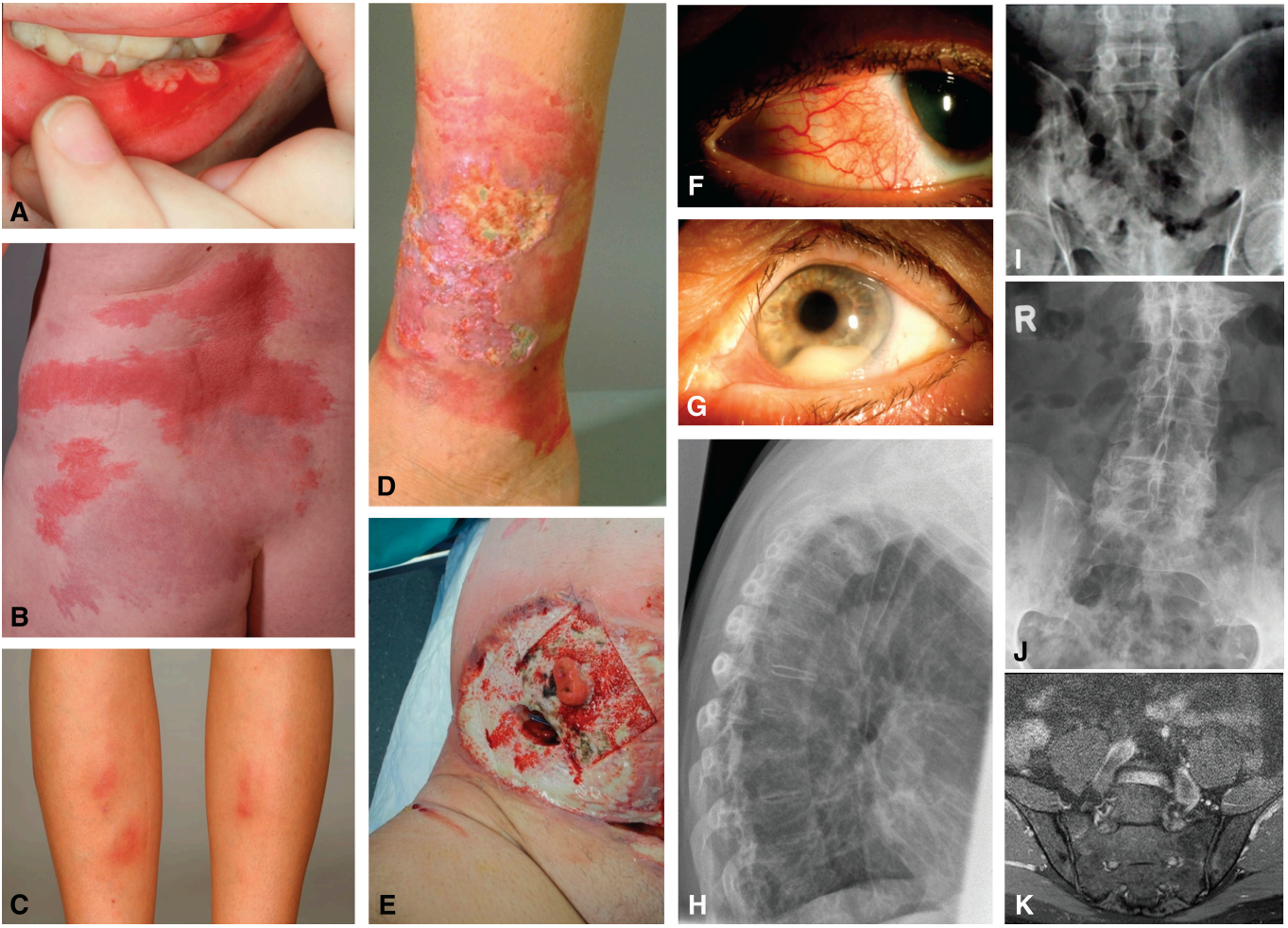

INFLAMMATORY BOWEL DISEASE:
Extraintestinal Manifestations (EIMs)

Mashiko Setshedi 27 Oct 2018

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ECCO Guideline/Consensus Paper

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The First European Evidence-based Consensus on Extra-intestinal Manifestations in Inflammatory Bowel Disease

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Overview

EIMs adversely impact QOL (e.g. PSC, VTE)

Clinical spectrum of EIMs varies from mild transitory to very severe lesions - sometimes more incapacitating than the intestinal disease

CD (colonic) > UC

Most EIMs parallel IBD **except** AS, Type 2 arthropathy, uveitis

Lichtenstein GR, et al. *Am J Gastroenterol*. 2009;104(2):465-468
Cobrin GM, et al. *Immunol Rev*. 2005;206:277-295
Carter MJ, et al. *Gut*. 2004;53(suppl V):v1-v16.
Ardizzonea S et al. *Dig Liver Dis*. 2008;40S:S253-S259
Ott C, et al. *World of Gastroenterol*. 2014;20(34):12269-12276
Parbhukot R. *Am J Gastroenterol*. 2011:S433-434

Overview

20-40% of IBD patients will have at least one EIM in lifetime

Cumulative probability of 2nd EIM is 70% at 10 years follow up

25% have EIMs before diagnosis

Lichtenstein GR, et al. *Am J Gastroenterol*. 2009;104(2):465-468
Cobrin GM, et al. *Immunol Rev*. 2005;206:277-295
Carter MJ, et al. *Gut*. 2004;53(suppl V):v1-v16.
Ardizzonea S et al. *Dig Liver Dis*. 2008;40S:S253-S259
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Common genes, inflammatory pathways, environmental factors - there are tissue-specific factors

Immune-mediated

Reactive manifestations often associated with intestinal inflammation

Reflects common pathogenic pathway (e.g. arthritis, EN, PG, apthtous stomatitis)

Autoimmune disease independent of bowel disease

e.g. AS, PSC, psoriasis

Non-immunological

Metabolic and other processes

Osteoporosis, biliary or urinary lithiasis, anaemia

Therapy-related

Roberts H, et al. *Digestion*. 2014;90:122-129
Ardizzone S, et al. *Dig Liver Dis*. 2008;405:S253-S259
Vavricka SR et al. *Curr Drug Targets*. 2014;15:1064-1073
Danese S, et al. *World J Gastorenterol*; 2005;11(46):7227-7236

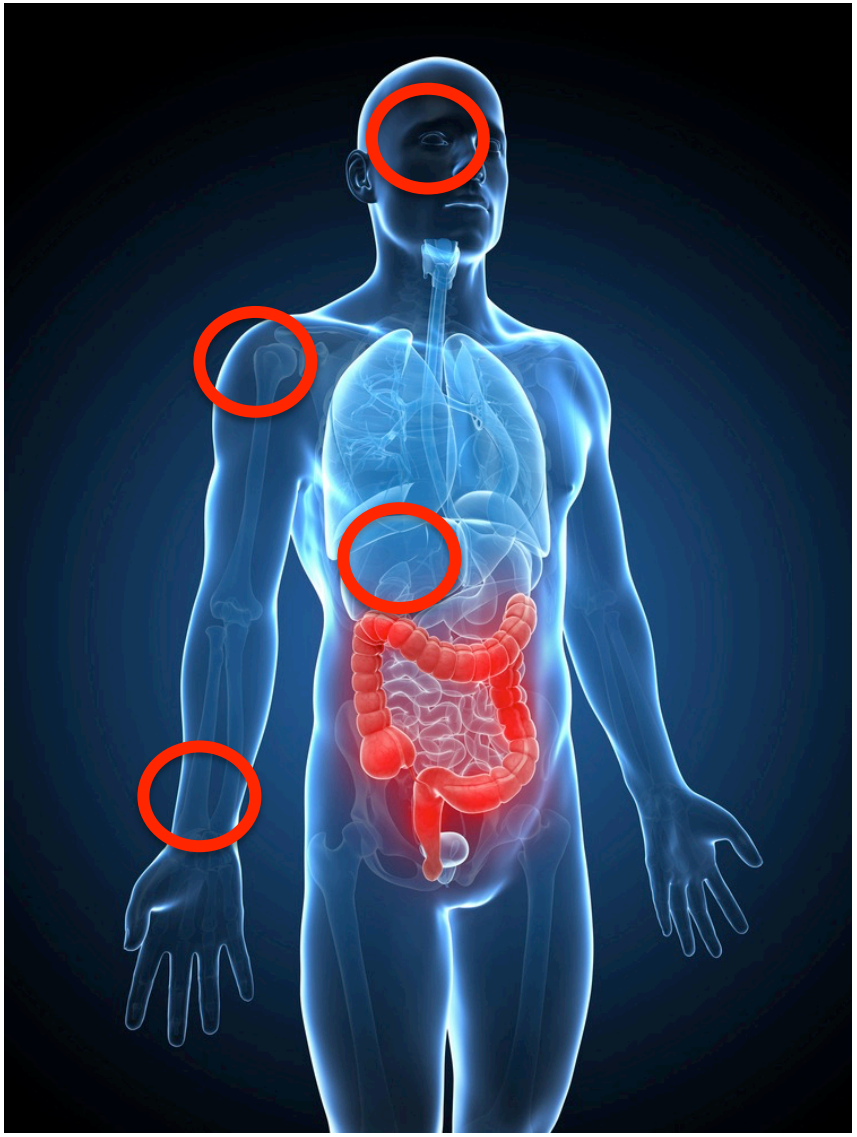
Commoner EIMs

Eyes

Joints

Liver

Skin



Joints

Peripheral arthritis
Ankylosing spondylitis/ sacroiliitis

Eyes

Episcleritis
Anterior uveitis
Iritis
Conjuctivitis

Skin

Erythema nodosum
Pyoderma gangrenosum
Sweet syndrome
Psoriasis
Aphtous stomatitis
Hidranitis suppurativa
Anti-TNF induced skin inflammation

Liver

Primary sclerosing cholangitis
Others

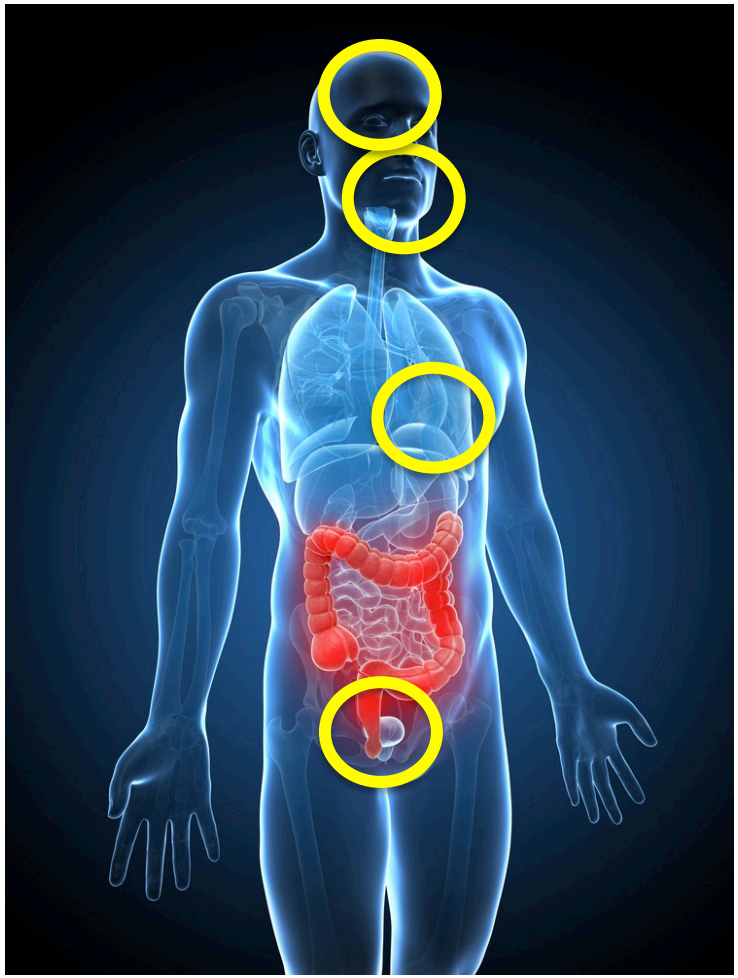
Other EIMs

Mouth, aural, nasal

Mouth ulcerations,
Pseudopolyps
Labial swelling
Often associated with perineal disease
Nasal septal abscess
Hearing loss

Urogenital

Nephrolithiasis
Secondary amyloidosis
Others



Heart

↑ CVD, CVA
Mesenteric ischaemia
Hyperhomocysteinaemia 4x > than in general population

Brain

Peripheral neuropathy (rare)
Venous sinus thrombosis
Stroke
Central demyelination
PRES (infliximab)
Vasculitis /arteritis

Lung

Respiratory EIMs

Anatomical site	Pathology	Symptoms/investigations
Larynx, glottis, trachea	Inflammation and stenosis	Stridor, hoarseness, cough Bronchoscopy ± biopsy
Bronchi	Chronic bronchitis [non-specific, granulomatous] Bronchiectasis	Cough, sputum production Bronchoscopy ± biopsy High resolution CT scan
Bronchioles	Granulomatous bronchiolitis Diffuse pan-bronchiolitis	Dyspnoea, cough, bronchorrhoea, wheezing Bronchoscopy ± biopsy High resolution CT scan
Parenchymal tissues	Usual interstitial pneumonia Organising pneumonia Lymphocytic interstitial pneumonia Desquamative interstitial pneumonia Eosinophilic interstitial pneumonia Granulomatous interstitial lung disease	Dyspnoea, fever, acute respiratory failure, chest pain High resolution CT scan Lung biopsy

Rare EIMs
Association between IBD and COPD (1.8 -2x risk, independent of smoking)
Most common is drug-induced parenchymal disease (5-ASA, MTX)

NB - Respiratory symptoms in patients receiving corticosteroids, immunomodulators, and/or anti-TNF therapy may indicate a serious opportunistic infection

Harbord M et al. *J Crohn's and Colitis*. 2016; 239–254

Hepatopancreatic EIMs

TABLE 1. Association Between Inflammatory Bowel Disease (IBD) and Hepatopancreatobiliary (HPB) Manifestations

HPB manifestations with a possibly shared pathogenesis and mechanism as IBD	Primary sclerosing cholangitis (PSC)
	Small-duct PSC
	Cholangiocaracinoma
	Autoimmune hepatitis/PSC overlap
	IgG4 associated cholangitis
	Idiopathic pancreatitis (acute and chronic)
HPB manifestations parallel the pathophysiology associated with IBD	Gall stones
	Portal vein thrombosis and hepatic abscess
HPB manifestations associated with treatment of IBD	Drug induced hepatitis (azathioprine, 6-mercaptopurine, methotrexate, cyclosporine, infliximab)
	Reactivation of hepatitis B (infliximab)
	Drug induced pancreatitis (azathioprine, 6 mercaptopurine)
	Hepatosplenic T-cell lymphoma
HPB manifestations possibly associated With IBD	Autoimmune pancreatitis
	Fatty liver
	Hepatic amyloidosis
	Granulomatous hepatitis
	Primary biliary cirrhosis

30% IBD patients have abnormal LFTs

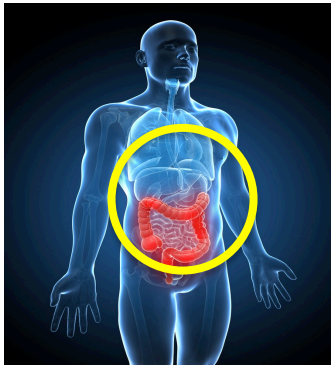
Chronic Pancreatitis
Exocrine insufficiency > pain
Pancreatic duct abnormalities

Portal Vein Thrombosis
IBD-specific factors - intraabdominal abscesses, fistulising dx, colitis severity, malnutrition, protein loss, drugs

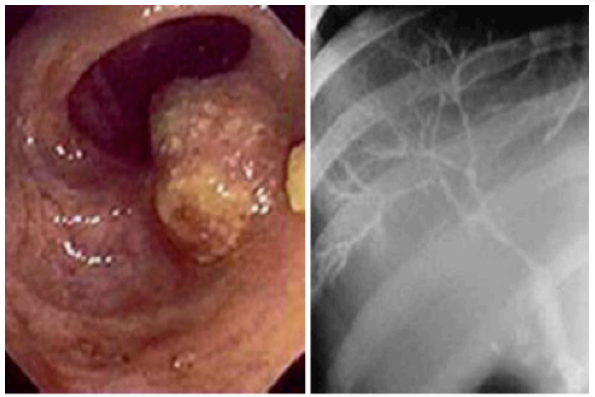
Udayakumar N et al. *Inflam Bowel Dis*. 2010;16(9):1598-1619

Primary Sclerosing Cholangitis (PSC)

Strong association with IBD
75% have UC, 10% CD
Only 5% of UC patients and 2% CD develop PSC
Increased ALP
Typical MRCP features or liver biopsy (small-duct PSC or suspected AIH)
Hereditary component (16 susceptibility loci)
Complications – biliary strictures
CCA



Treatment
ERCP with stenting
OLTx
Indomethacin (PEP)
Prophylactic antibiotics
Annual surveillance colonoscopy



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Arthropathy and Arthritis

Most common EIM (9-53%)
Not athralgia
Axial (F = M, all IBD types)
Peripheral (F > M, CD > UC)
Colonic > SB disease
CD > UC pancolitis > L sided disease

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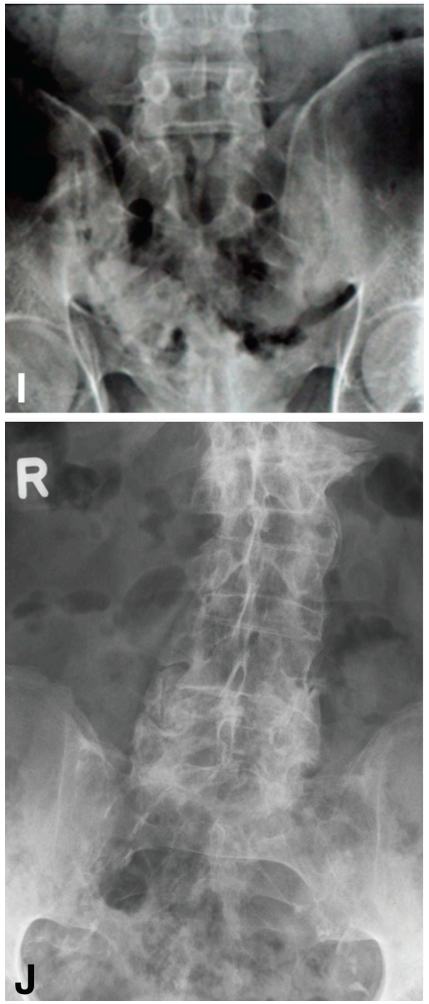
Ankylosing Spondylitis (AS)

Ankylosing Spondylitis (AS)
Progressive (1-10%), inflammatory back pain AND MRI/radiographic features of sacroiliitis
Radiological evidence of sacroiliitis occurs in 20–50%
Associated with HLAB27 (70% vs 94% in idiopathic SpA), therefore unreliable
Poor prognosis, poor QOL (increased CRP with active inflammation on MRI)
Related to AS not IBD

Treatment
Joint management with rheumatologists
Intensive physiotherapy
Short-term NSAIDS
SSZ, MTX have limited efficacy
Anti-TNF for intolerant/refractory cases



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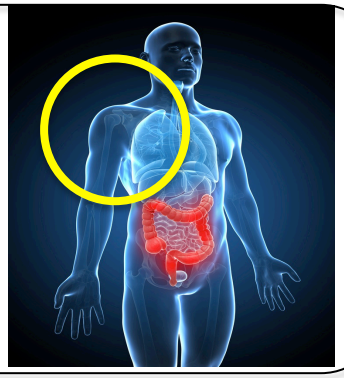
Peripheral Arthritis

Peripheral arthropathy based on signs of inflammation and exclusion of other specific forms of arthritis
NOT erosive
Usually coincides with IBD
Prognosis good
Enthesopathies/dactylitis less studied



Type 1
Pauciarticular (< 5 large joints)
Symptom duration < 10 weeks
Asymmetric
Parallels activity

Type 2
Polyarticular (> 5 joints including MCP)
Months to years
Symmetrical
Independent of activity

Treatment
Treating underlying IBD sufficient
Short-term NSAIDS/local steroids symptomatic relief
SSZ/MTX may have a role (persistent arthritis) esp increased ESR
Anti-TNF (resistant cases)

Harbord M et al. *J Crohn's and Colitis*. 2016; 239–254
Levine J, et al. Gastroenterolo hepatol (NY). 2011; 7: 235-241

Ocular EIMs

Episcleritis

Most common

Painless, asymptomatic

Parallels activity

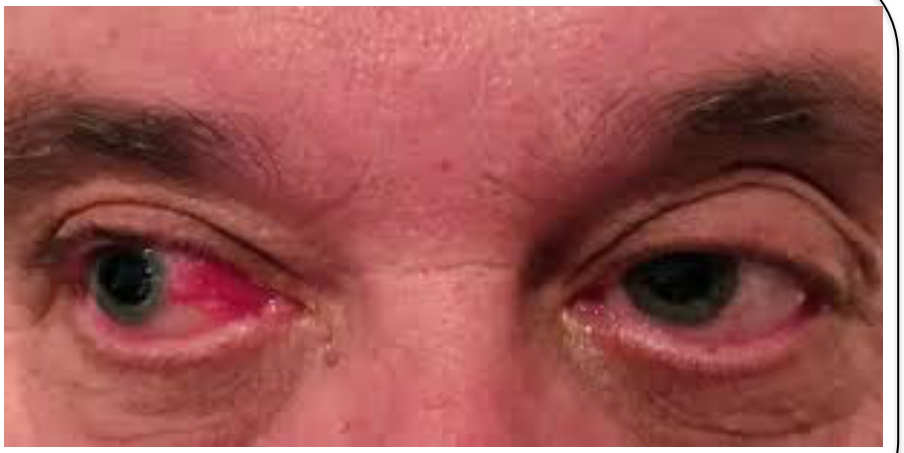
May resolve spontaneously

Treatment

Topical/systemic NSAIDs

Topical corticosteroids (symptomatic)

Immunomodulators and anti-TNF agents



Scleritis

Painful

Rapidly progressive therefore needs urgent referral

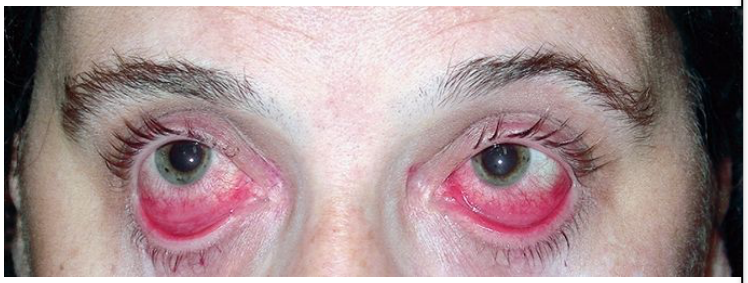
Treatment

Guided by an ophthalmologist

Topical/systemic corticosteroids

AZA, MTX

infliximab, adalimumab (resistant cases)



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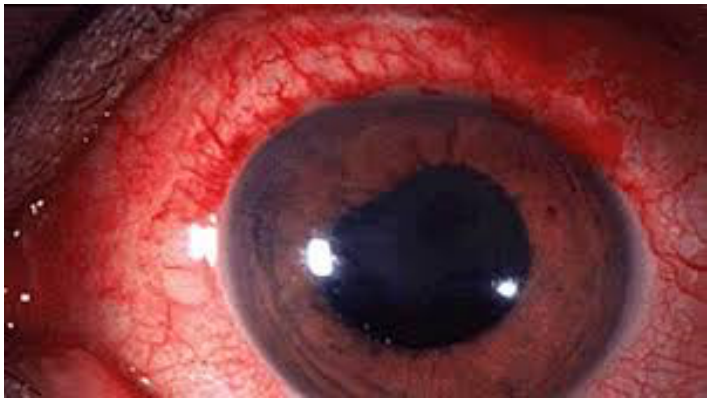
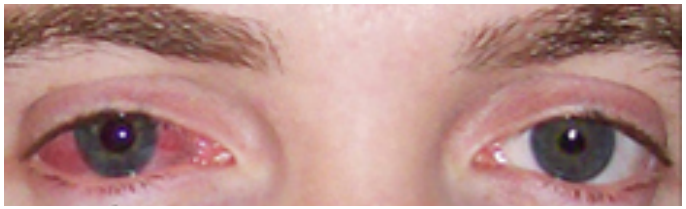
Levine J, et al. Gastroenterolo hepatol (NY). 2011; 7: 235-241

Ocular EIMs

Uveitis
Bilateral, symptoms
Least common, **most serious**
Often before IBD
Genetic associations (NOD2, MICA)
Immediate slit lamp evaluation
Treatment
Corticosteroids, cyclosporin or anti-TNFs



Iritis
Painful, headaches, photophobia
Can lead to loss of vision



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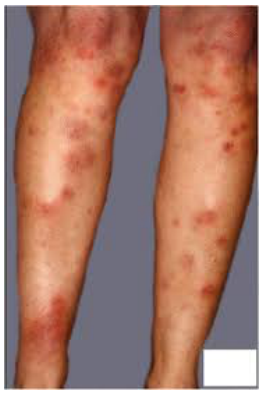
Levine J, et al. Gastroenterolo hepatol (NY). 2011; 7: 235-241

Dermatological EIMs

2-34% of IBD patients
Diagnosis is on clinical grounds based on characteristic features

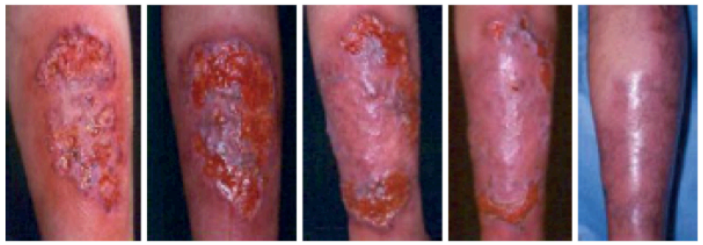
Erythema nodosum (EN)
Associated with fatigue, arthralgia
Parallels disease (CD>UC)
Biopsy rarely necessary (panniculitis)

Treatment
Treat underlying IBD
Corticosteroids
AZA, infliximab, or adalimumab



Pyoderma gangrenosum (PG)
UC>CD
Pathergy
Variable behaviour w.r.t clinical course in relation to disease activity
Recurs in 25%

Treatment
Daily wound care
Corticosteroids, immunomodulators, or anti-TNFs
Topical/oral calcineurin inhibitors (refractory)



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Levine J, et al. Gastroenterolo hepatol (NY). 2011; 7: 235-241
Trikudanathan G, et al. Drugs.2012;72(18): 2333-2349

Drug-Induced Dermatological EIMs

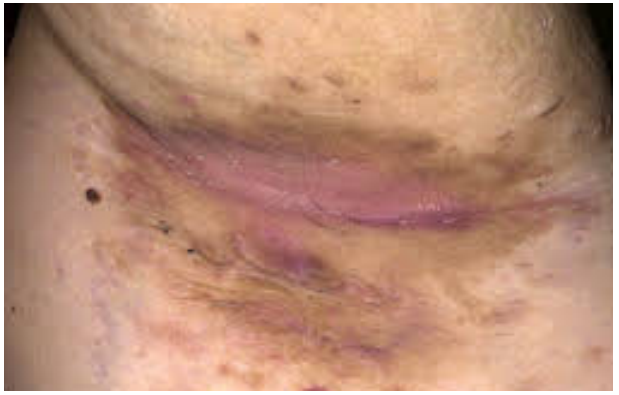
Drug	Adverse events	Prevalence/comments
Thiopurines	Skin and soft tissue infection	Frequently cellulitis
	Non-melanoma skin cancer	Patient education, sun protection, and routine annual skin check important
	Drug hypersensitivity	Prevalence up to 10%[377]
	Shingles	Patients aged > 60 years treated in combination with systemic corticosteroids are at higher risk [378,379]
Anti TNF	Skin reactions	Subcutaneous injection site reaction and delayed infusion reaction [380]
	Drug-induced lupus erythematosus [DILE]	Rare; no class effect [381]
	Skin and soft-tissue infection	Cellulitis, erysipelas, abscess [0.1% to 7%] [382,383]
	Melanoma	Slight increased risk [382,383,384]
	Paradoxical skin reactions: eczema-like, psoriasis-like	Psoriasis: pustular phenotype [commonly palms and soles]; eczema: atopic diathesis [385,386]
Sulfasalazine	Exfoliative dermatitis, StevensJohnson syndrome, and toxic epidermal necrolysis	Rare but serious skin reactions, some fatal; discontinue drug if skin or mucosal lesion[387]
Methotrexate	Alopecia	< 10%; more common long term
	Generalised skin rash	Less frequent than reported
	Oral and intertriginous lesions	Rare; consider drug over-dosage [daily instead of weekly][388]
Vedolizumab	Infusion-related and hypersensitivity reactions	Requires previous antihistamine, hydrocortisone. and/or paracetamol[389]
	Rash, pruritus, eczema, acne	

Harbord M et al. *J Crohn's and Colitis*. 2016; 239–254

Dermatological EIMs

Anti-TNF induced skin inflammation
22% of patients treated with anti-TNF
Eczematous/psoriatic lesions in patients receiving anti-TNFs
F>M
Anti-neutrophilic antibodies common
Any type of anti-TNF
Treatment
Topical treatment
Anti-TNF can be maintained

Hidranitis Suppurativa (HS)
? Shared IBD pathogenesis
NB to differentiate it from perianal CD
Typical features: skin discoloration,
axilla, groin involvement



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Levine J, et al. Gastroenterolo hepatol (NY). 2011; 7: 235-241
Van der Zee, et al. *Br J Dermstolo*. 2010;162;195-197

Metabolic EIMs

Osteoporosis (T<-2.5)
Common in IBD (5-37%)
40-50% have osteopaenia (T<-1 to >-2.5)
Factors include chronic inflammation, steroid treatment, extensive SB or resection, age, smoking, low physical activity, nutritional deficiencies (e.g. **Vit D**)
A significant proportion of IBD patients can normalise BMD after 3 years in stable remission

Treatment
Treat underlying disease
Weight-bearing exercise, stopping smoking
Adequate dietary calcium 1 g/day
Calcium and Vit D prophylaxis (steroids)
Bisphosphonates and other therapies
Vitamin D 800–1000 IU/day

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Haematologic EIMs

Venous thrombo-embolism (VTE)
At least 2-fold higher in IBD
Related to IBD activity
Fistulising or stenosing disease independently associated with greater risk
Usual RF but IBD-related surgery CD>UC
NB: other chronic inflammatory/bowel diseases e.g. RA/CD no excess risk of VTE
IBD-related mortality is increased when VTE occurs (17.0 vs 4.2 per 1000 hospitalisations for CD; $p < 0.0001$)

Management
Prophylaxis is recommended in hospital
Considered following discharge (incl at OPD) and after recent surgery
Treatment should follow established antithrombotic therapy guidelines (Vit K/non-Vit K antagonists, NOACs)

Harbord M et al. *J Crohn's and Colitis*. 2016; 239–254

ORIGINAL ARTICLE

Increased risk of acute arterial events in young patients and severely active IBD: a nationwide French cohort study

Julien Kirchgesner,[1,2] Laurent Beaugerie,[1,3] Fabrice Carrat,[2,4] Nynne Nyboe Andersen,[5,6] Tine Jess,[5,6,7] Michaël Schwarzinger,[8,9] for the BERENICE study group

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/gutjnl-2017-314015).

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ABSTRACT

Objective Magnitude and independent drivers of the risk of acute arterial events in IBD are still unclear. We addressed this question in patients with IBD compared with the general population at a nationwide level.

Design Using the French National Hospital Discharge Database from 2008 to 2013, all patients aged 15 years or older and diagnosed with IBD were identified and followed up until 31 December 2013. The rates of incident acute arterial events were calculated and the impact of time with active disease (period around hospitalisation for IBD flare or IBD-related surgery) on the risk was assessed by Cox regression adjusted for traditional cardiovascular risk factors.

Results Among 210 162 individuals with IBD (Crohn's disease (CD), n=97 708; UC, n=112 454), 5554 incident acute arterial events were identified. Both patients with CD and UC had a statistically significant overall increased risk of acute arterial events (standardised incidence ratio (SIR) 1.35; 95% CI 1.30 to 1.41 and SIR 1.10; 95 CI 1.06 to 1.13, respectively). The highest risk was observed in patients under the age of 55 years, both in CD and UC. The 3-month periods before and after IBD-related hospitalisation were associated with an increased risk of acute arterial events in both CD and UC (HR 1.74; 95 CI 1.44 to 2.09 and 1.87; 95% CI 1.58 to 2.22, respectively).

Conclusion Patients with IBD are at increased risk of acute arterial events, with the highest risk in young patients. Disease activity may also have an independent impact on the risk.

Significance of this study

What is already known on this subject?

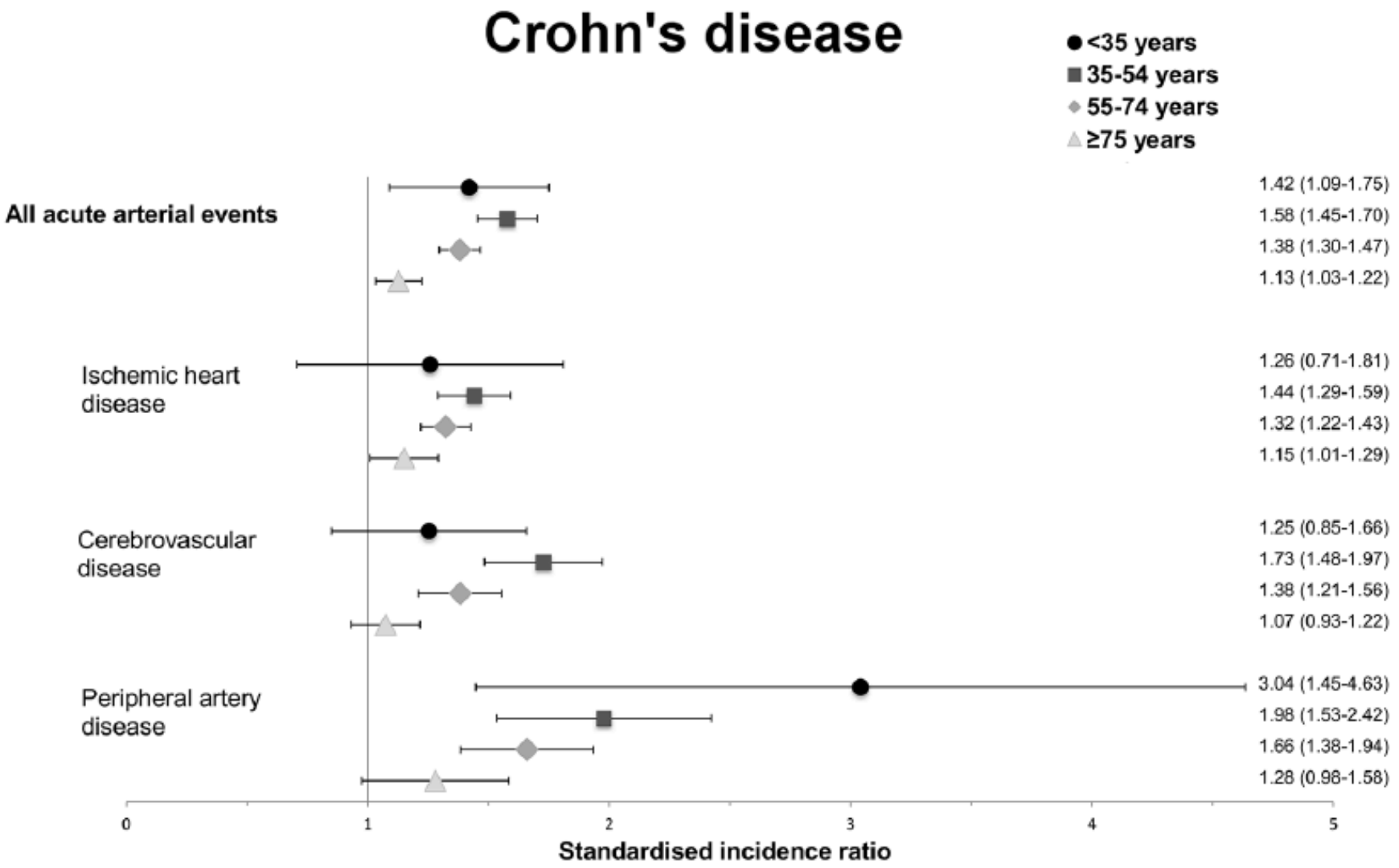
- Chronic systemic inflammation is associated with an increased risk of acute arterial events.
- Risk of acute arterial events in IBD remains debated, while risk differences between age categories and the impact of disease activity remain largely unexplored and may explain previous contradicting findings.

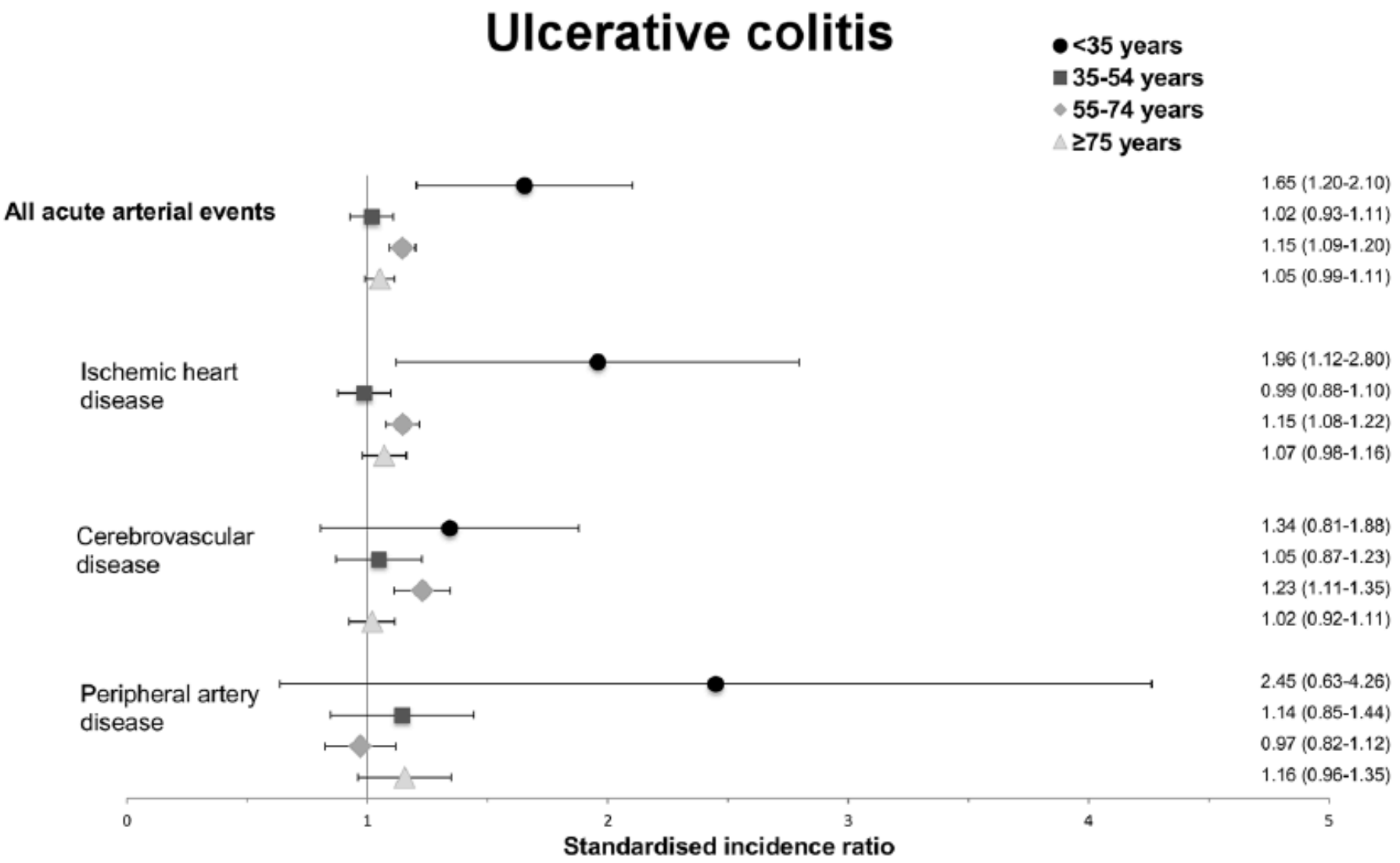
What are the new findings?

- Patients with IBD are at increased risk of acute arterial events, with the highest risk in younger patients for all arterial disease groups.
- Disease activity may be an independent risk factor of acute arterial events.

How might it impact on clinical practice in the foreseeable future?

- Our nationwide population-based cohort study suggests an increased risk of ischaemic heart disease, cerebrovascular disease and peripheral artery disease in patients with IBD, notably in younger patients and those with severely active disease. Strategies for optimising control of inflammation should be assessed to decrease the risk of acute arterial events in this patient population.


Crohn's disease
<35 years
35-54 years
55-74 years
≥75 years
All acute arterial events
1.42 (1.09-1.75)
1.58 (1.45-1.70)
1.38 (1.30-1.47)
1.13 (1.03-1.22)
Ischemic heart disease
1.26 (0.71-1.81)
1.44 (1.29-1.59)
1.32 (1.22-1.43)
1.15 (1.01-1.29)
Cerebrovascular disease
1.25 (0.85-1.66)
1.73 (1.48-1.97)
1.38 (1.21-1.56)
1.07 (0.93-1.22)
Peripheral artery disease
3.04 (1.45-4.63)
1.98 (1.53-2.42)
1.66 (1.38-1.94)
1.28 (0.98-1.58)
0
1
2
3
4
5
Standardised incidence ratio


Ulcerative colitis
<35 years
35-54 years
55-74 years
≥75 years
All acute arterial events
1.65 (1.20-2.10)
1.02 (0.93-1.11)
1.15 (1.09-1.20)
1.05 (0.99-1.11)
Ischemic heart disease
1.96 (1.12-2.80)
0.99 (0.88-1.10)
1.15 (1.08-1.22)
1.07 (0.98-1.16)
Cerebrovascular disease
1.34 (0.81-1.88)
1.05 (0.87-1.23)
1.23 (1.11-1.35)
1.02 (0.92-1.11)
Peripheral artery disease
2.45 (0.63-4.26)
1.14 (0.85-1.44)
0.97 (0.82-1.12)
1.16 (0.96-1.35)
0
1
2
3
4
5
Standardised incidence ratio

Summary

EIMs common - predate, coincide or follow IBD diagnosis

EIMs indicative of greater morbidity in IBD, early recognition critical

Treat underlying IBD
Treatment based on severity of symptoms and disease activity

Multidisciplinary team is best