



GHAPP

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Approach to Crohn's Disease Complications

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Disclosures

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Disclosures

Janette Villalon, PA

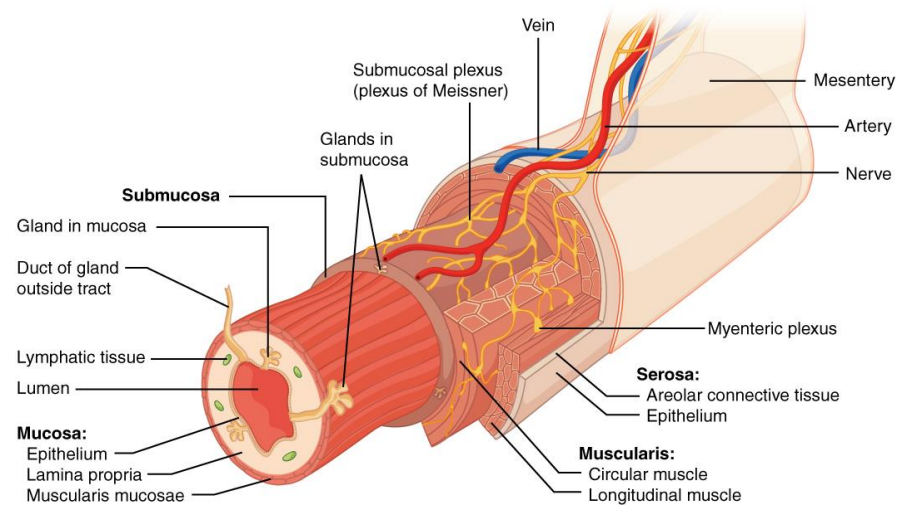
Speaker Bureau: AbbVie, Clinical Area – IBD

Goals of Discussion

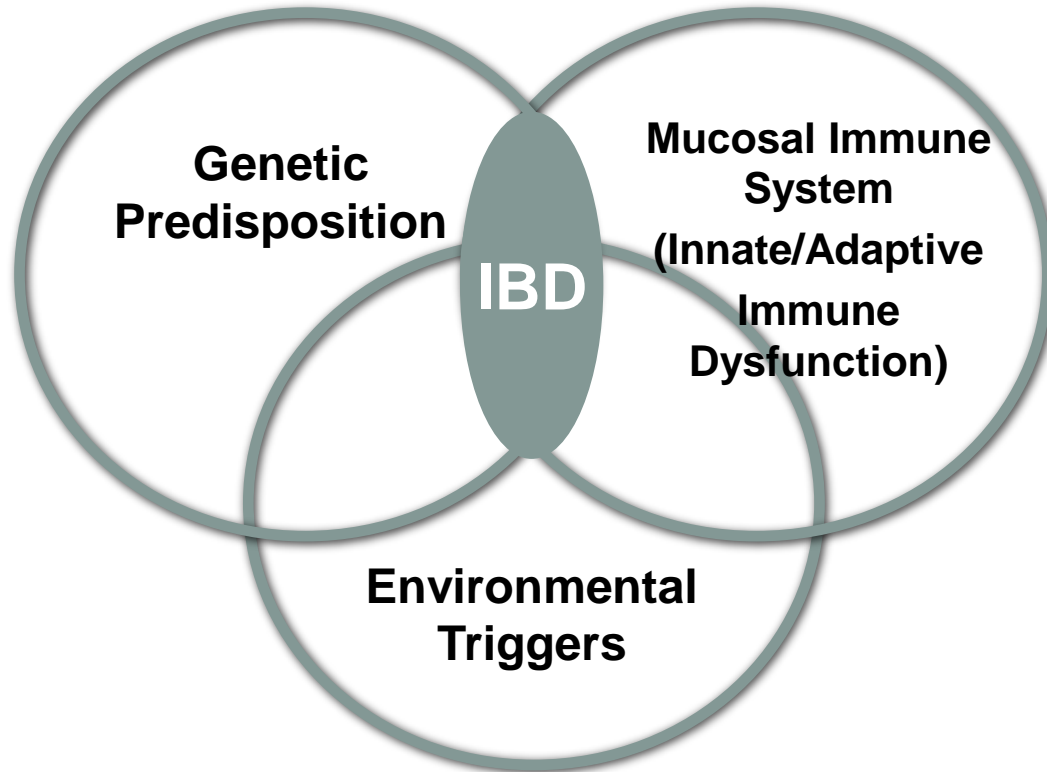
- What is Crohn's Disease?
- Complications of Crohn's Disease
 - Extra Intestinal Manifestations
 - Perianal Fistulas / Abscess
 - Strictures
 - Neoplasm
- Discuss management of each

What Is Crohn's Disease

- Crohn's Disease is a non curable, idiopathic, chronic, transmural inflammatory autoimmune disease that can affect the GI tract from mouth to anus
- There are 4 layers to the GI tract:
 1. Mucosa
 2. Submucosa
 3. Muscularis
 4. Serosa
- Transmural inflammation affects all 4 layers which result in the complications we may see in CD



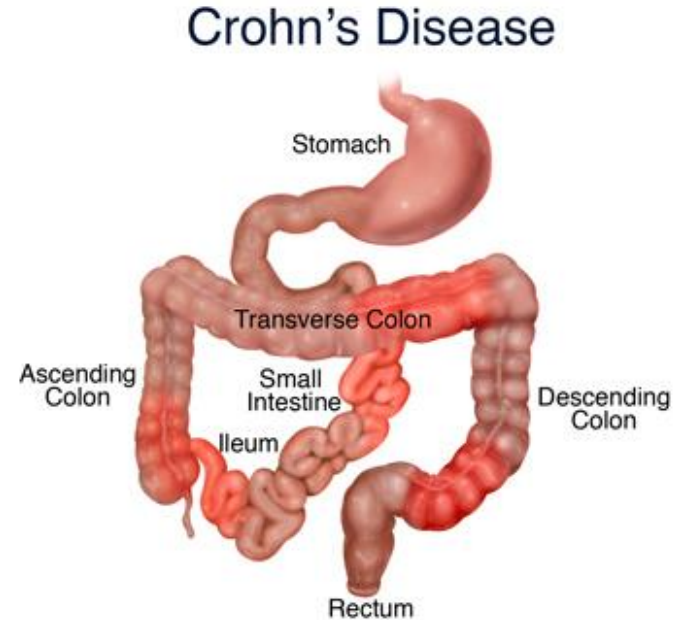
Etiologic Theories in Inflammatory Bowel Disease



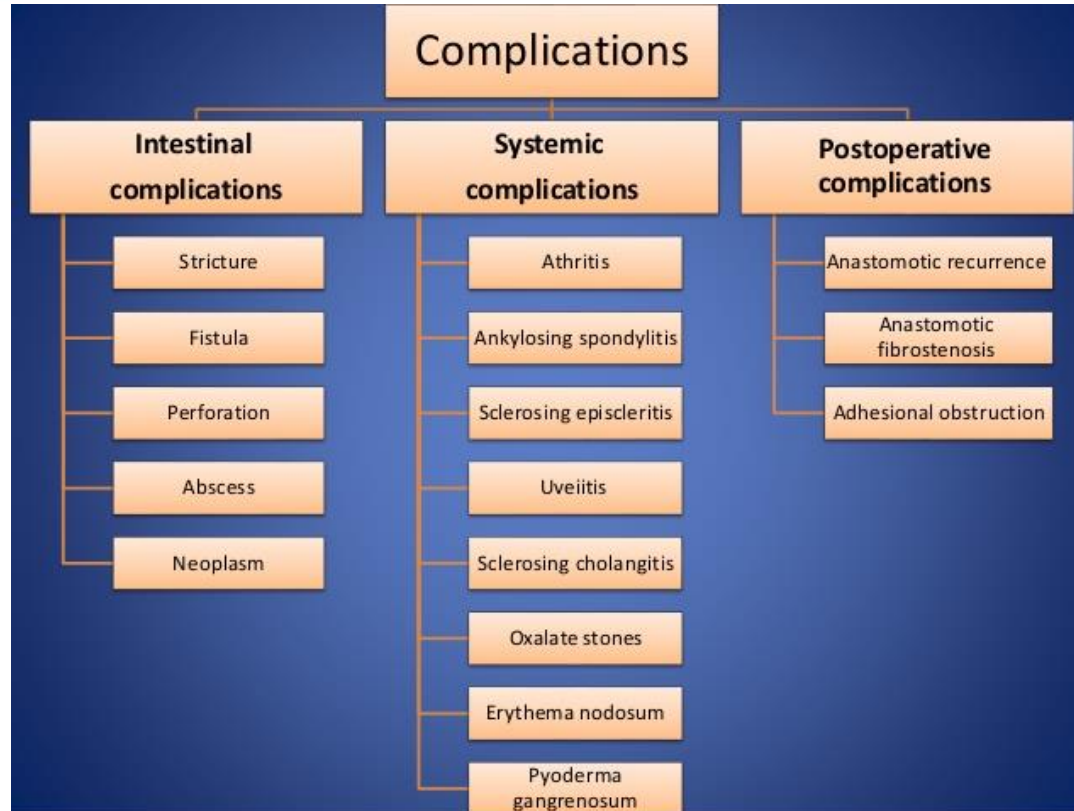
Crohn's Disease

Disease Location at time of Diagnosis:

1. 44.8% Terminal ileum
 2. 26.7 % Isolate colon (1/3 of pts will have perianal disease)
 3. 24.2% ileocolonic
 4. 4.3% Upper GI
- The site of Disease, small intestine or colon, tends to remain stable over time with 6%-14% having a change in disease locations over time

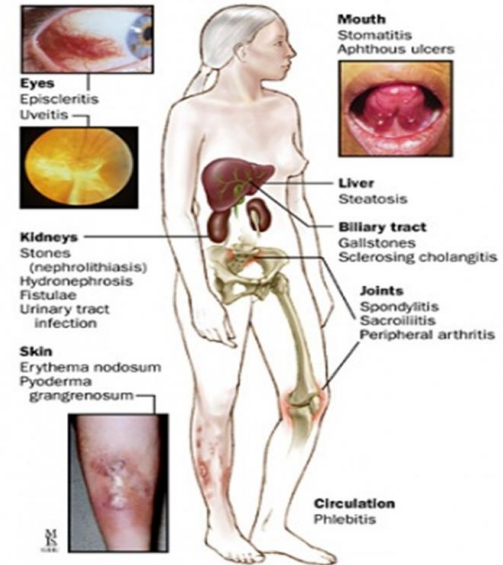


Complications of Crohn's Disease



Extra Intestinal Manifestations of Crohn's Disease

- Up to 25% - 40 % of patients with IBD are affected with EI.
- 25% have more than 1 EIM
- EIM involving the skin, eyes and joints usually correlate with some degree of intestinal inflammation.
- Arthritis can affect about 30% of patients
- Dermatologic EIM up to 20% such as Erythema Nodosum and Pyoderma Gangrenosum, an ulcerative neutrophilic dermatosis can occur in 1% - 5% of IBD pts
- 30% - 60% can develop osteopenia to osteoporosis
- Uveitis/Episcleritis reported at 4 – 12% in IBD patients(Episcleritis more common in CD).

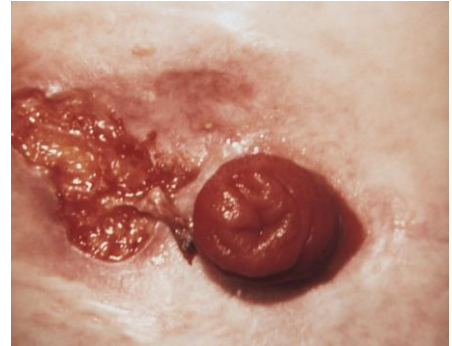


Primary Sclerosis Cholangitis

- The prevalence of IBD in pts with PSC approaches 90%.
- UC pts have a 5% chance of having PSC.
- CD pts is less at 1%.
- Among patients with IBD, an increased risk of CRC in patients with ulcerative colitis (UC) complicated by PSC has been observed in a number of studies.
- In one case-control study, the cumulative absolute risk of CRC or dysplasia after 10, 20, and 25 years of colitis in patients with PSC and UC was significantly higher as compared with patients with UC alone (9, 31, and 50 percent versus 2, 5, and 10 percent, respectively).
- The CRC risk in concomitant CD pts is unclear but is likely very comparable to UC in Crohn's colitis pts.
- AGA and ACG guidelines recommend colonoscopy annually in concomitant PSC and IBD patients.
- Patients with PSC should be followed regularly with a Hepatologist.

Pyoderma Gangrenosum

- Peristomal Pyoderma makes up about 15% of all cases of pyoderma.
- Lesions are painful. Develop quickly
- To treat must work with Dermatologist (r/o other etiologies: Squamous cell cancer, cutaneous lymphoma, infection)
- Treatment (Collaborate care with Dermatologist)
- No specific treatment exists and there are few trials
- Mostly use a stepwise approach
- Treatment is largely empirical and dependent on provider experience



Topical Treatment of PG

Topical:

- Tacrolimus: Currently available 0.1% and 0.03%
- Cyclosporine topical
- Intralesional Kenalog (triamcinolone injections)
40 mg/ml: often used in conjunction with topical and oral corticosteroids

Oral Treatment of PG

Oral Therapies:

- Corticosteroid: Prednisolone most common (60–120 mg). (Can use in conjunction with minocycline, cyclosporine, dapsone).
- Cyclosporine: Oral therapy with dose of 3–5 mg/kg/day. Serious side effect include nephro and hepatic toxicity, HTN increased malignancy risk. Most pts show improvement in about 3 weeks.
- Tacrolimus: dose of 0.1–3 mg/kg/day. Dosing may vary and duration of therapy unclear.
- Study done comparing Cyclosporine v. Prednisone (NOT IBD): 112 pt for analysis comparing healing at 6 weeks and 6 months. Concluded that these two oral medications did not differ in ulcer healing rates, recurrence of PG or adverse reactions.

Brooklyn T et al. Diagnosis and treatment of Pyoderma Gangrenosum. *BMJ*. 2006 July 22; 333: 181 – 184;
Lyon, Kirby, Griffith: Recalcitrant Pyoderma gangrenosum treated with systemic tacrolimus. *British Journal of Derm.*
Vol 140 (3), pg 562–564; Ormerod AD et al. Comparison of two most commonly used treatments for pyoderma: results of the STOP GAP RCT. *BMK*. 2015;350.

Systemic Treatment of PG

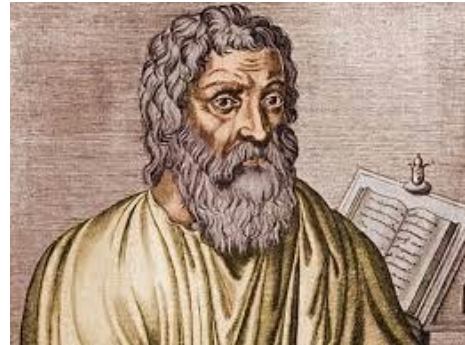
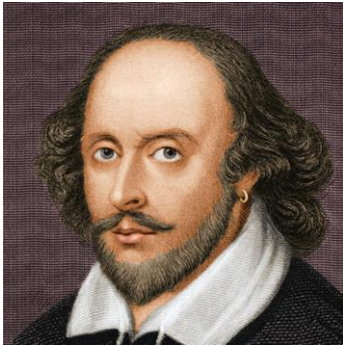
- IV solumedrol: 1 gm IV x 3–5 days as pulse therapy (with or without minocycline)
- Biologics: Infliximab
 - 30 pts: 13 received ifx, 17 placebo
 - At week 2, 46% of IFX pts versus 6% of placebo had improved
 - Those with no response at wk 2 got IFX
 - 29 pts received IFX total. By wk 6, 69% (20pts) had improved and 21% (6/29) were in complete remission
- Stelara: Case reports have demonstrated possible use in tx for PG

Key to Treatment of EIM

- Determine if patient has associated active intestinal disease.
 - Check labs: cbc cmp, crp, esr, fecal calprotectin
 - Imaging and endoscopic evaluation as needed
- Must coordinate care with appropriate specialist to determine best medical or surgical therapy (Dermatologist, Ophthalmologist, Hepatologist, Primary Care)

Peri Anal Fistula History

- William Shakespeare's Comedy All's Well That Ends Well written in 1603 uses a cure for fistula as a central plot
- Hippocrates (460-357 BC) made reference to surgical treatment of Anal Fistula



Management of Rectal Abscess

- Abscess are very painful (perianal swelling, induration and fluctuation)
- Can be low (intersphincteric, perianal, ischiorectal)
- Can be high (submucosal, supralelevator)
- DX: Physical Exam (painful, fluctuance, tenderness), EUA, and imaging

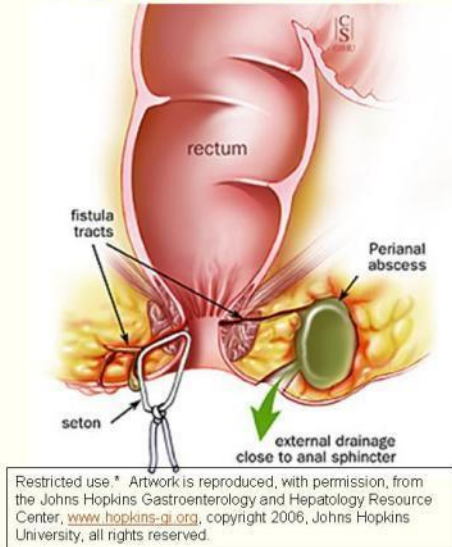


Anal Abscess:

- Priority: Draining the abscess (I&D). Antibiotics alone not enough because the wall of the abscess has necrotic and occluded blood vessels, so antibiotics won't penetrate
- Surgeons should be careful to avoid incision of external sphincter in CD pt, because it can help shorten any fistulas tract and make management easier in the future
- If the abscess does not heal alone in 2–3 months, you should suspect a fistula
- Should antibiotics be used after I&D of abscess? Study done of 307 patients determined that a course of antibiotics like cipro and flagyl for 7–10 days is helpful in preventing fistula formation post I&D

Abcarian H. Anorectal Infection: Abscess-Fistula. *Clin Colon Rectal Surg*. 2011 March 24(1): 14 -21; Ghahramani L et al. Antibiotic therapy for prevention of fistula in –ano after incision and drainage of simple perianal abscess: A randomized single blind clinical trial. *Surgery*. 2017 (Nov; 162(5): 1017–1025.

Perianal Disease



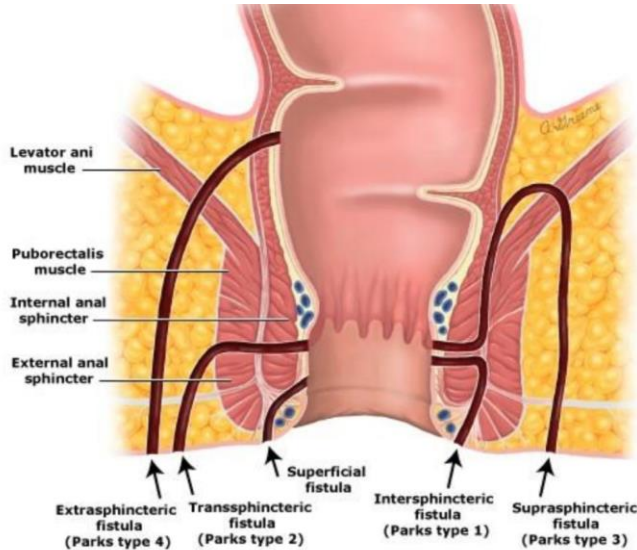
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(c) 2007, Laurence S. Bailen, MD

- The lifetime risk of developing a fistula in patients with Crohn's ranges from 20-40 % (1)
- The cumulative frequency of fistula occurrence was 12% at 1 year, 21% at 10 years and 26% at 20 years (2)
- Perianal disease at time of Dx may indicate more severe clinical course (3)

Sandborn et al. AGA technical review on perianal Crohn's Disease. *Gastro* 2003; 125: 1508–30; Langholz, Ebbe. Current trends in Inflammatory Bowel Disease. *Therap Adv Gastro*. Marc 2010;3(2) 77–86; Lichenstein G et al. ACT Clinical Guideline: management of Crohn's Disease in Adults. *Am Journal of Gastro*. April 2018, Volume 113 Issue 4. pg 481–517.

Management of Anal Fistulas



AGA distinguishes between simple and complex

- Simple fistulas are low and include superficial, intersphincteric or intrasphincteric below the dentate line, with 1 opening and no complications, and involved <0
 - Heal better than complex fistulas (88.2% vs 64.6%)
- Complex fistulas are high and include intersphincteric, transsphincteric, extrasphincteric, suprasphincteric, above dentate line, with many external openings and associated with complications (abscess, rectal stricture, connection to bladder to vagina), and involve >30% of the external sphincter
 - Have higher rates of recurrence than Simple Fistulas (41.9% vs 26.7%)
 - Regarding Surgical Outcomes they are higher to end up needing permanent fecal diversion (63.5% vs 26.7%)

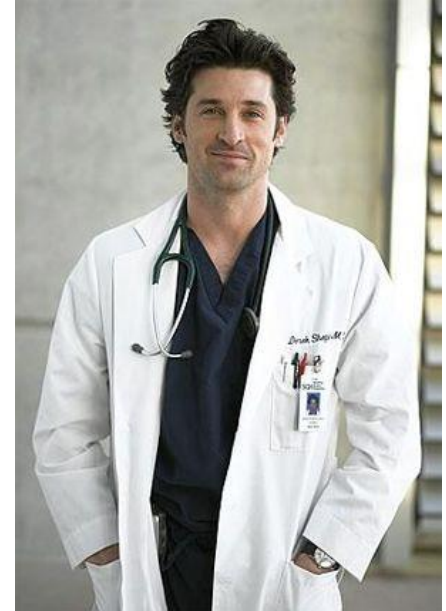
Diagnosis of Anal Fistulas

- Obtain imaging to study anatomy, assess for abscess and infection.
- MRI: Diagnostic specificity 76–100%
- EUS: In a study of 90 patients, 95% of fistulas were identified by EUS which coincided with surgical findings in 85 percent of patients, and chronic fistula cavities were confirmed by surgery in 75 percent of patients (Limitation is the Interventionalist experience)
- Meta Analysis of 4 studies comparing MRI to EUS demonstrated comparable sensitivities but MRI had slightly high specificity than EUS

- EUA is considered by ECCO to be gold standard to dx of perianal disease with 90% accuracy.
- EUA procedures including abscess drainage, seton placement and fistulotomy can be done.
- Accuracies of diagnosis complex perianal disease was 87% (MRI), 91% (EUS) and 91% (EUA)

Treatment of Perianal Fistula

- Antibiotics:
 - Ciprofloxacin and metronidazole
 - Augmentin can be used;
 - IV Antibiotics for sepsis
- I & D of abscess
- Steroids do not show efficacy and should be avoided
- Coordinate care with surgeon
- Best treatment if combination medical and surgical therapies



Antibiotics:

- Do not use alone as therapy
- Do not induce healing alone
- Cipro and Flagyl preferred
- Best when used in combination with other therapy
- Metronidazole was not found to help with in PDAI score but did reduce perianal drainage

Authors and study design	Group 1	Group 2	Results
Thia <i>et al</i> [31] Multicenter, prospective, doubled-blind, placebo-controlled study (n=25)	Ciprofloxacin (500 mg b.i.d.) or metronidazole (500 mg b.i.d.) for 10 weeks	Placebo for 10 weeks	Ciprofloxacin 40% response vs. metronidazole 14.3% vs. placebo 12.5% (P=0.43)
Dejaco <i>et al</i> [32] Prospective, open-label study (n=52)	Ciprofloxacin (500-1000 mg/day) and/or metronidazole (1000-1500 mg/day) for 8 weeks	Ciprofloxacin (500-1000 mg/day) and/or metronidazole (1000-1500 mg/day) for 8 weeks, plus azathioprine (2-2.5 mg/kg) from 0 or 8 week	Azathioprine group 48% response vs. no azathioprine group 15% (P=0.03)
West <i>et al</i> [33] Prospective, double-blind, placebo-controlled study (n=24)	Ciprofloxacin (1000 mg/day) for 12 weeks plus infliximab 5 mg/kg at weeks 6, 8, and 12	Placebo for 12 weeks plus infliximab 5 mg/kg at weeks 6, 8, and 12	Ciprofloxacin group 73% response vs. placebo group 39% (P=0.12)
Dewint <i>et al</i> [34] Prospective, doubled-blind, placebo-controlled study (n=76)	Ciprofloxacin (500 mg b.i.d.) for 12 weeks plus adalimumab (160/80 mg week 0, 2 and 40 mg every other week) for 24 weeks	Placebo for 12 weeks plus adalimumab (160/80 mg week 0, 2 and 40 mg every other week) for 24 weeks	Ciprofloxacin group 71% response vs. placebo group 47% (P=0.047)
Maeda <i>et al</i> [35d] Prospective, doubled-blind, placebo-controlled study (n=74)	Metronidazole 10% ointment t.i.d. for 4 weeks	Placebo ointment for 4 weeks	Reduction in PCDAI score of at least 5 points in metronidazole group 10 of 27 vs. placebo group 4 of 34 (P=0.031)

PDAI, perianal Crohn's disease activity index.

Castro L A et al. Management of complex perianal Crohn's Disease. *Ann Gastroenterol.* 2017;30 (1) 33-44.

Medical Therapies to Note

- Thiopurines:
 - Lack of controlled trials to demonstrate efficacy
 - Case series and secondary endpoint findings of 5 studies demonstrated some effectiveness in inducing remission
 - Can take months to work
 - Side effect profile must be considered

- Calcineurins:
 - Tacrolimus (0.2mg/kg/day) in a small study showed some effectiveness in sx control versus placebo (43% v 8%) but not fistula closure
- Thalidomide: little data, severe side effects (neuropathy, leukopenia, hepatotoxicity)
- Mycophenolate Mofetil (4 pt study, 75% had complete closure)
- **Studies for these are limited and large randomized studies are needed

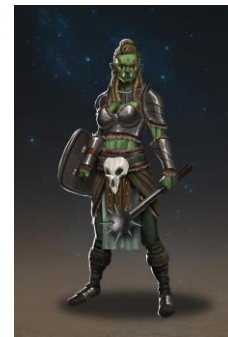
Infliximab and Peri Anal Fistula

- Recommended as choice for initial medical therapy
- Infliximab: Multiple RCCT done
 - IFX helped 68 % of pts achieve 50%(vs 26% placebo) decrease in drainage induce complete fistula closure in 55% pts (vs 13% placebo)
 - Secondary endpoint of ACCENT II trial showed IFX resulted in ongoing maintenance of closure without drainage in 36% at 54 weeks (vs 19% placebo)
 - Studies have also demonstrated that patients developed complete fistula closure with higher drug levels of >10



Other ANTI's

- Adalimumab:
 - CLASSIC I Trials demonstrated that 32 pts with perianal fistula had complete closure in 75% (vs 17% placebo).
 - The CHARM trial showed fistula closure in 33% of pts (vs 13%) at 56 weeks.
- Certolizumab Pegol:
 - limited and variable data available.
 - PRECISE I and II study did not show notably higher rates of closure compared to Placebo.
 - Other small studies, however, showed complete closure in 36% vs 17%, and survey study showed pts on Certolizumab experienced >50% decrease in drainage at 6 weeks. Not preferred anti-tnf.



Other Biologics for Fistula Treatment

- Currently dedicated RCCT with Vedolizumab or Ustekinumab in perianal fistulizing CD not available only subgroup analysis are limited.
- Ustekinumab:
 - CERTIFI trial subgroup analysis demonstrated fistula closure was 47% v 30% in placebo at 22 weeks.
 - IM-UNITI study data supported fistula response in 80% of pt v 46% in placebo at 44 weeks.
 - An open lab 2016 trial showed improvement in fistulizing disease in 61% (11/18 pts).



- Vedolizumab.
 - Limited Data.
 - Gemini II sub-analysis did show some efficacy in fistula closure versus placebo pts.
 - Post hoc analysis of a 1 year prospective study including 35 pts with active perianal disease demonstrated complete remission in 43% at 14 weeks, and maintenance of the closure in 54.3% at 1 year.



Intrafistulous Biologic Injections

Study	Drug	Study Type	Number of Patients	Dose (mg)	Number of Treatments; Dosage Interval	Findings
Lichtiger ⁵¹	Infliximab	Case series	9	20	3; 1-2 weeks	44% (4/9) of patients had complete fistula healing; 33% (3/9) of patients had a partial response at 4 weeks
Poggioli et al ⁵²	Infliximab	Case series	15	15-21	3-12; 4 weeks	67% (10/15) of patients had fistula healing after up to 12 injections
Alessandroni et al ⁵⁴	Infliximab	Open-label, non-RCT	12	20-25	≥2; 4-6 weeks	Persistent closure was seen in 88% (7/8) of patients 12 months after injection and concomitant fistulectomy
Asteria et al ⁵³	Infliximab	Pilot study	11	20	1-4; 4 weeks	73% (8/11) of patients had a clinical response; 36% (4/11) had fistula closure
Tonelli et al ⁵⁵	Adalimumab	Pilot study	12	20	4-16; 2 weeks	75% (9/12) of patients had complete cessation of drainage and significant improvement in disease activity score
Laureti et al ⁵⁶	Adalimumab	Case series	33	40	≥2; 2 weeks	40% of patients had complete fistula closure after an average of 9 injections following surgery
Poggioli et al ⁷⁷	Adalimumab	Case series	16	40	2 or 4; 2 weeks	13% (2/16) of patients had healing after 2 injections; 19% (3/16) had healing after 4 injections

- Series of case and small pilot studies using ADA and IFX.
- Results are promising, however, there exists variation in the studies designs and protocols and results are difficult to interpret and reproduce.
- More clinical controlled studies are needed.

RCT, randomized, controlled trial.

Gold S.L et al. Perianal Fistulas in Patients with Crohn's Disease, Part 1. *Gastroenterol Hepatology*. 2018 Aug. (8): 470–481.

Other Options:

- Hyperbaric Oxygen
 - Mechanism of action is unclear however the idea is that increasing oxygen kills helps tissue repair.
 - Limited data is promising and safe and may be considered a safe therapeutic and complementary therapy.
 - Systematic review study of ibd pts in 2014 of >600 pt was done. 40 had perianal disease.
 - 18/40 had complete healing, while 17/40 partial response.

- Stem Cell
 - Allogenic and autologous stem cells used from fat or bone marrow administered via intralesional local injection most commonly with variable success rates of 37–85%
- Fibrin Glue (fibrinogen and calcium)
 - Injected into fistula and forms a thrombin clot
 - Healing rates in CD pts range from 30–80%
- Fistula plug
 - Bioabsorbable plugs made of lyophilized porcine intestinal submucosa
 - Synthetic plugs of polyglycolic and trimethylene carbon
 - Limited, small studies with variable results
 - Systematic review of 20 studies showed closure rates of 23/42 pts (54.8%)
 - In a 2016 study, complete closure was 49/84 pts (58.3%) with recurrence of 3/22 (13.6%)
 - Plug extrusion about 8%

Surgical Management of Perianal Disease

Surgery (often needed to optimize results)

- Setons: Best results with combination medical therapy
 - Study by Regueiro found better healing in combo therapy (100%) v IFX alone 82.9%. Fistula recurrence also reduced (44% combo v 79% IFX alone)
- Endorectal Advancement Flap: Sphincter sparing procedure where flag of rectal mucosa, submucosa and muscle fibers used to cover the internal opening of the fistula tract
 - Success rate 50%–80%
- Fecal Diversion: can reduce inflammation and help healing
 - One study found that 62% of pts (53/86) required fecal diversion
 - Systematic review of long term data, pts with CD and fecal diversion had 63.8% healing rate
 - However, restoration of bowel and ostomy takedown was tried in 34.5% of pts, but only succeed in 16.6% and many required complete proctectomy



Indications for Surgery in Crohn's Disease

- Failure of medical management
- Recurrent Intestinal Obstruction
- Intra-abdominal abscess
- Intestinal Fistula
- Enterocutaneous Fistula
- Toxic Megacolon
- Free Perforation
- Massive Bleeding
- Carcinoma
- Extraintestinal Manifestation(Liver transplant for PSC)
- Growth Retardation
- Small Bowel Stricture: (most common)



Coordination of care with your surgeon is very important!

Stricturoplasty

Indications

- Diffuse small bowel involvement with multiple, short fibrotic strictures
- Hx of extensive small resection
- Rapid, symptomatic recurrence of stricture w/in 1year
- Isolated ileocolonic anastomotic stricture
- Reserved for small bowel stricture not colonic

Contraindications

- Abdominal Sepsis (phlegmon)
- Suspicion of Cancer
- Poor nutrition
- Macroscopic active disease at stricture site is not contraindication

Strictureplasty



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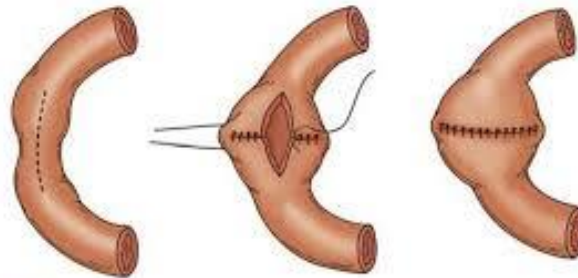


FIG. 1 Heineke-Mikulicz strictureplasty on an isolated stricture. A single-layer everting technique is performed to close the longitudinal enterotomy transversely, reconstructing an unobstructed lumen.

Balloon Dilation of Small Bowel Stricture

- An alternative to surgery
- Study done of 95 pts:
 - Short term symptomatic relief: 66 pt (69.5%)
 - Procedure failure: 6 pt (6.3%)
 - Adverse reaction: 5 pt (5%)
- Works best for short segment stricture: <5
- Coordination of care with Interventionalist

Hirai et al. Efficacy of Endoscopic Balloon Dilation for Small bowel Strictures in Patients with Crohn's Disease: A Nationwide, Multi-centre, Open-Label, Prospective Cohort Study. *J Crohn's Colitis*. 2018 mar 28 12(4): 394-401;
Hirari, F et al. *J Crohn's and Colitis*. 2018 mar 28;12 (4); 394–401.

Surgery for Small Bowel CD

- Laparoscopic Surgery is the best
 - Resection
 - Ileocectomy
- Two RCT 120 pts
- Lap surgery associated with less wound infection
- Lap surgery reduced re-operation rates and complications

Conclusion: Laparoscopic Surgery Safe As Open

Surgical Goals

- Preserve Bowel Length (Short gut syndrome may develop when about $\frac{1}{2}$ of small bowel is removed. Small bowel is about 20 ft long.)
- Reduce Symptoms
- Identify all strictures
- Extensive resections do not reduce risk of recurrence



Neoplasm and Crohn's Disease

Background Risk of Cancer in Patients With IBD

Tumour	SIR in IBD	Incidence in background population	5-year Survival
Small bowel adenocarcinoma in CD	18.7–46	0.3–0.5	±40%
Colorectal cancer in IBD	1.7–8.6	0.5–0.8	64%
Cholangiocarcinoma [*IBD with PSC]	2–160*	0.08	8% ⁴
Gastric cancer in CD	2.8	0.3–1 ⁵	31% ⁶
Leukaemia in UC [**adult age]	2	0.015	24%**–67% ⁷
Urinary tract cancer in CD	2	0.5	77% ⁸

Abbreviations: PSC, primary sclerosing cholangitis; SIR, standardized incidence ratio.

Annese V. Small Bowel Adenocarcinoma in Crohn's Disease: an Underestimated Risk. *Journal of Crohn's & Colitis*.

Vol 14, issue 3, march 2020: pg 285-286.

Small Bowel Cancer in Crohn's Disease

- First case of small bowel cancer in CD pt was reported in 1965
- Incidence is higher in CD patients than general population. Meta analysis by von Roon, et al determined incidence rate at 1.55 per 100,000 pt years
- Relative risk in CD pt is a large range from 6 – 320
- Risk factor:
 - Anatomic location: higher in small bowel disease
 - Strictures: may hide underlying malignancy
 - Length of time of disease: >15 years
 - The cumulative risk of small bowel carcinoma was 0.2% and 2.2% after 10 and 25 years of small bowel Crohn's disease, respectively
 - Two year survival for SB carcinoma in CD was 9%, compared with 15%-25% for de novo cases

Colorectal Cancer Risk in CD Patients

- Weedon et al reported CRC in 8/449 pt with CD, about 1.2% which was 20X > than control group
- Another study by Gyde et al, reported a 4 fold increased risk in CD pt
- Risk factor:
 - Crohn's Colitis
 - Risk of CRC in CD is similar to UC with the same extent of colonic involvement
 - The risk of dysplasia in UC is 2% after 10 years of disease, 10% after 20 years of disease, and 18% after 30 years of disease
 - 8 – 10 year history of disease
 - Severe and extensive colon inflammation
 - Concomittant psc diagnosis
 - Family history