بسم الله الرحمن الرحيم

ECCO Guidelines 2017 On Diagnosis and Management of ulcerative colitis

Dr Nawal Alkhalidi

GIT &Hepatology subspecialist

Introduction ….

- UC is a lifelong disease arising from an interaction between genetic and environmental factors, observed predominantly in developed countries.

- Its precise aetiology is unknown, and therefore curative medical therapy is not yet available .

Introduction ….

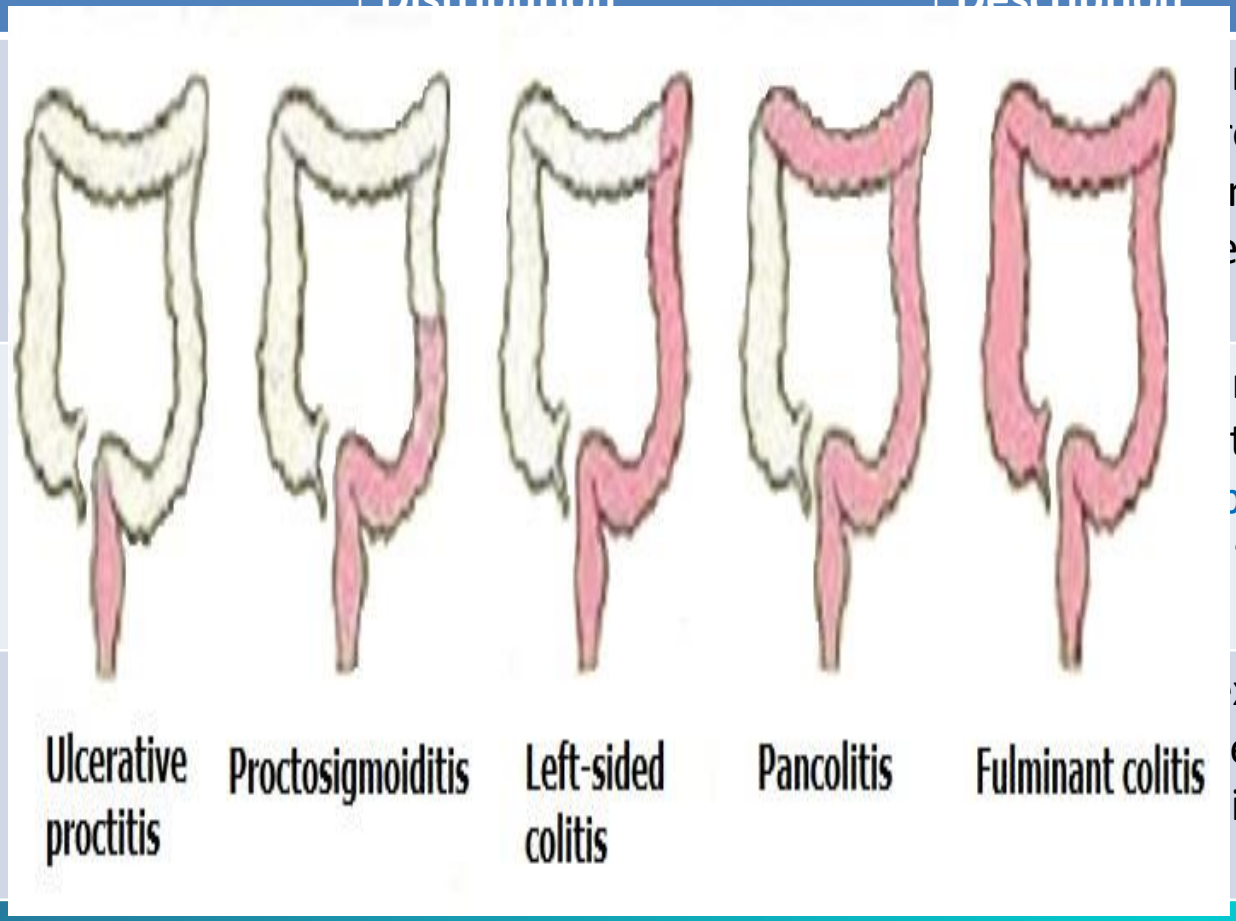
- It is a chronic inflammatory condition that causes continuous mucosal inflammation of the colon and is characterized by
- a relapsing and remitting course.

Classification according to disease extent

- Extent of inflammation influences the patient's management and the choice of delivery system for a given therapy.

Distribution of UC [adapted from Silverberg *et al.*].

Term	Distribution	Description
E1		mited to the oximal mmation is ecto-sigmoid
E2		mited to the the colon plenic flexure 'distal'
E3		xtends e splenic ing pan-



Classification according to disease severity

- Disease severity influences treatment modality and route of administration .

Disease activity in UC [adapted from Truelove & Witts]

	Mild	Moderate 'in between mild and severe'	Severe
Bloody stools/day	< 4	4 or more *if*	≥ 6 *and*
Pulse	< 90 bpm	≤ 90 bpm	> 90 bpm *or*
Temperature	< 37.5°C	≤ 37.8°C	> 37.8°C *or*
Haemoglobin	> 11.5 g/dl	≥ 10.5 g/dl	< 10.5 g/dl *or*
ESR	< 20 mm/h	≤ 30 mm/h	> 30 mm/h *or*
CRP	Normal	≤ 30 mg/l	> 30 mg/l

Montréal classification of disease activity in UC

	S0 Remission	S1 Mild	S2 Moderate	S3 Severe
Stools/ day	Asymptomatic	≤ 4	> 4	≥ 6 *and*
Blood		May be present	Present	Present
Pulse		All normal	Minimal, or no signs of systemic toxicity	> 90 bpm *or*
Temperature				> 37.5°C *or*
Haemoglobin				< 10.5 g/dl *or*
ESR				> 30 mm/h

Classification according to age at onset

- Early-onset disease has a less favorable course.
- Young patients (below 40 years) with UC tend to have more aggressive disease and require more immunomodulators [IMs] and surgical intervention compared with later-onset disease.

Activity and pattern of disease

- Confirm the presence of active colitis by flexible sigmoidoscopy and biopsy before starting treatment, which may identify unexpected causes of symptoms that mimic active disease such as cytomegalovirus [CMV] colitis, rectal mucosal prolapse syndrome, Crohn’s disease, malignancy, or even irritable bowel syndrome and haemorrhoidal bleeding

- All patients with presumed active disease require stool cultures including Clostridium difficile toxin assay to exclude enteric infection.

Microscopic involvement

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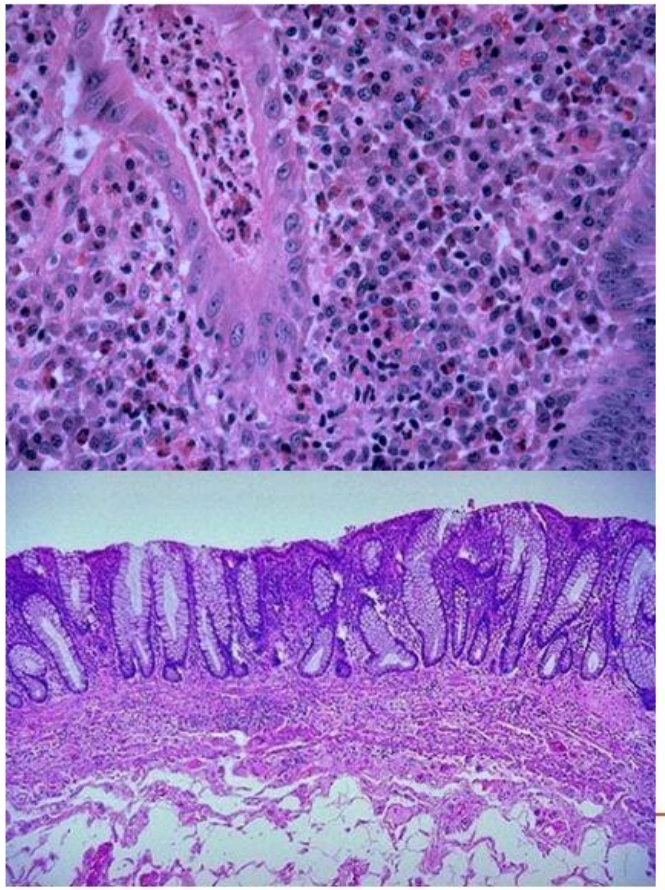
seen in

Ulcerative Colitis



- Microscopic Findings
  - Active colitis
    - Cryptitis
    - Crypt abscess formation
    - Mucosal ulceration
    - Inflammatory pseudopolyps
  - Chronic colitis
    - Increased lymphoplasmacytic lamina propria infiltrate
    - Architectural distortion
      - Branched, dilated irregular crypts
      - Crypts no longer reach the muscularis mucosae
    - Paneth cell metaplasia in left colon

- Relapse rates were higher in those with crypt abscesses, acute inflammatory cell infiltration , mucin depletion, and mucosal breaks.
- The degree of microscopic bowel inflammation is also a risk factor for CRC in patients with long-standing, extensive UC.

Remission

- There is no fully validated definition of remission.

- Combination of clinical parameters
- [stool frequency ≤ 3/day with
- no bleeding] and
- no mucosal lesions at endoscopy.

Clinical features

- Bloody diarrhea (more than 6 weeks), rectal bleeding (90%) , tenesmus, urgency, nocturnal defecation, fatigue and fecal incontinence.
- Abdominal pain, anorexia, and fever suggest severe colitis.
- Patients with proctitis usually present with rectal bleeding, urgency, tenesmus, and occasionally severe constipation

- Simple fistulae may occasionally occur in UC, recurrent or complex perianal fistulae should always raise the suspicion of Crohn’s colitis.

Clinical Presentation

- Usually insidious onset; symptoms are often present for weeks or even months before medical advice is sought.

- Presentation with a severe attack occurs in about 15%,

with systemic symptoms including weight loss, fever, tachycardia, nausea, and vomiting.

Extraintestinal manifestations

- EIMs, axial or peripheral arthropathy, episcleritis, and erythema nodosum may accompany the presentation in about 10–20% of cases an
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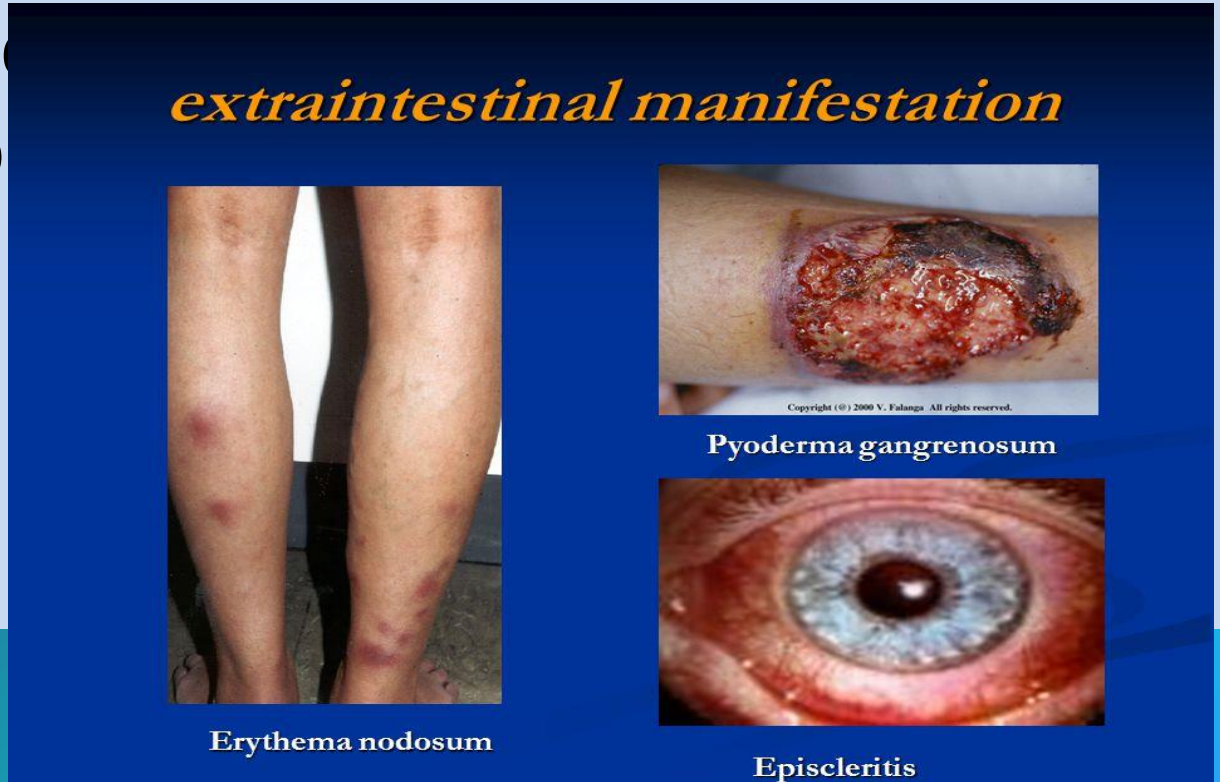

Risk factors for ulcerative colitis

- Family history of ulcerative colitis or Crohn's disease increases the risk for developing ulcerative colitis.
- Appendicectomy for proven appendicitis before adulthood, and smoking, reduce the risk and severity of UC.
- Smoking cessation may predispose to ulcerative colitis .

- Ex-smokers have approximately a 70% higher risk of developing the disease, which is often more extensive and refractory to treatment compared with individuals who have never smoked.
- Smoking might protect against PSC or pouchitis? Inconsistent data.

- NSAIDs may exacerbate the disease.
- In contrast, preliminary evidence suggests that short-term treatment with selective COX-2 inhibitors is safe.

Physical Examination

- Findings depend on the extent and severity of disease.
- Mild or moderate activity : unremarkable, apart from blood on rectal examination.
- Patients with a severe attack may exhibit fever, tachycardia, weight loss, abdominal tenderness, abdominal distension, and reduced bowel sounds.

Diagnosis

- A ‘gold standard’ for diagnosis of ulcerative colitis does not exist.
- An unremitting, continuous course occurs in approximately 5% of the cases, as does a single acute episode followed by prolonged remission.

The frequency of relapse is usually defined during the first 3 years, and may be characterized as

1. continuous : symptoms without remission
2. frequent : ≧ 2 relapses/year .
3. Infrequent : ≦ 1 relapse/year .

- Normal mucosal biopsies effectively exclude active UC as the cause of symptoms.
- In 10% of patients, the diagnosis may change to Crohn’s disease.

Initial Investigations

- It should include full blood count, electrolytes, liver and renal fu
D level, C-reactive
Calprotectin .
- The immunizatio
- Infectious diarrh
should be exclude
- Endoscopy and histology should be performed

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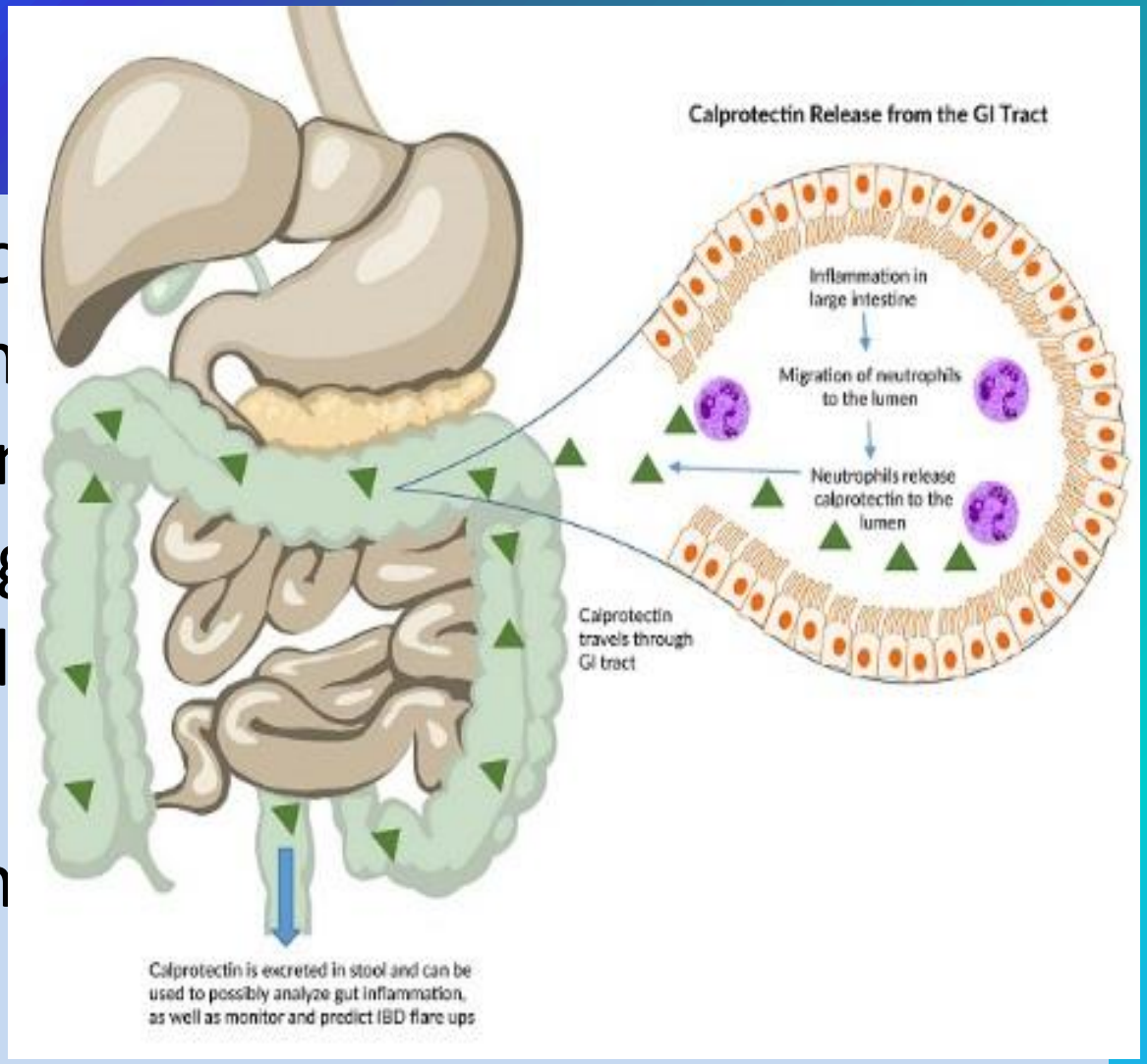
  for diagnosis ar
  severity [having
  endoscopic ind
  treatment] .
- It is used as a n



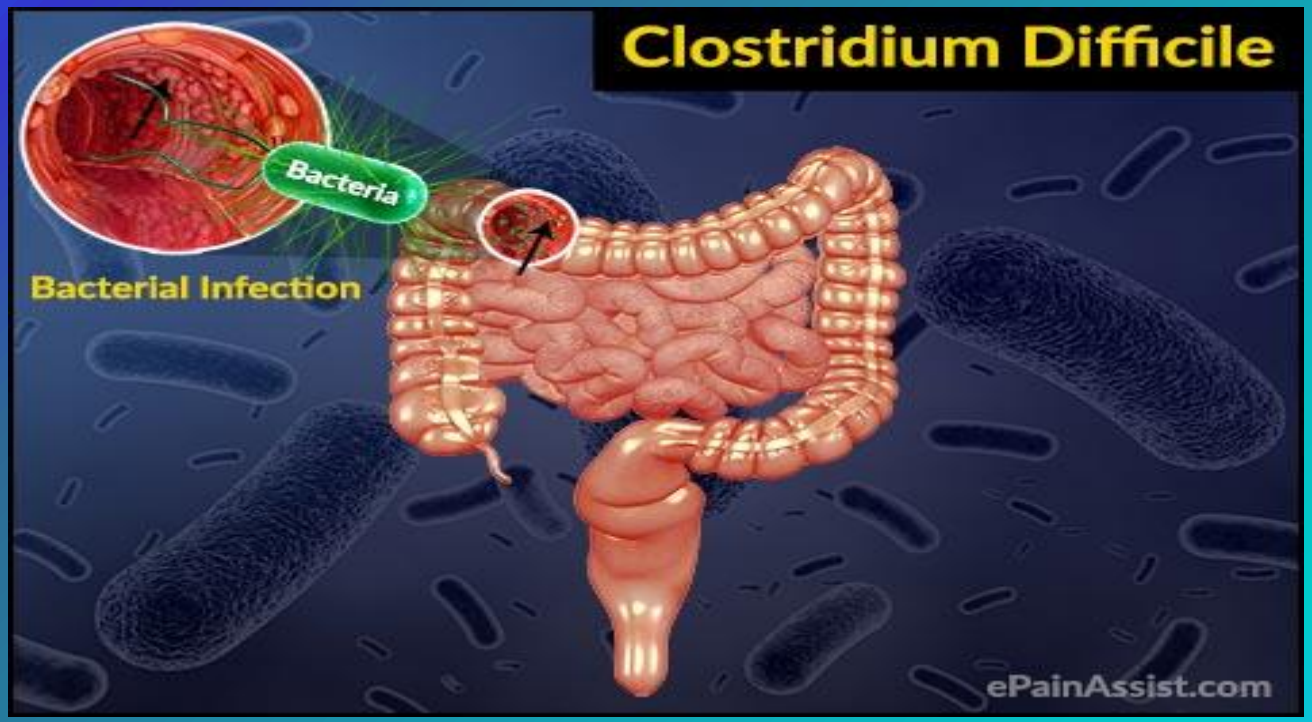
The full blood count may reveal

1. thrombocytosis as a result of the chronic inflammatory response.
2. anemia indicating severe or chronic active disease.
3. leukocytosis which raises the possibility of an infectious complication.

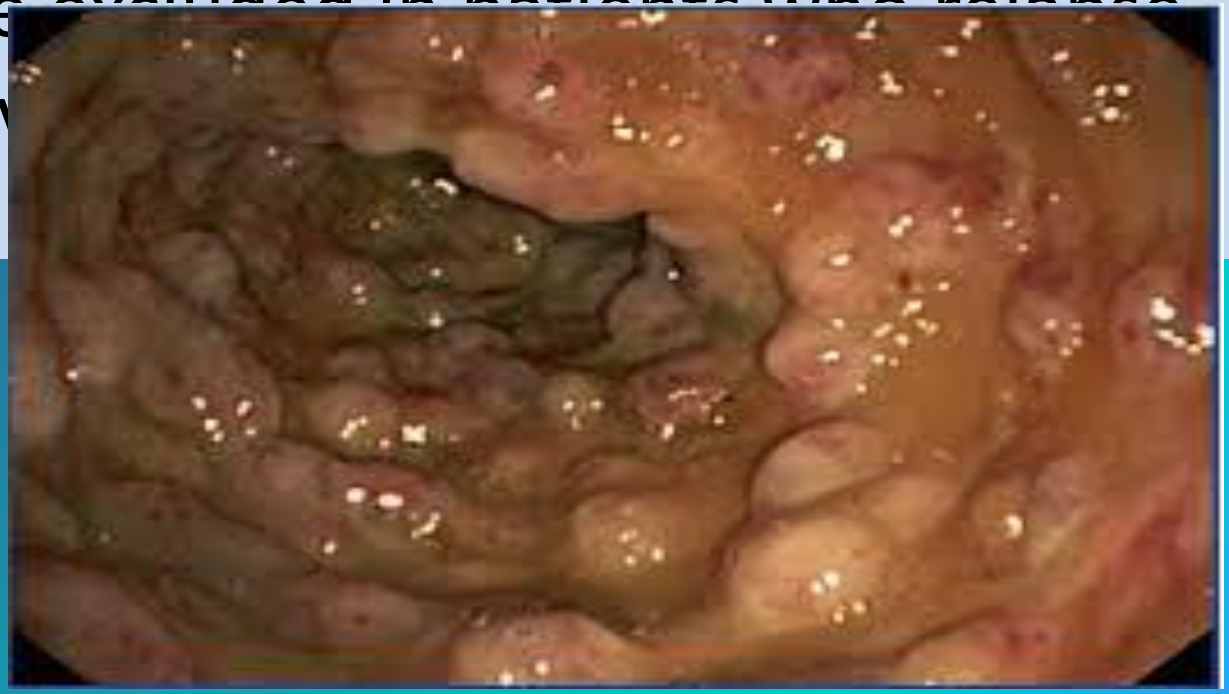
- For UC, and with the exception of proctitis, CRP correlates with clinical severity.

- CRP above 10 mg/l after a year of extensive colitis predicted an increased risk of surgery .

- ECCO guidelines now recommend screening for *C. Difficile* with every disease flare and in case of treatment-refractory or severe relapse.



- Reactivation of CMV can occur in UC, particularly in immunosuppressed patients with severe colitis.
- It should be excluded in patients who relapse while receiv



- Detection of CMV infection requires histology/immunohistochemistry rather than polymerase chain reaction [PCR] detection of CMV in the blood.
- Multiple but not occasional intranuclear inclusions are usually significant.

Biomarkers

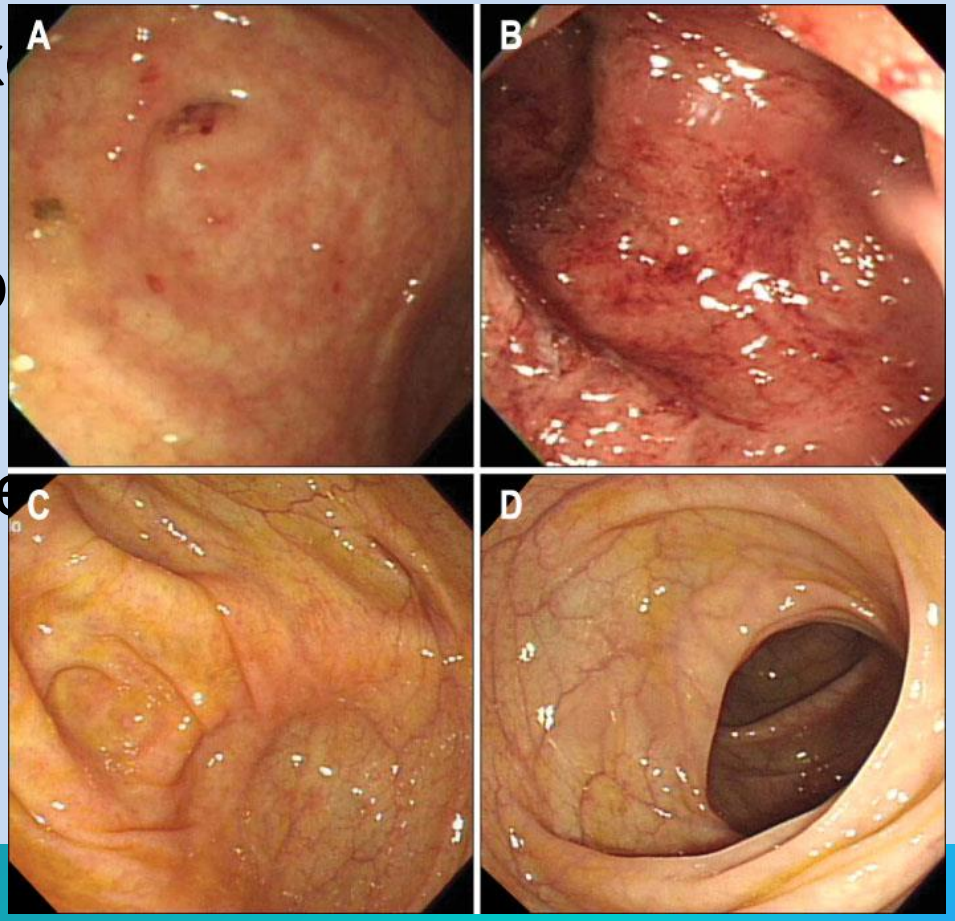
- Perinuclear anti-neutrophil cytoplasmic antibodies [p-ANCAs] up to 65% of patients with UC and in less than 10% of patients with Crohn's disease.

- Routine use for the diagnosis of UC and for therapeutic decisions is not clinically justified.

Discontinuous inflammation in UC:

1. A normal or patchy inflammation in the rectum is more lik
   therapy.

2.Patchy inflammatio
to as a ‘caecal patch’
patients with left-side



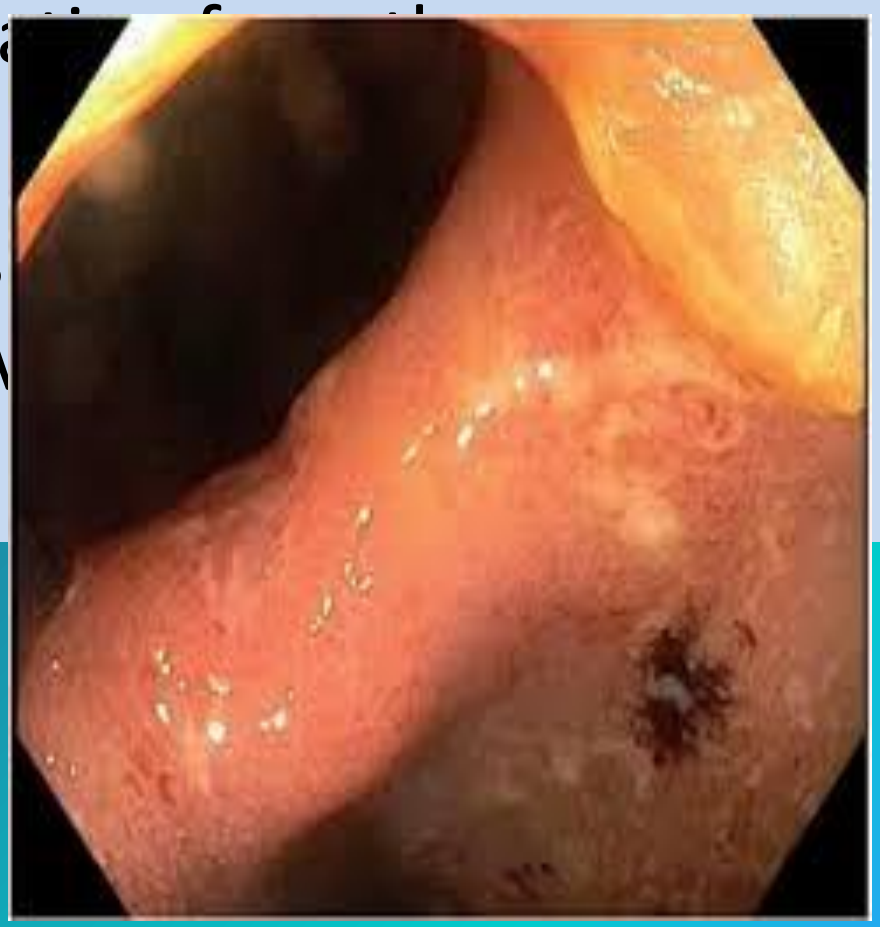
- The natural history of patients with patchy right colonic inflammation seems to be similar to those with isolated left-sided UC.

Appendiceal skip lesions

- Appendiceal inflammation has been associated with a more responsive course and a higher risk of pouchitis after ileal pouch anastomosis.

Backwash ileitis

- Continuous extension of macroscopic or histological inflamma
into terminal ileum .
- Rarely, ileal erosions
without caecal involv

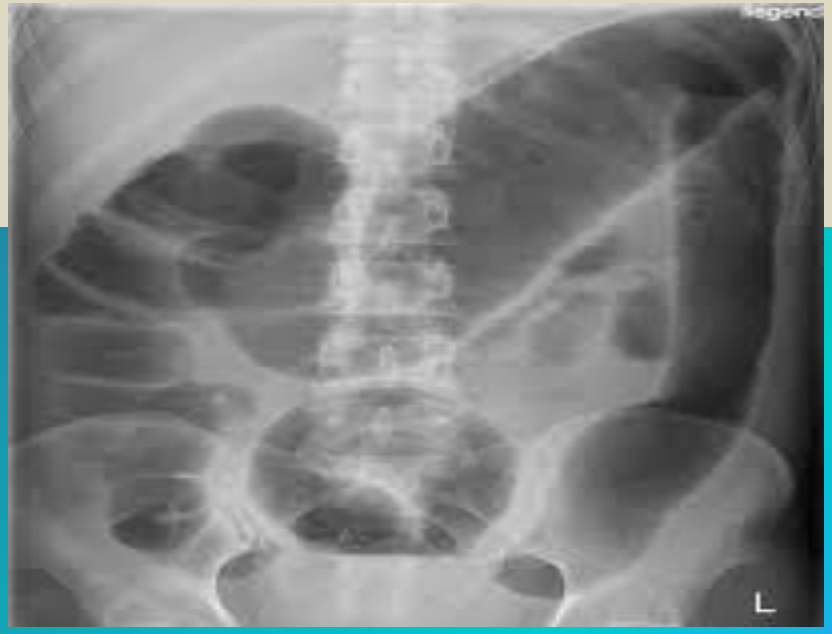


- Patients with backwash ileitis seem to be prone to a more refractory course of disease which may include an increased risk of colon neoplasia.
- However, it does not appear to be correlated with poor pouch outcomes.

Investigations for acute severe colitis at admission

- Patients with acute severe colitis should have full blood count, inflammatory markers [CRP or ESR], electrolytes, and liver function tests, along with a stool sample for culture and assay of C. difficile toxin.

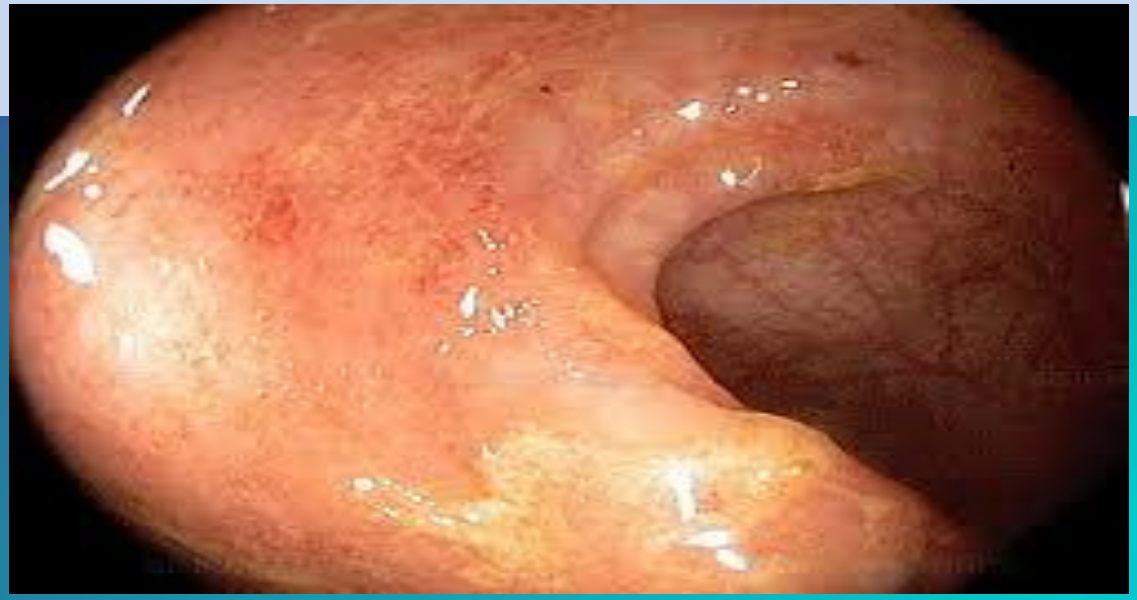
- A plain abdominal radiograph should be performed to exclude colonic dilatation [≧ 5.5 cm] and to estimate the extent of disease and look for features that predict response to treatment.



- Flexible sigmoidoscopy should confirm the diagnosis of severe colitis and help exclude infection, particularly CMV.
- Empirical treatment and urgent histopathology should be requested, within 4 hours.

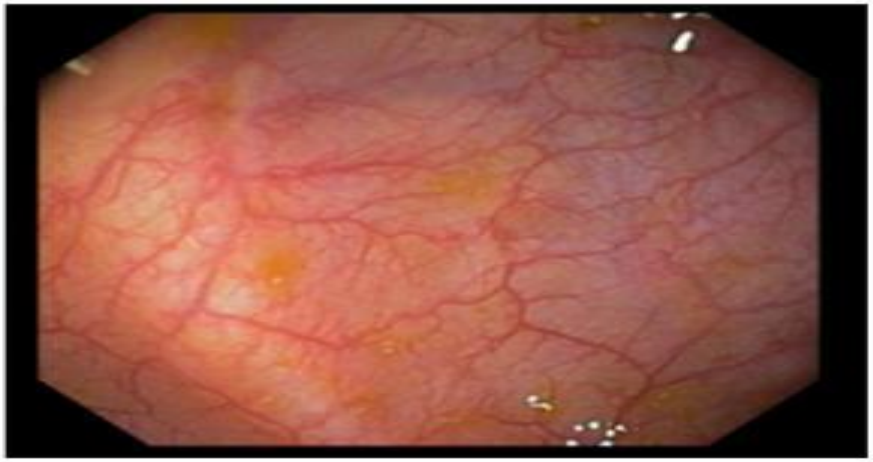
Endoscopic features

- The most common endoscopic feature is continuous, confluent colonic involvement with clear demarcation of inflammation and rectal involvement .

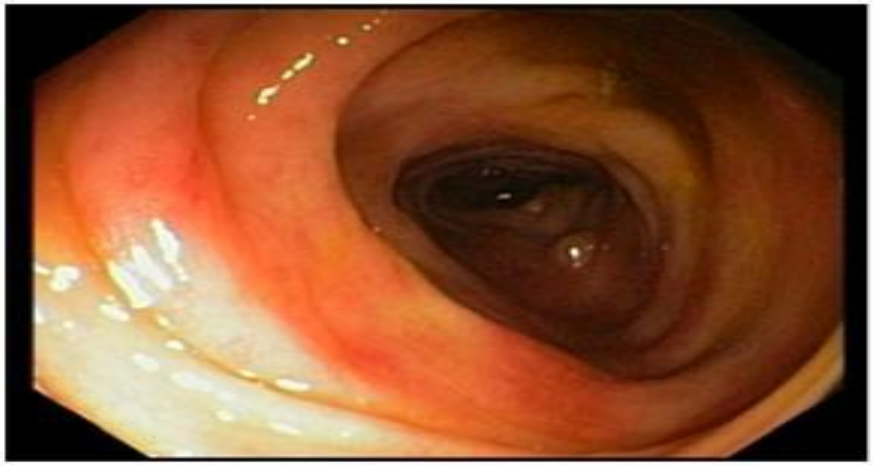


Endoscopic features

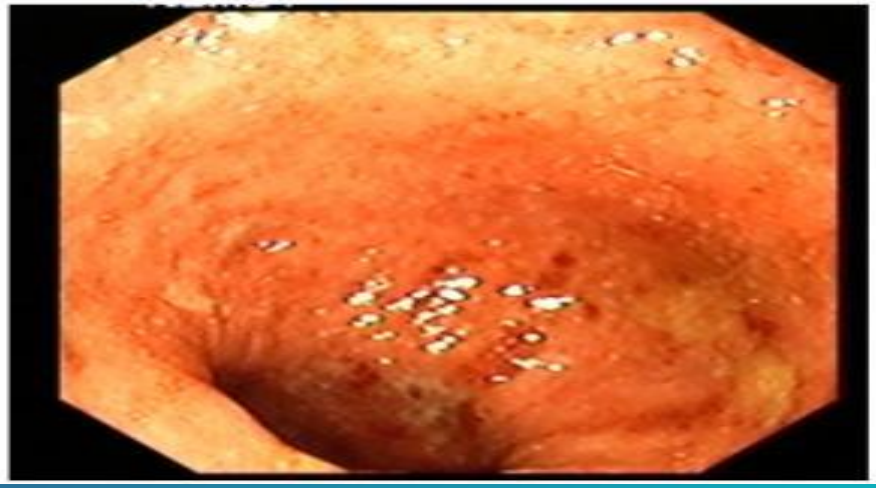
Normal mucosa



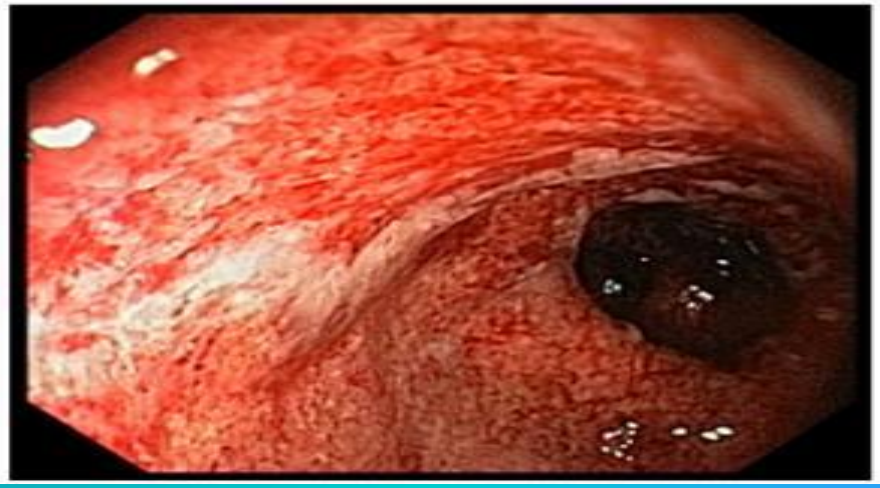
Mild inflammation



Moderate inflammation



Severe inflammation



- Granularity, vascular pattern loss, ulceration, and bleeding and/or friability have been reported to predict the global assessment of endoscopic severity.

- Mild inflammation : erythema, vascular congestion, and at least partial loss of the visible vascular pattern.

- Moderately active colitis : complete loss of vascular pattern, blood adherent to the surface of the mucosa, and erosions, often with a coarse granular appearance and mucosal friability .

- Severe colitis is characterized by spontaneous bleeding and ulceration.

- If colonoscopy is incomplete due to a stricture, CT colonography should assess the mucosal pattern proximal to the stricture and exclude extra-intestinal pathology.
- A minimum of two biopsies from at least five sites around the colon [including the rectum] and the ileum should be obtained.

Early stage disease

- Only about 20% of patients show crypt distortion within 2 weeks of the first symptoms of colitis.
- The distinction from infectious colitis which is characterized by preserved crypt architecture and acute inflammation, is important.

- Basal plasmacytosis is the earliest diagnostic feature with the highest predictive value for the diagnosis of ulcerative colitis .
- Preserved crypt architecture and the absence of a transmucosal inflammatory cell infiltrate do not rule out ulcerative colitis at an early stage.

- In quiescent disease, the mucosa may still show features related to architectural damage, as well as disappearance of basal plasmacytosis and increased transmucosal cellularity.
- Active inflammation is usually not observed.

Microscopic features—disease activity

- Histological inflammation may persist in cases with endoscopically quiescent disease and has been associated with adverse outcomes.
- Thus biopsies can be used to distinguish between quiescent and active disease, as well as to assess the different grades of disease activity.

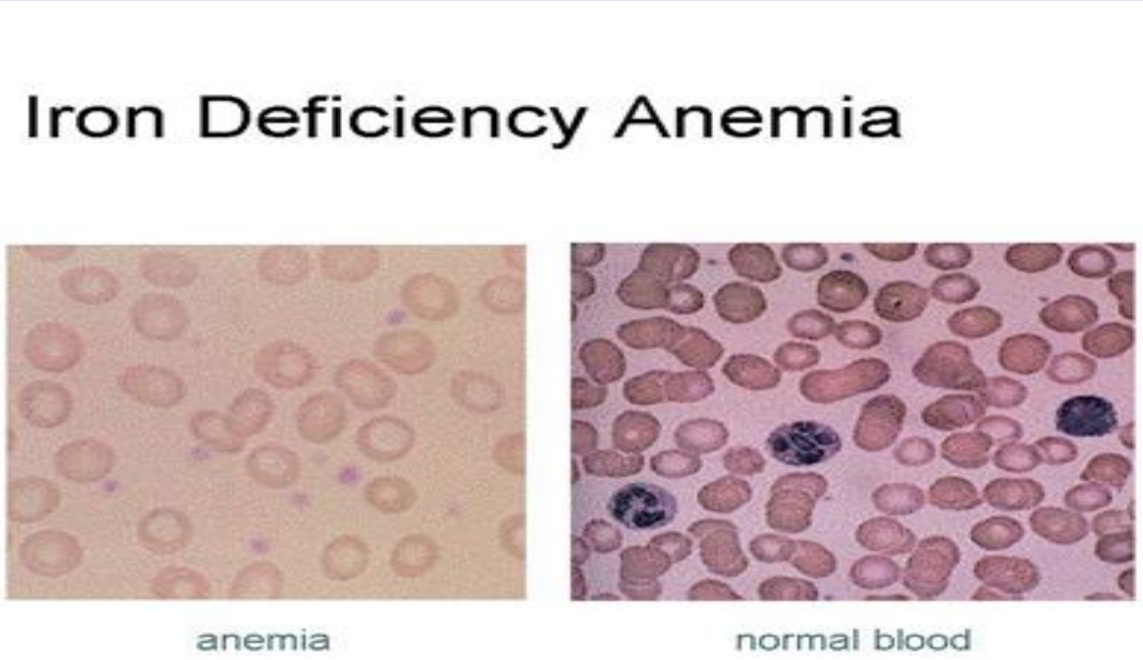
Microscopic features—upper gastrointestinal tract

- Minimal to mild non-specific and focally enhanced gastritis may be present .

EXTRAINTESTINAL MANIFESTATIONS

Anaemia

- Anemia is common in UC, found in 21% of all patients .
- are



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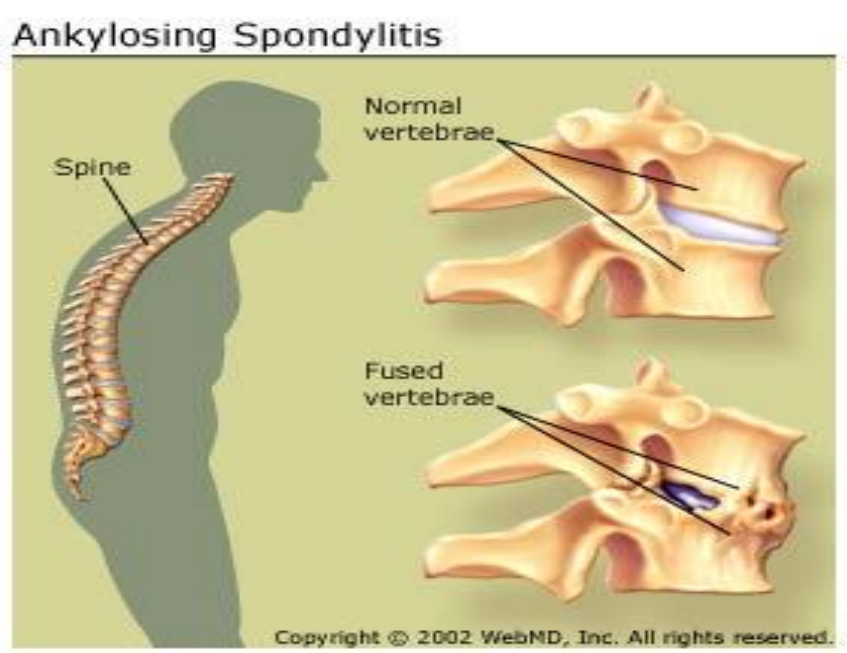
Arthropathy

- Joint involvement is the second most common EIM in UC.
- Arthritis can be classified as axial and peripheral



Metabolic bone disease

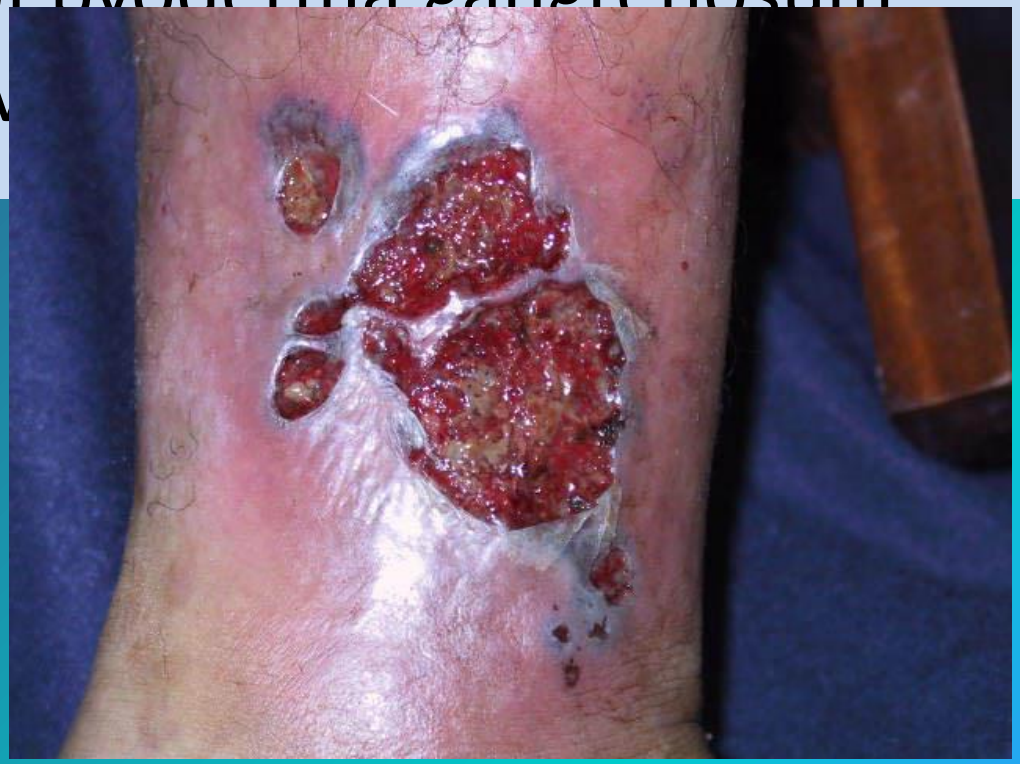
- Diagnosing osteoporosis is based on bone densitometry [T-score < -2.5], which should be assayed in all patients with persistently active UC, especially if repeatedly exposed to corticosteroids or with long disease duration.
- Calcium [500–1000 mg/day] and vitamin D [800–1000 IU/day] are recommended should the T score drop below -1.5 .

Cutaneous manifestations Erythema nodosum

- Diagnosis of erythema nodo clinical grounds.
- In atypical cases, a skin bio helpful , usually affects the of the lower extremities, pa anterior tibial areas, and ha distribution.

Pyoderma Gangrenosum

- lesions are often preceded by trauma, a phenomenon known as pathergy.
- The correlation of pyoderma gangrenosum with disease activ



Ocular manifestations

- Episcleritis generally para
- It can be self-limiting and to topical corticosteroids ar ed alongside treatment of t
- Uveitis has potentially more severe consequences ,should prompt urgent referral to an ophthalmologist

Hepatobiliary disease

- PSC is t
  cholan
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- Many c
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- PSC is a
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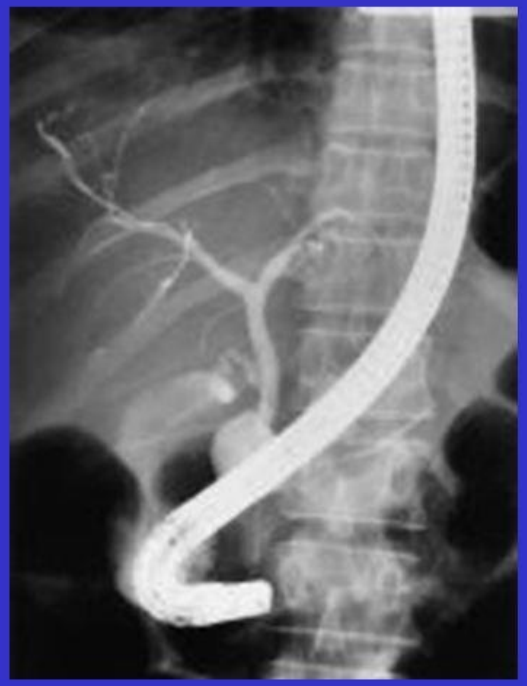
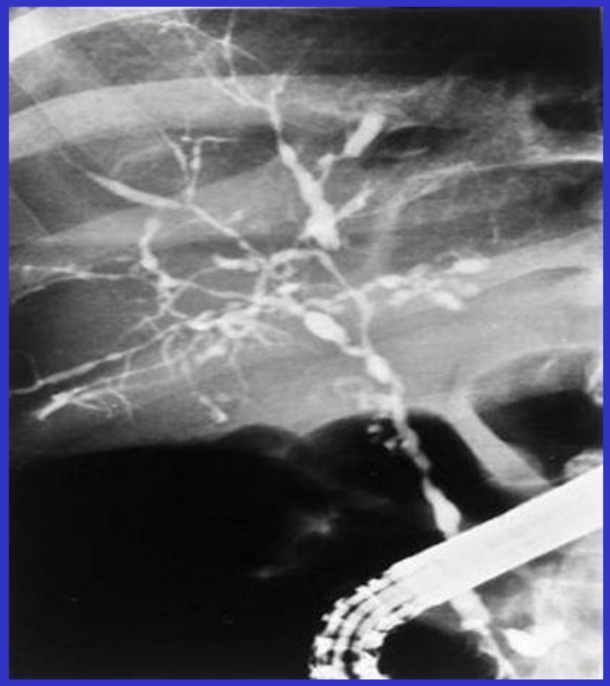
ERCP

Normal bile ducts



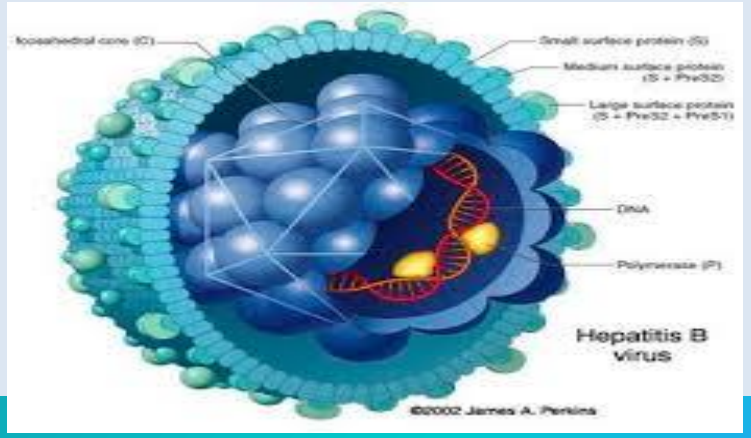
Scleros Cholangitis



- Ursodeoxycholic acid was shown to improve the levels of liver enzymes and to reduce the risk of CRC in PSC, but no therapy has been shown to reduce time to liver transplantation, cholangiocarcinoma, or death.

Viral infection

- All ulcerative colitis patients should be tested for HBV [HBsAg, anti-HBAbs, anti-HBcAb] at diagnosis.
- In patients with positive HBsAg, viraemia [HBV-DNA] should also be quantified



- HBV vaccination is recommended .
- Higher doses may be required.

- Patients who are HBsAg positive should receive potent anti-viral agents regardless of the degree of viraemia.

- UC patients should also be tested for HCV-Ab and, if positive, the result should be confirmed by HCV-RNA detection.
- IMs per se do not worsen HCV infection, unless a concomitant infection associated with HBV or HIV is present.

Mycobacterium tuberculosis

- Reactivation of latent tuberculosis in patients tre
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- La
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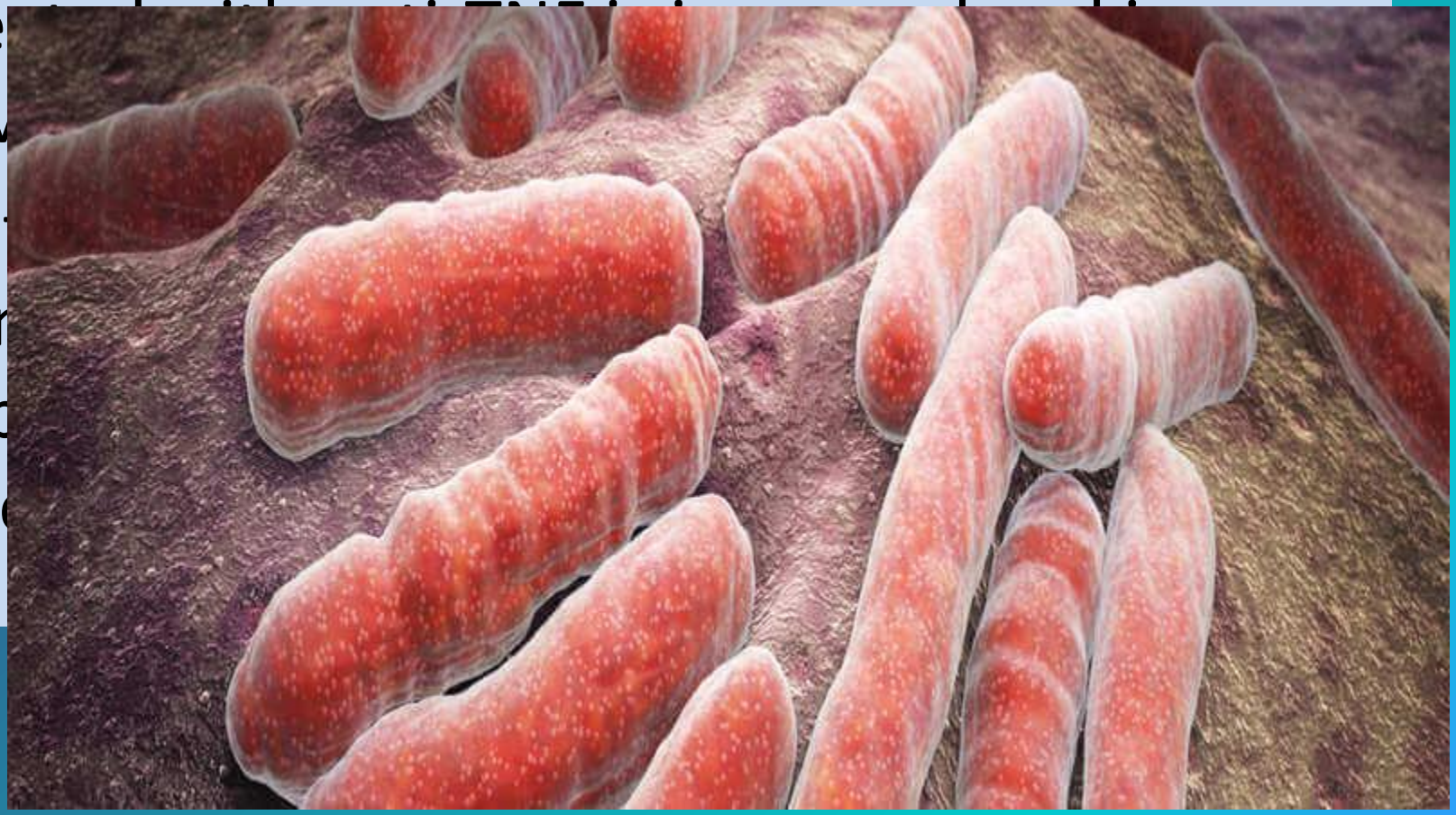


- Screening should be considered at diagnosis and always performed before anti-TNF therapy .
- Interferon-gamma release assays are likely to complement the tuberculin skin test and are preferred in BCG immunized individuals .

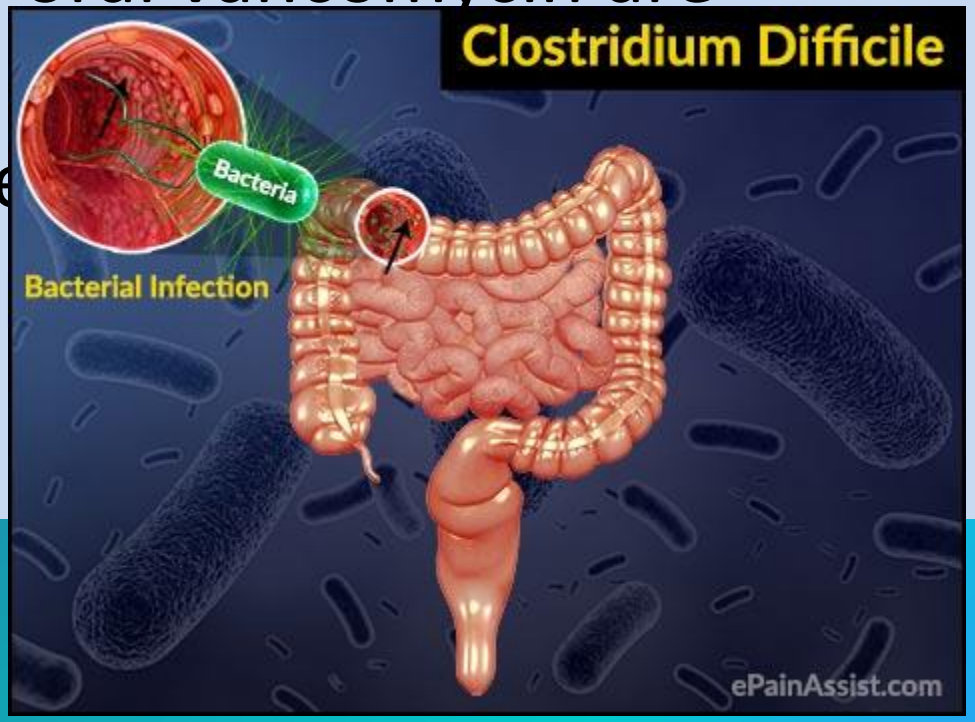
- Patients with latent TB should receive anti-tuberculous therapy before starting anti-TNF.
- In patients with active UC and latent TB, anti-TNF should be administered only after 3 weeks of anti-TB therapy .
- In case of active TB, anti-tuberculous therapy must be started and anti-TNF withdrawn for at least 2 months .

- Latent TB ….3 WKS
- Active TB…..2 MONS.

- Pneumococcal vaccination should be offered to UC patients before starting IM, and should ideally be administered 2 weeks before treatment initiation.

C.D INFECTION

- Ulcerative colitis is an independent risk factor for infection with C. difficile.
- Metronidazole and oral vancomycin are equally effective in
C. difficile-associate
- Other antibiotics s
possible.



- For severe disease, vancomycin is preferable.
- In C. difficile-associated disease, use of immunomodulators should be guided by careful risk benefit evaluation and clinical judgment.

Fertility

- There is no evidence that ulcerative colitis affects fertility .
- If conception occurs at a time of quiescent disease, the risk of relapse is the same as in non-pregnant women.
- Conception occurring at a time of active disease increases the risk of persistent activity during pregnancy.

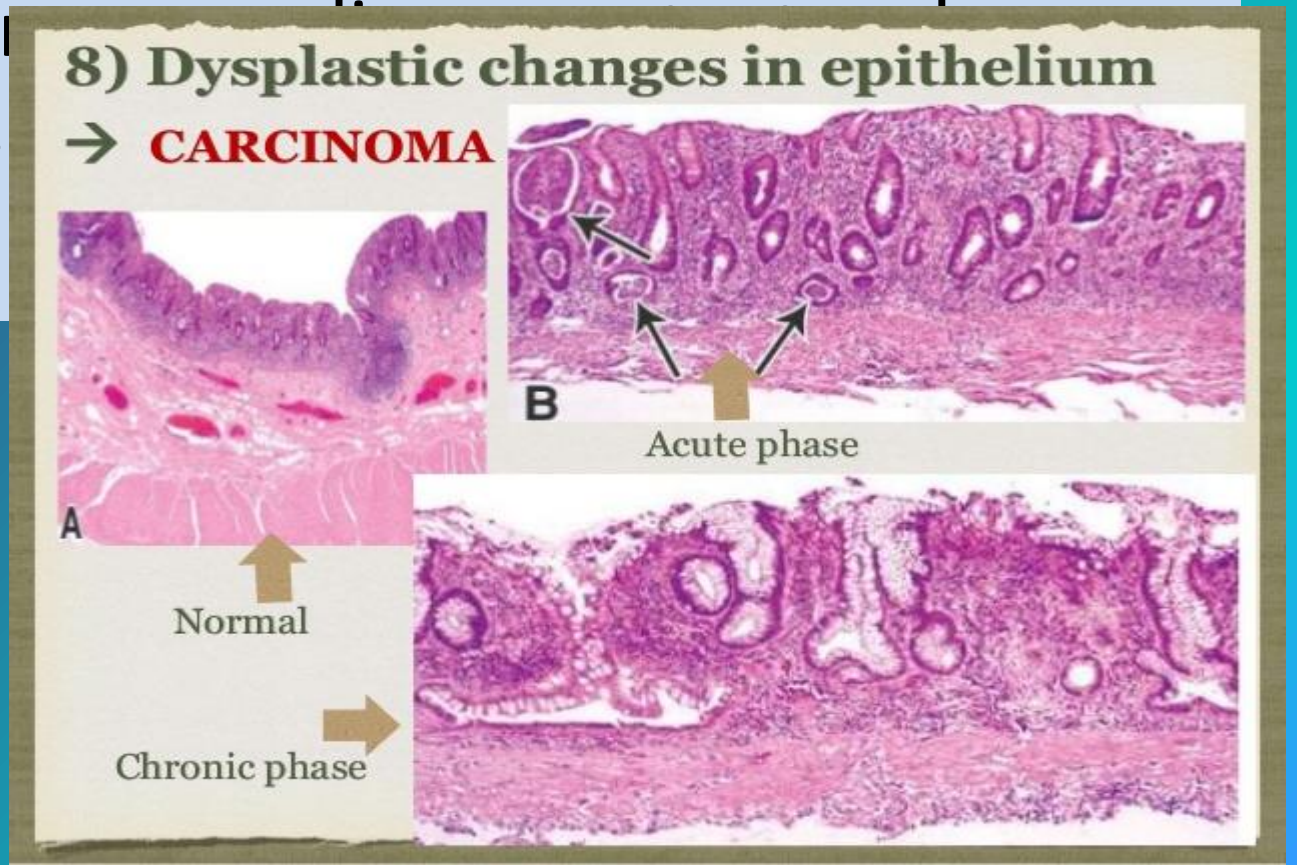
Pregnancy and delivery

- Disease activity during pregnancy is associated with preterm birth and low birthweight.
- The risk of congenital abnormalities in offspring from women with ulcerative colitis does not seem t

- Fetal exposure to most medications is considered of low risk to the child, except for methotrexate and thalidomide.

Surveillance issues

- Screening colonoscopy should be offered over 8 years following the onset of symptoms to all patients to
exclude dys



- Ongoing surveillance should be performed in all patients apart from those with proctitis .
- Patients with high risk features [e.g. stricture or dysplasia, primary sclerosing cholangitis, extensive colitis with severe active inflammation]
- should have their next surveillance colonoscopy scheduled for 1 year .

- Colonoscopic surveillance is best performed when ulcerative colitis is in remission, because it is otherwise difficult to discriminate between dysplasia and inflammation on mucosal biopsies

Management of dysplasia

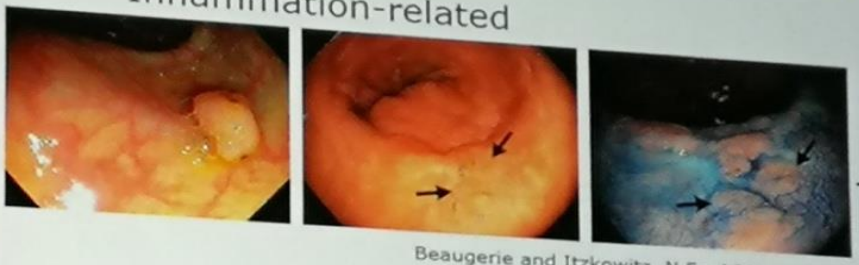
- Polypoid dysplasia can be adequately treated by polypectomy provided the lesion can be completely excised, and there is no evidence of non-polypoid or invisible dysplasia elsewhere in the colon

- If complete resection can be achieved, with no evidence of non-polypoid or invisible dysplasia elsewhere in the colon, continued surveillance colonoscopy is reasonable.
- Every other patient with non-polypoid dysplasia should undergo colectomy, regardless of the grade of dysplasia detected on biopsy analysis

ECCO

Cancer may occur as long-term complication of IBD due to different risk factors

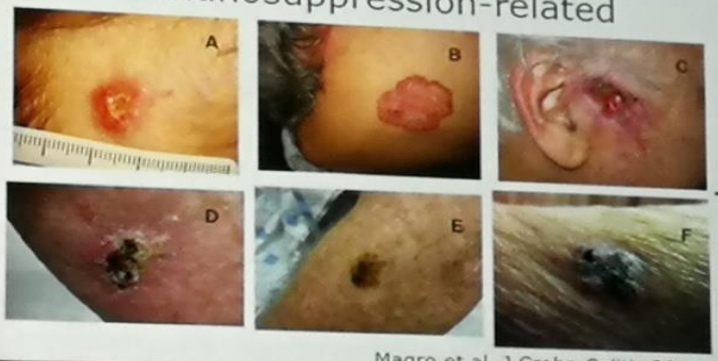
Inflammation-related



Beaugerie and Itzkowitz, N Engl J Med 2015

Risk factors:
- PSC
- Extensive colitis
- Longer disease duration
- Colonic inflammation ≥ 50%

Immunosuppression-related



Magro et al, J Crohn Colitis 2014

Risk factors:
- Azathioprine
  - Hematologic malignancies
  - Non-melanoma skin cancers
  - Urinary tract cancers
- Anti-TNF
  - Melanoma
  - Non-melanoma skin cancer

Medical Management

of

Active Ulcerative Colitis

Proctitis

- A mesalamine 1g suppository once daily is the preferred initial treatment for mild or moderately active proctitis .
- Mesalamine foa
alternative , but
more effectively
tolerated.
- Topical mesalar
topical steroids

- Combining topical mesalamine with oral mesalamine or topical steroids is more effective .
- Refractory proctitis may require treatment with systemic steroids, immunosuppressant, and/or biologics drugs.

left-sided ulcerative colitis

- Mild to moderately active left-sided ulcerative colitis should initially be treated with an aminosalicylate enema ≥ 1 g/day combined with oral mesalamine ≥ 2.4 g/day , which is more effective than oral or topical aminosalicylates, or topical steroids alone .
- Topical mesalamine is more effective than topical steroids .

- Once-daily dosing with mesalamine is as effective as divided doses .
- Systemic corticosteroids are appropriate in patients with moderate to severe activity and in those with mild activity who do not respond to mesalamine .

- Budesonide 9 mg/day can be considered in patients with mild to moderate disease who are intolerant or refractory to aminosalicylates.
- Severe left-sided colitis is an indication for hospital admission

- Mild to moderately active extensive ulcerative colitis should initially be treated with an aminosalicylate enema 1 g/day combined with oral mesalamine ≥ 2.4 g/ day.

- Systemic corticosteroids are appropriate in patients with moderate to severe activity and in those with mild activity who do not respond to mesalamine.

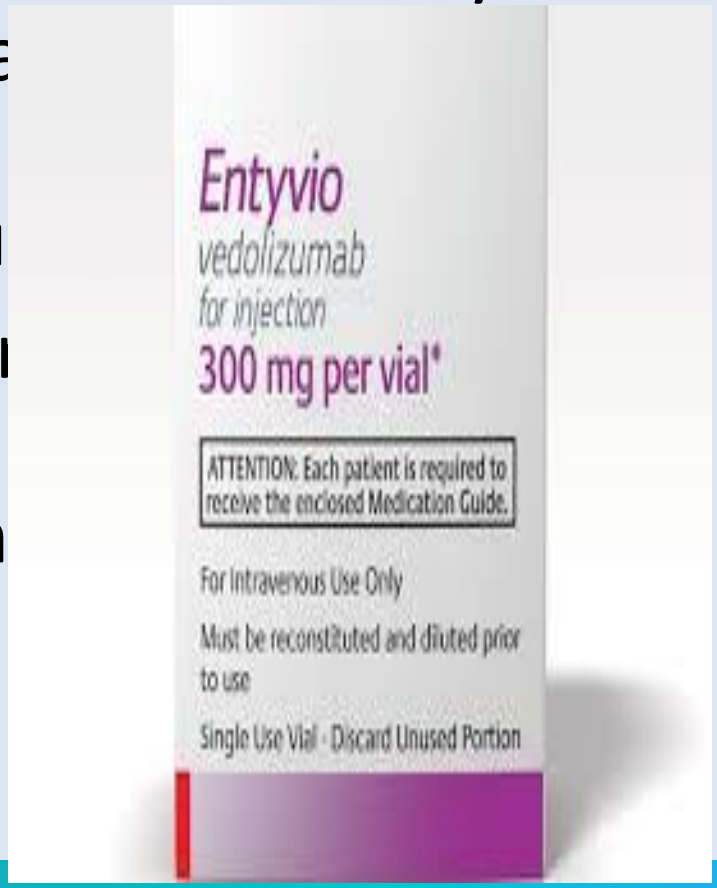
Severe extensive colitis

- Severe extensive colitis is an indication for hospital admission for intensive treatment.
- Initial recommended treatment for severe active ulcerative colitis is intravenous steroids.
- Monotherapy with intravenous cyclosporine is an alternative especially in cases of serious adverse events due to steroids.

- All patients should receive adequate volume of intravenous fluids, and low-molecular-weight heparin for thrombosis prophylaxis.
- Electrolyte abnormalities and anemia should be corrected, if needed .

- The response to intravenous steroids should be best assessed by the third day ; in non-responders, treatment options including cyclosporine , infliximab , tacrolimus , or surgery should be considered.
- Colectomy is recommended if there is no improvement following 4–7 days of salvage therapy.

- Patients with moderate colitis refractory to thiopurines should be trea
  preferably combined with
  for infliximab , or vedolizu
- In case of treatment failu
  TNF or vedolizumab shou
  and colectomy recommen
  medical therapy does not
  clinical benefit



- The goal of maintenance therapy in ulcerative colitis is to maintain steroid-free remission, defined clinically and endoscopically

- Mesalamine compounds are the first-line maintenance treatment in patients responding to mesalamine or steroids [oral or rectal] .
- Rectal mes ce in proctitis ar olitis.
- A combina mine may be use treatment

- Thiopurines are recommended for: patients with mild to moderate disease activity who have experienced early or frequent relapse while taking mesalamine at optimal dose or who are intolerant of mesalamine .
- Patients who are steroid-dependent ; and patients responding to cyclosporine or tacrolimus

- Infliximab, an anti-tumor necrosis factor alpha (TNF-α) monoclonal antibody, is the first biologic to have received the (FDA) approval and to be clinically used for ulcerative colitis.
- Recently, the TNF antagonists adalimumab and golimumab have shown significant effectiveness in large scale clinical studies, and have been in use since receiving FDA approval.
- Other biologics with different mechanisms have also been introduced. Recently, vedolizumab, integrin receptor antagonist, was approved by the FDA.
- In addition, etrolizumab, another integrin receptor antagonist and tofacitinib, kinase (JAK) inhibitor are emerging as new medications.

- In patients responding to anti-TNF, maintaining remission by continuing anti-TNF therapy with or without thiopurines is appropriate.
- The use of thiopurine maintenance is an alternative option

- Anti-TNF or vedolizumab may be used as first-line biological therapy.
- Vedolizumab is effective in patients failing anti-TNF.
- In patients responding to vedolizumab, maintenance therapy with vedolizumab is appropriate

- In thiopurine-naïve patients with severe colitis responding to steroids, cyclosporine or tacrolimus, thiopurines are appropriate to maintain remission.
- Patients responding to infliximab should continue infliximab with or without thiopurines; thiopurine maintenance is an alternative option.

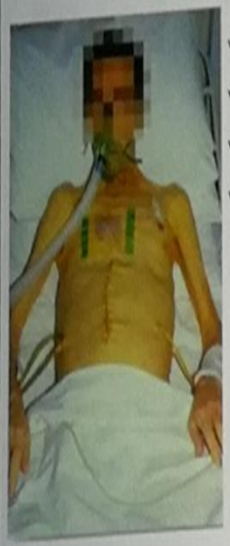
- Mesalamine maintenance treatment should be continued long-term ; this may reduce the risk of colon cancer
- No recommendation can be given for the duration of treatment with azathioprine, anti-TNF, or vedolizumab, although prolonged use of these medications may be needed .

- There is some evidence for a therapeutic benefit of probiotics when added to standard therapy to induce remission, particularly VSL#3.

Biosimilar products ,Infliximab CT-P13

Biosimilar use could greatly decrease costs for IBD patients, as it is estimated to be 40% less expensive. The author's conclusion is that biosimilar switching is, "safe and effective", finding no differences in drug levels and disease activity between infliximab biosimilar and innovator. "Switching to biosimilar and performing therapeutic drug monitoring as part of routine care can optimize infliximab therapy efficiently and make it more cost-effective," they wrote.

The old myth of surgery

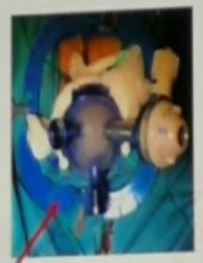


- ✓ Midline laparotomy
- ✓ Drains
- ✓ NG Tube
- ✓ **Prolonged fasting** pre and postop course

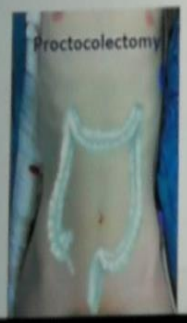
P McAleese, Ann Surg 1994

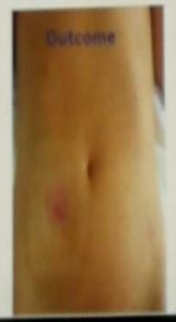
Single port surgery for UC: impact on postop?

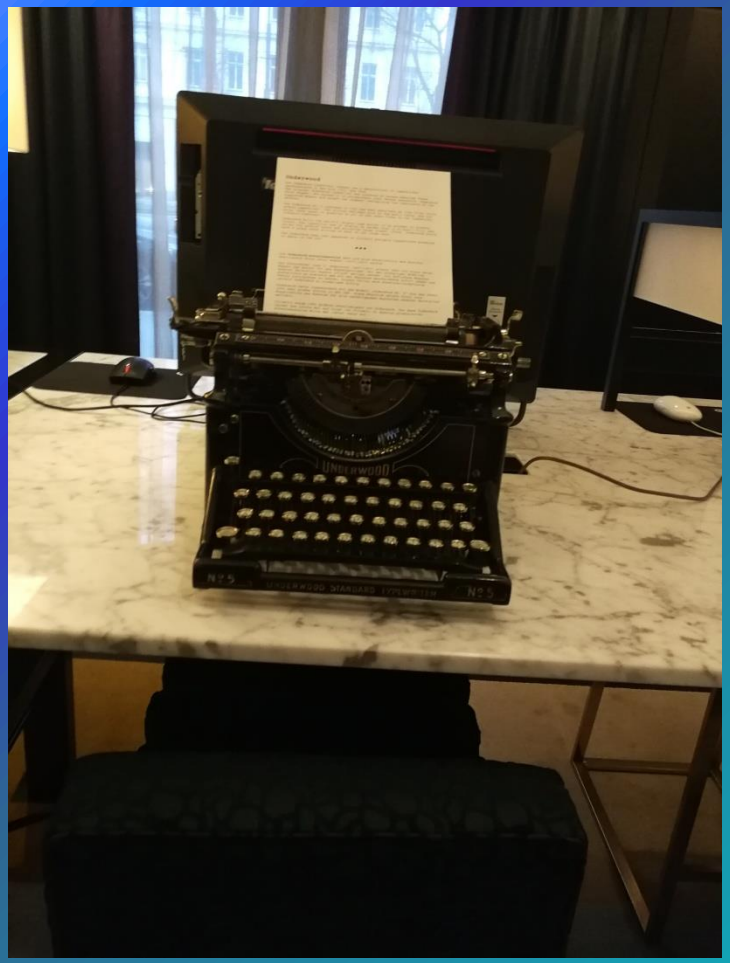
Two team approach



Trans-stomal trans-anal proctectomy and IPAA:
Double single port approach






UNDERWOOD
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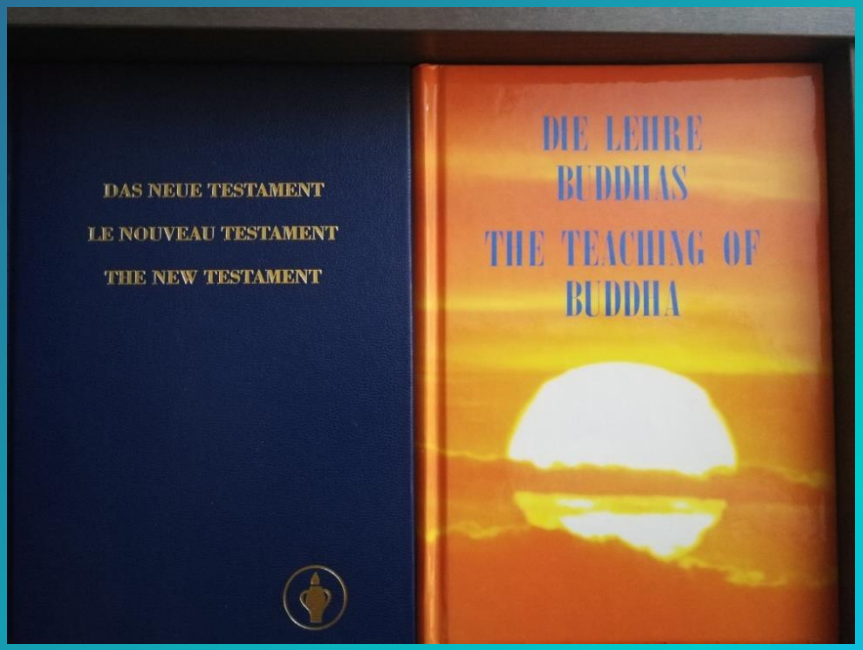
DAS NEUE TESTAMENT
LE NOUVEAU TESTAMENT
THE NEW TESTAMENT
DIE LEHRE BUDDHAS
THE TEACHING OF BUDDHA


grazzi
tanan
dakujem
efcharisto
havala
dekuji
paldies
obrigada
spasibo
Thank You
obrigado
kiitos
grazie
Merci
dekui
gracias
dzieki
multumesc
Danke
dank
koszi
blagodarya
tack