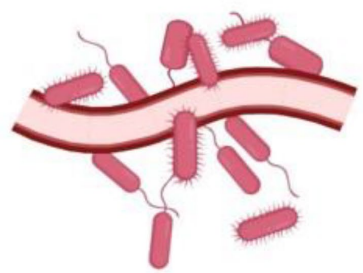
A)



B)

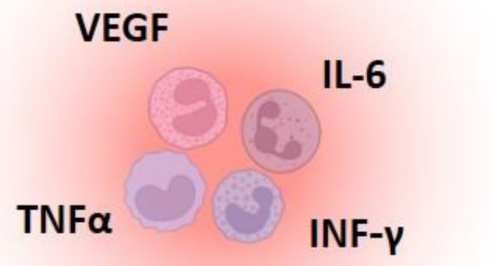


C)



Gut-indipendent inflammatory events

D)



E)



F)

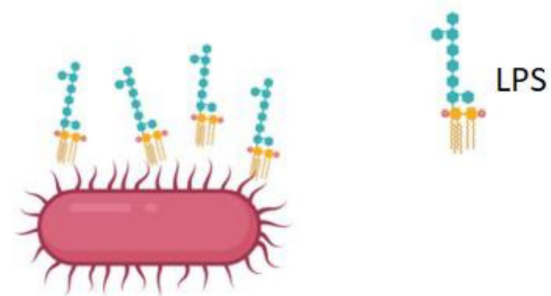


Figure 1. Potential pathophysiology of EIMs. Extension of immune responses from the intestine: (A) ectopic expression of adhesion molecules and chemokines, such as the abnormal expression of MAdCAM-1 and CCL25 in the vascular endothelium of the portal tract; (B) microbial antigen crossreactivity, such as molecular mimicry, occurs between enteric bacteria and self-antigens presented by host's major histocompatibility complex molecules; (C) microbial antigen translocation [8]. EIMs as independent inflammatory events: (D) shift in inflammatory tone influenced by genetic, environmental, or microbial factors, or by a systemic increase in key inflammatory mediators; (E) systemic changes in innate immune function, for example, neutrophil priming; (F) gut microbiota-induced distant inflammation driven by microbial products such as lipopolysaccharide, through changes in gut permeability and microbiota-derived metabolites [8]. MAdCAM-1: mucosal vascular addressin cell adhesion molecule 1; CCL25: chemokine (C-C motif) ligand 25; CCR9: C-C motif chemokine receptor 9; VEGF: vascular endothelial growth factor; IL-6: interleukin-6; TNFα: tumor necrosis factor α; INFγ: interferon γ; LPS: lipopolysaccharide.

Table 1. Extraintestinal Manifestations of Inflammatory Bowel Diseases

Organ system	Manifestations	Prevalence
Gastrointestinal	PSC	UC: up to 5%; CD: rare
	Autoimmune pancreatitis	Rare
	Autoimmune hepatitis	Rare (< 1%)
Mucocutaneous	EN	5%–15% in CD; 2%–10% in UC
	PG	0.4%–2.6% in IBD
	Oral aphthous ulcers	5%–50% in CD
	Sweet syndrome	Rare
	Orofacial granulomatosis	Rare
Musculoskeletal	IBD-related arthritis	CD: 10%–20% ; UC: 4%–14%
	Peripheral arthritis	Up to 50% in CD (asymptomatic)
	Axial arthritis	
	Enthesitis	
Ocular	Episcleritis and scleritis	Scleritis: up to 1%;
	Anterior uveitis	CD: 5%–12%; UC: 3.5%–4.1%
Pulmonary	Pneumonitis	Rare
Vascular	Cardiovascular disease	NA
	Thromboembolism	3- to 4-fold increase
	Portal vein thrombosis	Rare

Table 2. Musculoskeletal Conditions Associated With Inflammatory Bowel Disease: Classification of Arthritis Associated With Inflammatory Bowel Disease

Type of arthritis	Characteristics	Prevalence, %
Arthralgia without arthritis	Joint pain without synovitis	5–16
Axial arthropathy		
AS	Inflammatory back pain with imaging evidence of sacroiliitis and/or spinal inflammation	1–12
Isolated sacroiliitis	Sacroiliac joint erosions or sclerosis on imaging	16–46
Inflammatory back pain	Back stiffness without radiologic findings	17–22
Dactylitis	Swelling of entire digit	2–5
Enthesitis	Tendon, ligament, or joint capsule insertion pain	6–54

Table 3. Musculoskeletal Conditions Associated With Inflammatory Bowel Disease: Therapy of Peripheral and Axial Arthritis in Inflammatory Bowel Disease

Variable	Prevalence	Diagnosis	Therapy
Peripheral arthritis (peripheral SpA)	5%–14% in UC 10%–20% in CD	Clinical (and US or MRI)	Treatment of intestinal inflammation COX-2 inhibitors Corticosteroids (short term) Sulfasalazine (especially in UC) Methotrexate Anti-TNF
Axial arthritis/ axSpA	Up to 50 % in CD symptomatic in up to 8%	Clinical and MRI	Anti-TNF

MRI, magnetic resonance imaging; US, ultrasound.

Table 2. Treatments of extraintestinal manifestation in inflammatory bowel disease.

System Involved	Disease	Synchronous with IBD	Treatment That Should Be Considered	Treatment That May Be Considered	Treatment That Cannot Be Recommended
Musculoskeletal EIM 13% (12.9–13.7)	Ankylosing spondylitis	no	Anti TNF-α	JAKi	vedolizumab, ustekinumab
	Sacroiliitis	no	Anti TNF-α	JAKi	vedolizumab, ustekinumab
	Peripheral arthritis type 1	yes	Anti TNF-α, JAKi, ustekinumab	vedolizumab	-
	Peripheral arthritis type 2	no	Anti TNF-α, JAKi, ustekinumab	vedolizumab	-
Skin EIM 5% (4.7–5.2)	Erythema nodosum	yes	-	Anti TNF-α	vedolizumab
	Pyoderma gangrenosum	yes or no	systemic steroids	Anti TNF-α, JAKi, ustekinumab	vedolizumab
Ocular EIM 2.1% (1.9–2.2)	Uveitis	yes or no	topical steroids, anti TNF-α (100%)	JAKi, ustekinumab	vedolizumab
	Episcleritis	yes	topical lubricants	NSAIDs, corticosteroids	-
	Scleritis	yes or no	COX-2 inhibitors, topical NSAIDs, systemic corticosteroids	MTX, AZA, mycophenolate mofetil, calcineurin inhibitors, IFX	-
Hepatobiliary EIM 0.75% (0.6–0.8)	Primary sclerosing cholangitis	no	-	Ursodeoxycholic acid	-
	Autoimmune hepatitis	yes or no	Systemic steroids, AZA	infliximab	-

IBD: inflammatory bowel disease; EIM: extraintestinal manifestation; TNF-α: tumor necrosis factor- α; JAKi: Janus kinase inhibitor; NSAIDs: non-steroidal anti-inflammatory drugs; COX-2 inhibitors: Cyclooxygenase-2 inhibitors; MTX: methotrexate; AZA: azathioprine.

ARTICULAR MANIFESTATIONS

Inactive IBD – In patients with inactive IBD and related arthritis, initial therapy consists of a **short course of nonsteroidal antiinflammatory drugs (NSAIDs)**. Selected patients may also receive adjunctive therapies, such as **intraarticular glucocorticoid injections** for limited peripheral arthritis and/or **physical therapy** for axial arthritis.

Patients with persistent symptoms despite or intolerance of NSAIDs are treated with **systemic immunosuppression**, with the choice of therapy guided by the specific location of the arthritis .

Specifically, patients with isolated peripheral arthritis are started on selected conventional synthetic disease-modifying antirheumatic drugs **(csDMARDs),** while those with axial disease are typically started on monoclonal tumor necrosis factor **(TNF) inhibitors**.

Active IBD – In patients with active IBD and related arthritis, treatment is focused on **targeting the gastrointestinal manifestations** and may also involve short-term use of NSAIDs.

ECCO Guidelines on Extraintestinal Manifestations in Inflammatory Bowel Disease

Journal of Crohn's and Colitis, 2024, **18**, 1–37

Statement 14
Prevalence and investigation of osteoporosis and osteopenia

Patients with IBD have an increased risk of developing **osteoporosis** and **osteoporotic fractures**, particularly of the spine [EL2].

In patients with IBD at high risk for osteoporosis, **bone mineral density measurement** through a dual-energy X-ray absorption scan is recommended [EL2] [consensus: 100%]

Statement 15
Management of bone demineralization

Appropriate daily dietary intake of **calcium and vitamin D**, **smoking cessation**, and **physical activity** should be promoted to prevent osteopenia and osteoporosis [EL5].

Supplementation with **calcium and vitamin D** is recommended in patients treated with corticosteroids and/or with known osteopenia or risk factors for low bone mineral density [EL2].

Treatment with **bisphosphonates** is recommended in patients with corticosteroid-induced or postmenopausal **osteoporosis** [EL1] [consensus: 84%]

Statement 16
Prevalence and clinical manifestations of rheumatological EIMs

Clinical symptoms of joint disease in IBD are common, such as peripheral and axial spondyloarthropathy [EL2].

Articular symptoms may occur before and after diagnosis of IBD [EL2] [consensus: 100%].

Statement 17
NSAID use in the management of joint disease in IBD

There is no evidence of an association between NSAID use and UC flare [EL1], although there is potentially an association with CD flare [EL2].

We recommend that the decision to use NSAIDs for the management of arthropathy is made on a case-by-case basis [EL3].

Selective COX-2 inhibitors may be used for **short periods** of time [EL2] [consensus:91%].

Statement 18
Management of axial spondyloarthropathy

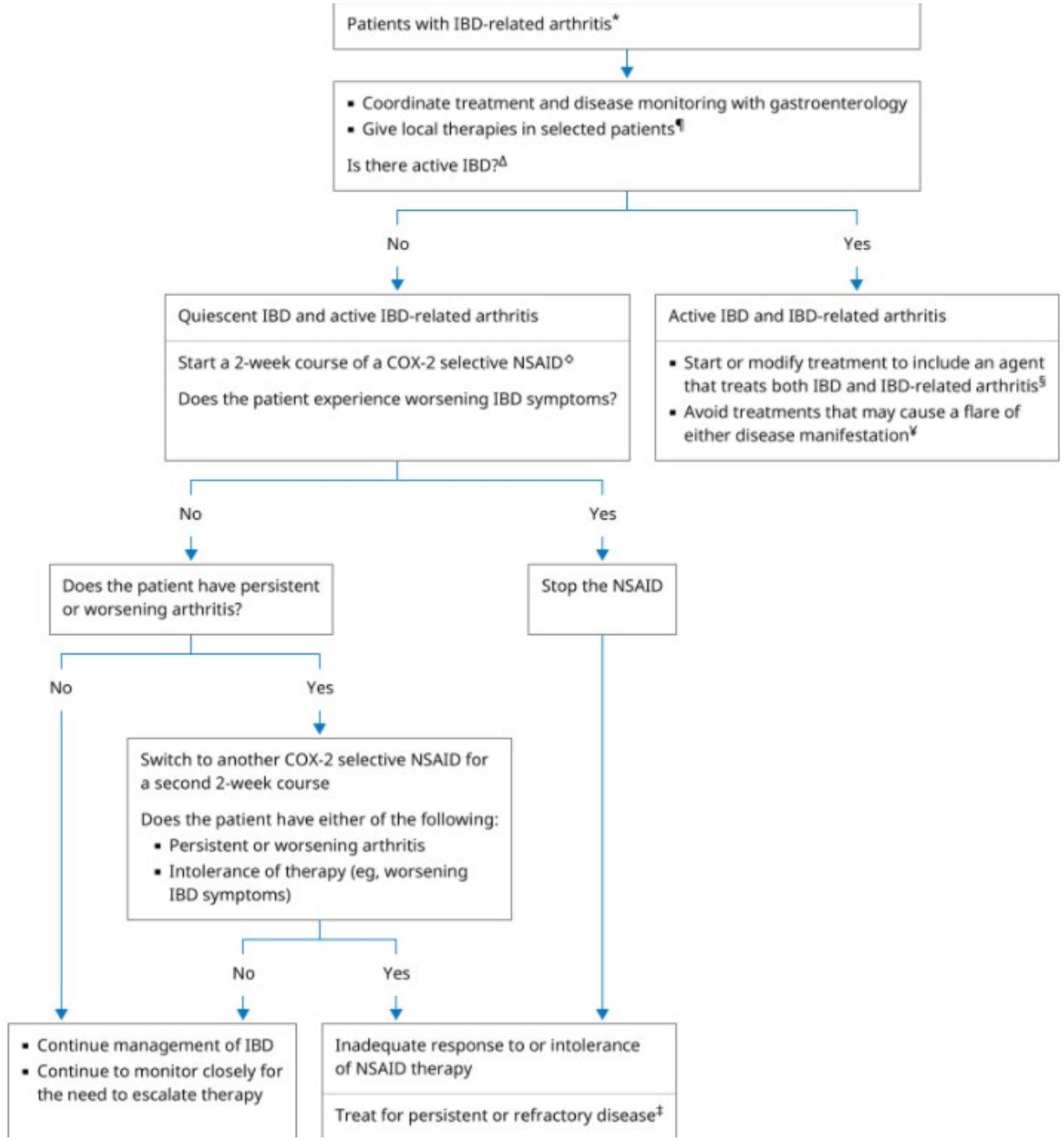
TNFα antagonists are recommended for treatment of axial spondyloarthropathy associated with IBD.

Vedolizumab and ustekinumab are **not recommended** in axial spondyloarthropathy associated with IBD [EL2] [consensus:96%]

Statement 19
Management of non-axial spondyloarthropathy

TNFα antagonists are recommended for treatment of IBD associated non-axial spondyloarthropathy [EL2].

There are also data to support use of ***methotrexate***, ***sulfasalazine***, *and* ***ustekinumab*** [EL3] [consensus: 100%]


Patients with IBD-related arthritis*
Coordinate treatment and disease monitoring with gastroenterology
Give local therapies in selected patients¶
Is there active IBD?Δ
No
Yes
Quiescent IBD and active IBD-related arthritis
Start a 2-week course of a COX-2 selective NSAID◇
Does the patient experience worsening IBD symptoms?
Active IBD and IBD-related arthritis
Start or modify treatment to include an agent that treats both IBD and IBD-related arthritis§
Avoid treatments that may cause a flare of either disease manifestation¥
No
Yes
Does the patient have persistent or worsening arthritis?
Stop the NSAID
No
Yes
Switch to another COX-2 selective NSAID for a second 2-week course
Does the patient have either of the following:
Persistent or worsening arthritis
Intolerance of therapy (eg, worsening IBD symptoms)
No
Yes
Continue management of IBD
Continue to monitor closely for the need to escalate therapy
Inadequate response to or intolerance of NSAID therapy
Treat for persistent or refractory disease‡

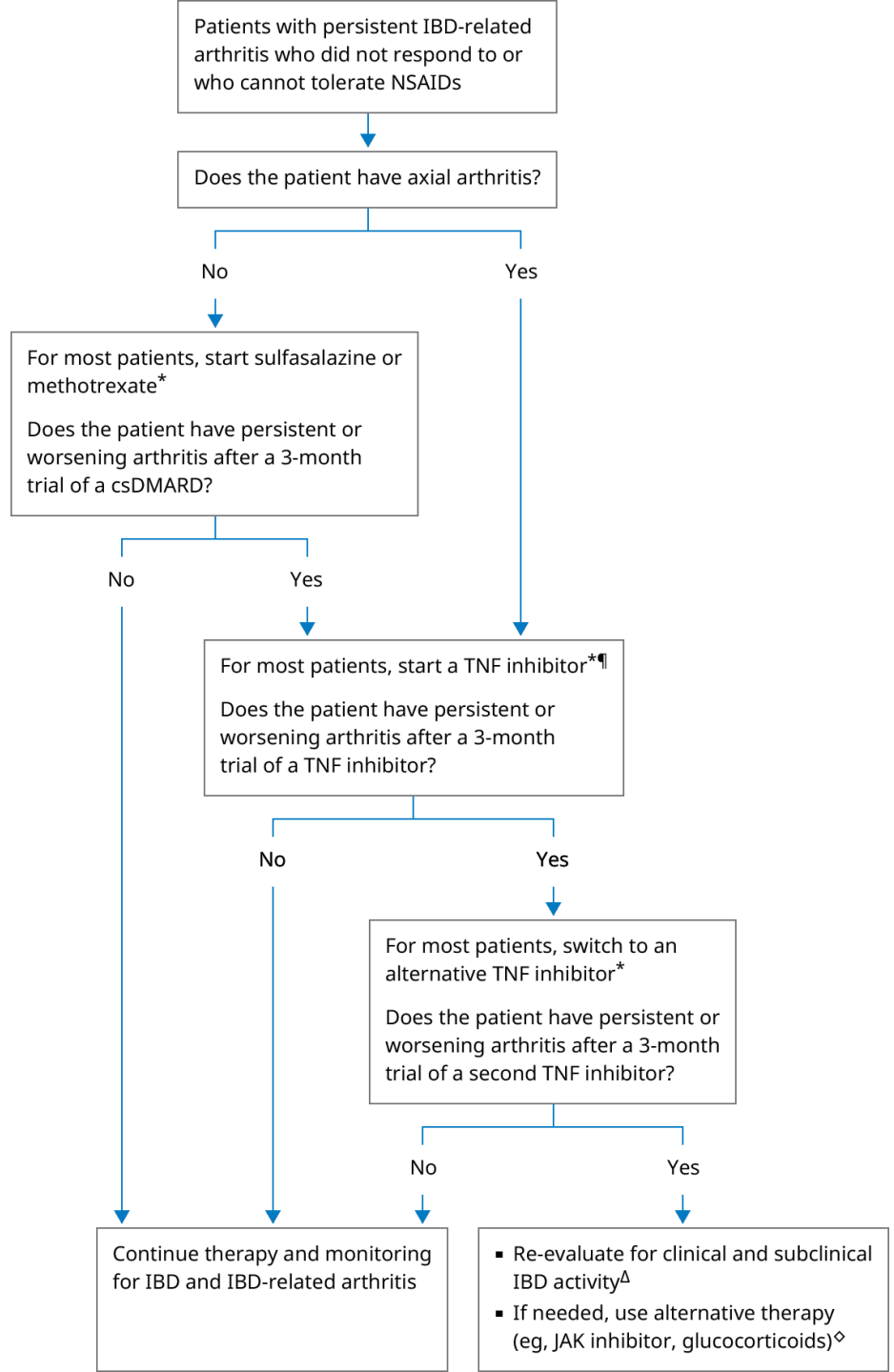

Patients with persistent IBD-related arthritis who did not respond to or who cannot tolerate NSAIDs
Does the patient have axial arthritis?
No
Yes
For most patients, start sulfasalazine or methotrexate*
Does the patient have persistent or worsening arthritis after a 3-month trial of a csDMARD?
No
Yes
For most patients, start a TNF inhibitor*¶
Does the patient have persistent or worsening arthritis after a 3-month trial of a TNF inhibitor?
No
Yes
For most patients, switch to an alternative TNF inhibitor*
Does the patient have persistent or worsening arthritis after a 3-month trial of a second TNF inhibitor?
No
Yes
Continue therapy and monitoring for IBD and IBD-related arthritis
Re-evaluate for clinical and subclinical IBD activityΔ
If needed, use alternative therapy (eg, JAK inhibitor, glucocorticoids)◇

Table 7. Management of axial and non-axial spondyloarthropathy in IBD [adapted from Greuter *et al*[338]

	Agent	Axial spondyloarthropathy	Non-axial spondyloarthropathy
	Sulfasalazine		
	Methotrexate		
TNF-antagonist[a]			
JAK inhibitor			
Anti-integrin	Vedolizumab		
Anti-IL-12/23	Ustekinumab		
S1P-R modulator	Ozanimod		

[a]Does not apply for etanercept.
Green: can be used.
Yellow: may be used.
Red: should not be used.

VEDOLIZUMAB = great for GUT , poor for joints

USTEKINUMAB = May be mild benefit for peripheral arthritis but not great for Axial disease

AITI TNF = most effective for Gut and Joint (peripheral or axial)

paradoxical articular manifestations

About 30% of the patients present musculoskeletal manifestations during treatment with anti-TNF, suggesting that it could be a frequent issue.

However, only half of those were inflammatory articular manifestations and even less (5.2%) were considered as **paradoxical**, that is, flare or new onset of articular manifestations whereas IBD was in remission.

In the literature, the frequency of paradoxical articular manifestations ranged from **1.6%** to **11%.6**

CUTANEOUS MANIFESTATIONS

Statement 20

Skin diseases associated with IBD are among the most common

EIMs and their relationship with underlying intestinal disease may be either:

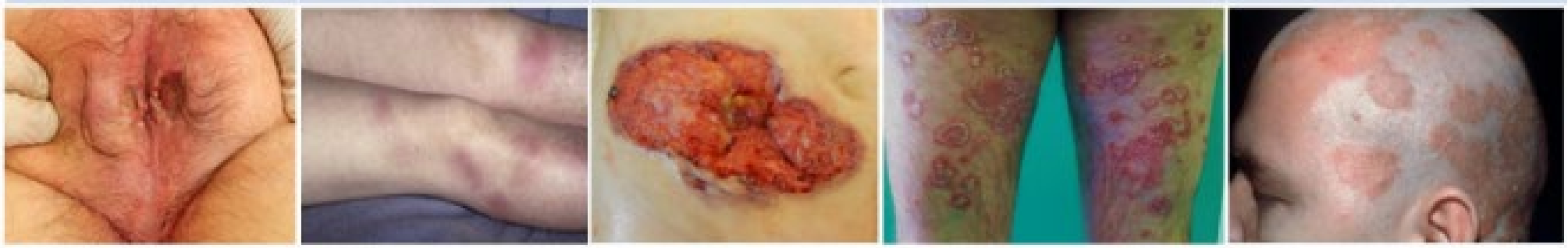
- **specific** [metastatic CD],
- **reactive**[pyoderma gangrenosum, Sweet syndrome, erythema nodosum, oral lesions],
- **associated** [hidradenitis suppurativa, psoriasis], or
- **treatment-related** [TNFα antagonist-induced skin lesions, other drug hypersensitivities, skin cancer] [EL3].

We recommend early involvement of a dermatologist when appropriate

[consensus: 95%]

Figure 1. Mucocutaneous manifestations associated with inflammatory bowel disease (IBD).

Specific manifestations	Disorders associated with inflammatory bowel disorders	Reactive manifestations	Muco-cutaneous conditions secondary to treatment of inflammatory bowel disorders	Cutaneous manifestations secondary to nutritional malabsorption
Continuous/contiguous Crohn's disease Metastatic Crohn's disease	Aphthous stomatitis Erythema nodosum Psoriasis Epidermolysis bullosa acquisita	Pyoderma gangrenosum Sweet's syndrome Bowel-associated dermatosis-arthritis syndrome Aseptic abscess ulcers Pyodermatitis-pyostomatitis vegetans SAPHO syndrome PAPA syndrome	Adverse muco-cutaneous reactions (injection site reactions, infusion reactions, paradoxical reactions, eczematiform and psoriasiform reaction, life-threatening disorders) Cutaneous infections Cutaneous malignancies	Stomatitis Glossitis Angular cheilitis Pellagra Scurvy Purpura Acrodermatitis enteropathica Phrynoderma Seborrheic-type dermatitis Hair and nail abnormalities



Erythema nodosum
Statement 21



Erythema nodosum is very often associated with underlying active intestinal IBD, although other causes should be excluded and managed.

When erythema nodosum is associated with IBD activity, the primary aim is **control of underlying intestinal disease** activity; the skin lesions usually resolve when intestinal disease activity is controlled. [EL3] [consensus: 100%]

Pyoderma gangrenosum Statement 22



Treatment with TNFα antagonists, particularly **infliximab**, is recommended for the treatment of pyoderma gangrenosum [EL2].

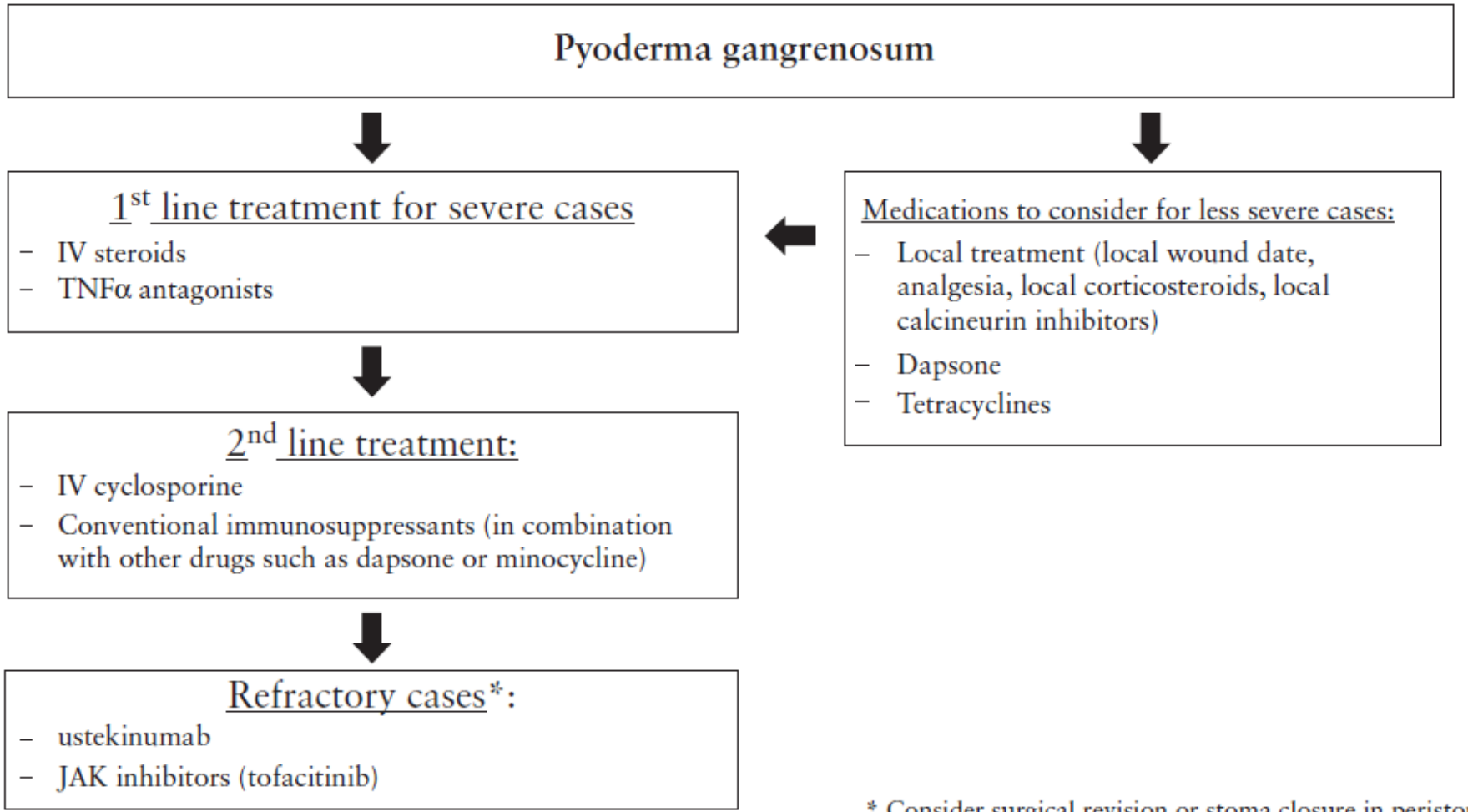
Early use should be considered, particularly for severe manifestations.

Other treatments that may be considered include **systemic steroids** [EL3], **ciclosporin** [EL3], **ustekinumab** [EL4], **dapsone** [EL3], **metronidazole** [EL3], and **tetracyclines** [EL4].

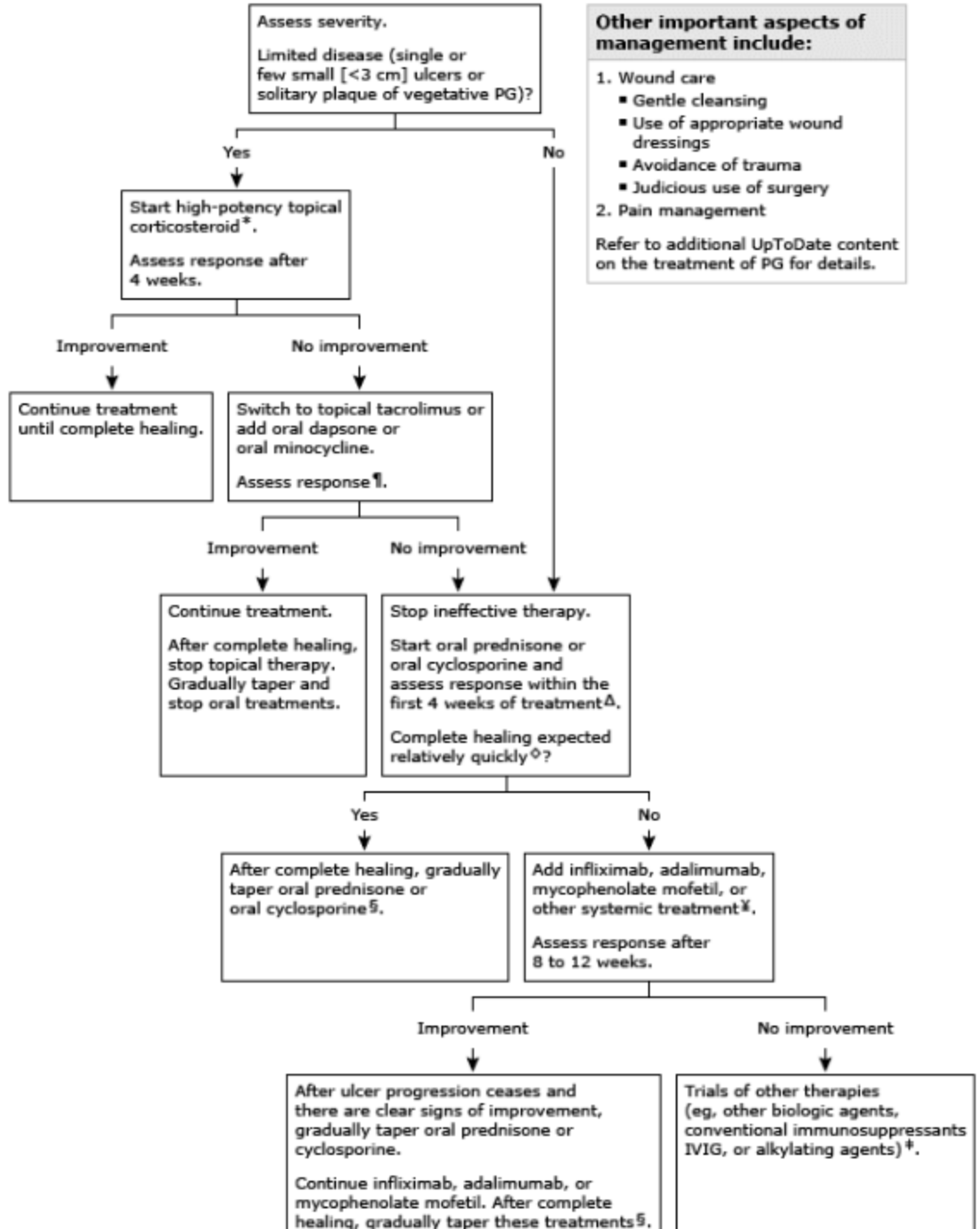
For milder disease, **topical steroids** and **topical calcineurin inhibitors** may be considered [EL3].

We recommend early involvement of a dermatologist [consensus:
95%]





Management of pyoderma gangrenosum.


Assess severity.
Limited disease (single or few small [<3 cm] ulcers or solitary plaque of vegetative PG)?
Yes
No
Start high-potency topical corticosteroid*.
Assess response after 4 weeks.
Improvement
No improvement
Continue treatment until complete healing.
Switch to topical tacrolimus or add oral dapsone or oral minocycline.
Assess response¶.
Improvement
No improvement
Continue treatment.
After complete healing, stop topical therapy. Gradually taper and stop oral treatments.
Stop ineffective therapy.
Start oral prednisone or oral cyclosporine and assess response within the first 4 weeks of treatmentΔ.
Complete healing expected relatively quickly◇?
Yes
No
After complete healing, gradually taper oral prednisone or oral cyclosporine§.
Add infliximab, adalimumab, mycophenolate mofetil, or other systemic treatment¥.
Assess response after 8 to 12 weeks.
Improvement
No improvement
After ulcer progression ceases and there are clear signs of improvement, gradually taper oral prednisone or cyclosporine.
Continue infliximab, adalimumab, or mycophenolate mofetil. After complete healing, gradually taper these treatments§.
Trials of other therapies (eg, other biologic agents, conventional immunosuppressants IVIG, or alkylating agents)ǂ.
Other important aspects of management include:
1. Wound care
▪ Gentle cleansing
▪ Use of appropriate wound dressings
▪ Avoidance of trauma
▪ Judicious use of surgery
2. Pain management
Refer to additional UpToDate content on the treatment of PG for details.

Sweet syndrome
Statement 23

We recommend use of **systemic corticosteroids** as first-line treatment for Sweet syndrome [EL4]. **TNFα antagonists** may be used in steroid-dependent or refractory cases [EL4] [consensus: 95%]



Mild disease without significant systemic symptoms – For adults who present with mild Sweet syndrome (eg, less than 5 percent body surface area involvement and absence of significant systemic symptoms), we suggest the use of high potency topical corticosteroids or intralesional corticosteroid injections as initial treatment due to the relative safety of these interventions .

- **Extensive disease and/or systemic symptoms** – For adults with more extensive involvement and/or systemic symptoms, we suggest treatment with systemic glucocorticoid therapy .

For adults with Sweet syndrome who cannot be treated with systemic glucocorticoids due to comorbidities or other factors, we suggest treatment with colchicine or dapsone .Potassium iodide is also effective.

- **Initial treatment for children** – For children with Sweet syndrome, we suggest systemic glucocorticoid therapy
- **Refractory disease** – Pulsed intravenous glucocorticoids and other immunomodulatory therapies may be effective for patients with refractory disease.

Hidradenitis suppurativa Statement 24

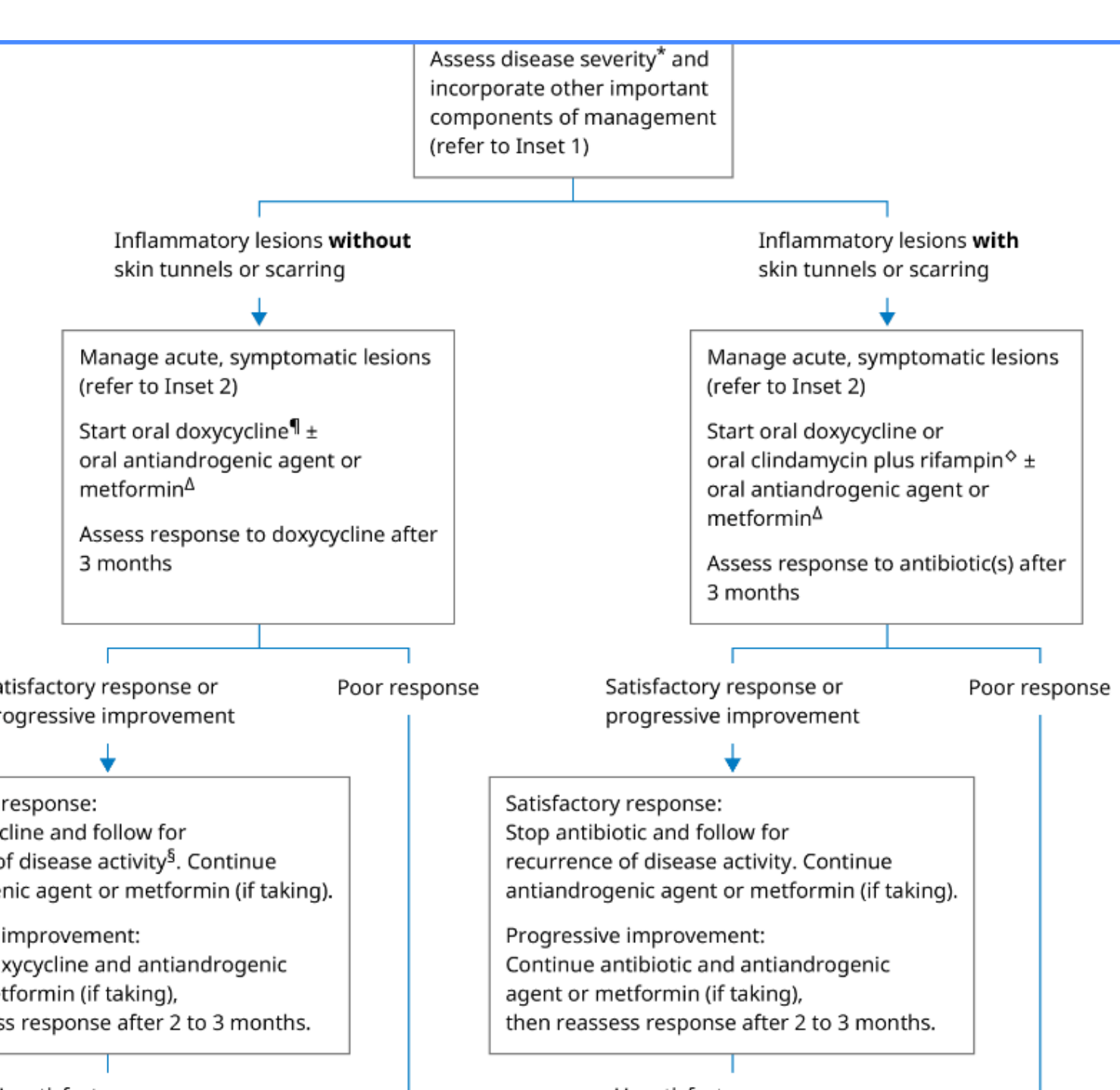


Hidradenitis suppurativa is a condition associated with IBD and is more commonly observed in **CD** than in UC.

Topical treatment or systemic treatment [**antibiotics** and **dapsone**] may be used in mild-to-moderate disease.

Adalimumab is recommended as first-line treatment for severe disease, with early dose intensification frequently required.

Other management options include **infliximab**, **ustekinumab**, or **surgery** [EL3] [consensus: 100%]



Inset 1: Additional important components of management

- Education and support
- Wound and skin care
- Pain management
- Assessment and management of comorbidities

Refer to additional UpToDate content on the management of HS for guidance on these interventions

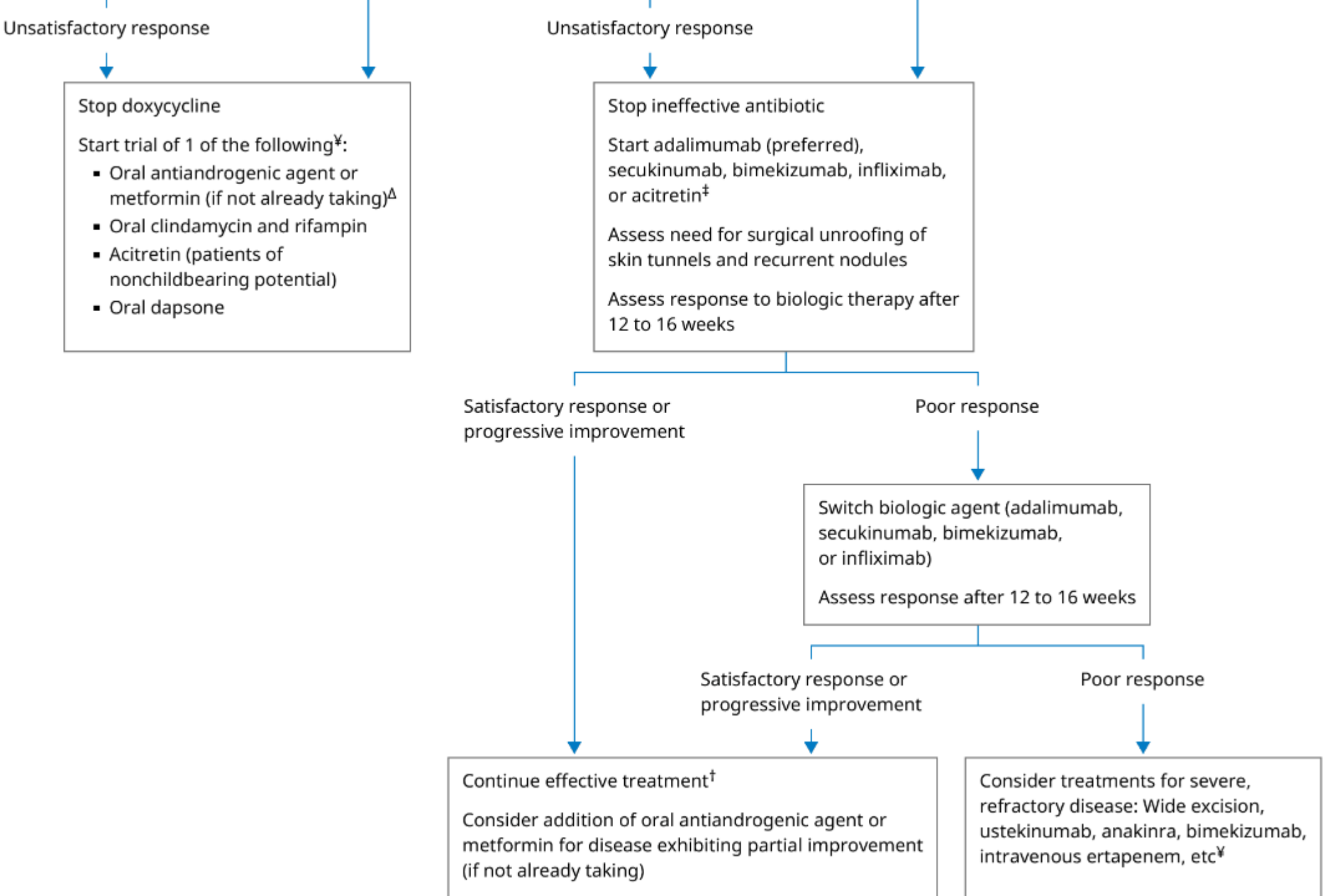
Inset 2: Role of adjunctive surgery and procedures

Immediate management of acute, symptomatic lesions:

- Intralesional corticosteroid injections
- Punch debridement
- Topical resorcinol
- Incision and drainage (reserved for cases for which other techniques are not feasible)
- Systemic glucocorticoids (for severe flares)

Skin tunnels and recurrent nodules:

- Surgical unroofing (deroofing)
- Wide excision (in the setting of severe, extensive HS)


Unsatisfactory response
Stop doxycycline
Start trial of 1 of the following¥:
Oral antiandrogenic agent or metformin (if not already taking)Δ
Oral clindamycin and rifampin
Acitretin (patients of nonchildbearing potential)
Oral dapsone
Unsatisfactory response
Stop ineffective antibiotic
Start adalimumab (preferred), secukinumab, bimekizumab, infliximab, or acitretin‡
Assess need for surgical unroofing of skin tunnels and recurrent nodules
Assess response to biologic therapy after 12 to 16 weeks
Satisfactory response or progressive improvement
Poor response
Switch biologic agent (adalimumab, secukinumab, bimekizumab, or infliximab)
Assess response after 12 to 16 weeks
Satisfactory response or progressive improvement
Poor response
Continue effective treatment†
Consider addition of oral antiandrogenic agent or metformin for disease exhibiting partial improvement (if not already taking)
Consider treatments for severe, refractory disease: Wide excision, ustekinumab, anakinra, bimekizumab, intravenous ertapenem, etc¥

Metastatic CD
Statement 25



Metastatic CD is a rare extraintestinal manifestation affecting the skin and genital area.

Systemic and intralesional **corticosteroids**, **azathioprine**, **metronidazole**, and **TNFα antagonists** can be used [EL3] [consensus: 90%]





Epidermolysis bullosa acquisita

Skin cancer

melanoma nonmelanoma skin cancer



Psoriasis vulgaris

Table 8. Diagnosis and management of common cutaneous EIMs in IBD

Classification of EIM	Cutaneous EIM	Diagnostic features	Management
Reactive			
	Erythema nodosum	Symmetrical, raised, tender, erythematous, or violaceous subcutaneous nodules [1–5 cm] Extensor surface of lower limbs [pretibial] > head and neck, trunk, arms	– Treat underlying IBD – Supportive: bed rest, elevation, analgesia, compression hosiery – Skin directed: topical corticosteroids – Systemic: corticosteroids [if severe], potassium iodide, dapsone, TNFα antagonists, hydroxychloroquine
	Pyoderma gangrenosum	Single or multiple erythematous papules/pustules, rapid necrosis to excavating ulcers with irregular violaceous margins and purulent [sterile] material, 2–20 cm, often following trauma [pathergy], secondary infection may occur. Shins and peristomal areas most common	– Supportive: wound care, analgesia, avoidance of trauma – Skin directed: topical corticosteroids, topical tacrolimus – Systemic: corticosteroids, TNFα antagonists, dapsone, tetracyclines, metronidazole – Severe: IV cyclosporin, TNFα antagonists, ustekinumab, JAKi
	Sweet syndrome [acute febrile neutrophilic dermatosis]	Acute onset of tender erythematous papules and nodules on limbs, trunk, head, and neck; varying sizes, associated with fever and neutrophilia	– Treatment of underlying IBD – Skin directed: topical corticosteroids – Systemic: corticosteroids, immunomodulators, TNFα antagonists, granulocyte-monocyte apheresis
	Oral lesions	Aphthous ulcers: painful ovoid or round ulcers, labial or buccal mucosa, pseudomembranous base and erythematous margin Periodontitis: swelling, redness, bleeding of gingiva, loose teeth, associated with perianal disease and smoking Peristomatitis vegetans: pustules, haemorrhagic erosions, ulcers Orofacial granulomatosis: recurrent and persistent buccal swelling and oral ulcers, facial palsy, cervical lymphadenopathy	– Treat underlying IBD – Antiseptic and anaesthetic mouthwashes – Topical corticosteroids – Systemic: corticosteroids, TNFα antagonists
Specific			
	Metastatic CD	Extraintestinal sites: legs, intertriginous areas > facial, genital Abscesses, fistulae, ulcers, nodules	– Topical, intralesional, or systemic corticosteroids – Systemic: antibiotics [metronidazole], immunomodulators [azathioprine], TNFα antagonists
Associated			
	Hidradenitis suppurativa	Recurrent, painful inflamed skin lesions, developing abscesses and interconnected sinus tracts in flexural sites [axillae, inguinal, perianal]	– Supportive: pain management, wound care – Lifestyle modification: smoking cessation, optimize BMI – Skin directed: topical clindamycin, antiseptic wash – Systemic: antibiotics [tetracycline, clindamycin plus rifampicin], retinoids, dapsone, TNFα antagonists – Surgery in selected cases – Consensus management guidelines are available[343, 344]

Classification of EIM	Cutaneous EIM	Diagnostic features	Management
Complications			
	TNFα antagonist adverse effects	Paradoxical psoriasis: erythematous, scaly plaques, pustules, itching and burning; body, scalp, face; flexures > extensors [in contrast to typical psoriasis], palmoplantar pustulosis, nail involvement Eczema-like/psoriasiform eczema: xerosis and itchy, erythematous, ill-defined plaques and vesicles, *Staphylococcus* superinfection may occur Paradoxical hidradenitis suppurativa: typical HS with recurrent inflamed nodules, abscesses, sinus tracts, fistulae and scarring	Paradoxical psoriasis: – Skin directed: emollients, soap substitutes, topical corticosteroids, vitamin D analogues – Discontinuation of TNFα antagonists [required in 5–35% of cases] – Systemic: consider ustekinumab if severe or recurrent; acitretin, methotrexate, or ciclosporin as alternatives Eczema-like and psoriasiform eczema: – Skin directed: emollients, soap substitutes, menthol cream, topical corticosteroids, topical corticosteroid/antibiotic combinations, topical tacrolimus – Systemic treatment: oral antibiotics for *Staphylococcus aureus* superinfections, antihistamines – Discontinuation of TNFα antagonist if severe and refractory, consider ustekinumab Palmoplantar pustulosis: – Skin directed: ultrapotent topical corticosteroid [with addition of salicylic acid or coal tar] – Systemic treatment: tetracyclines, acitretin, methotrexate ,or ciclosporin may be considered in severe or refractory cases

