Anorectal Crohn's Disease: Current Best Practice and What's in Store

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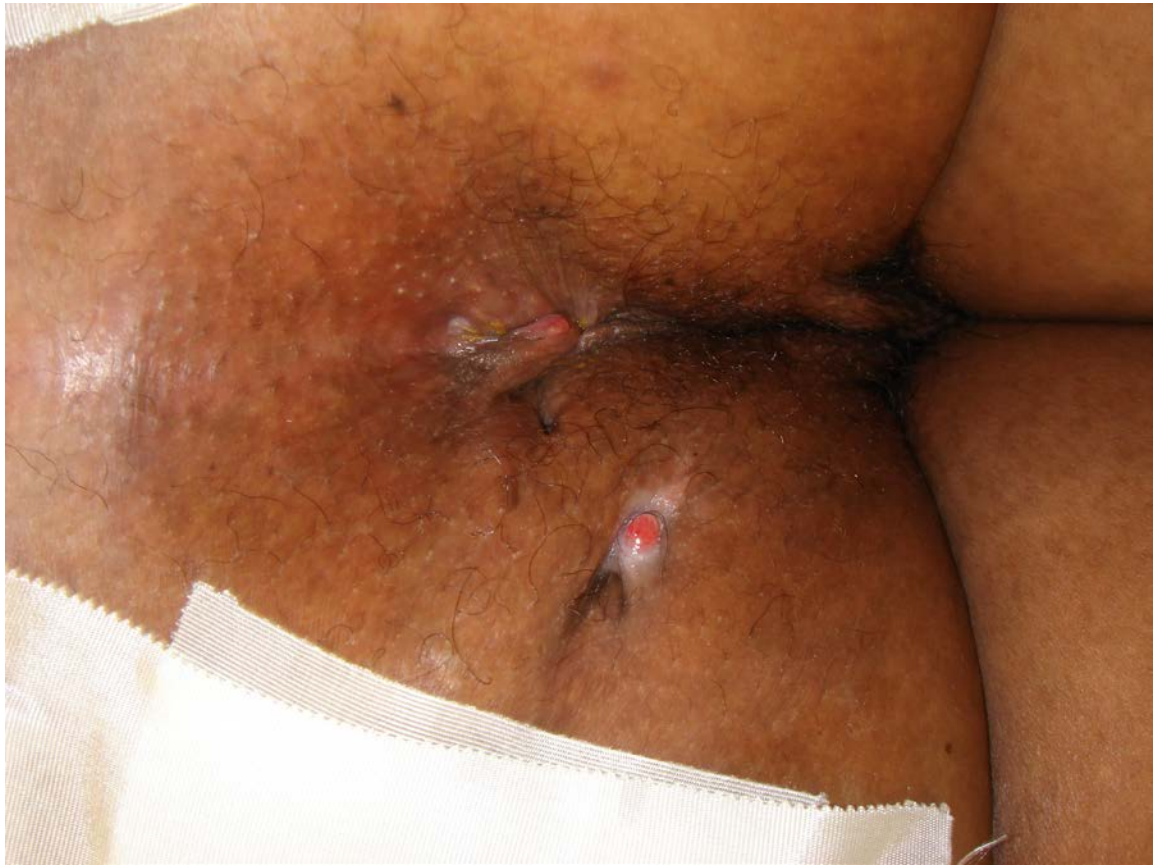
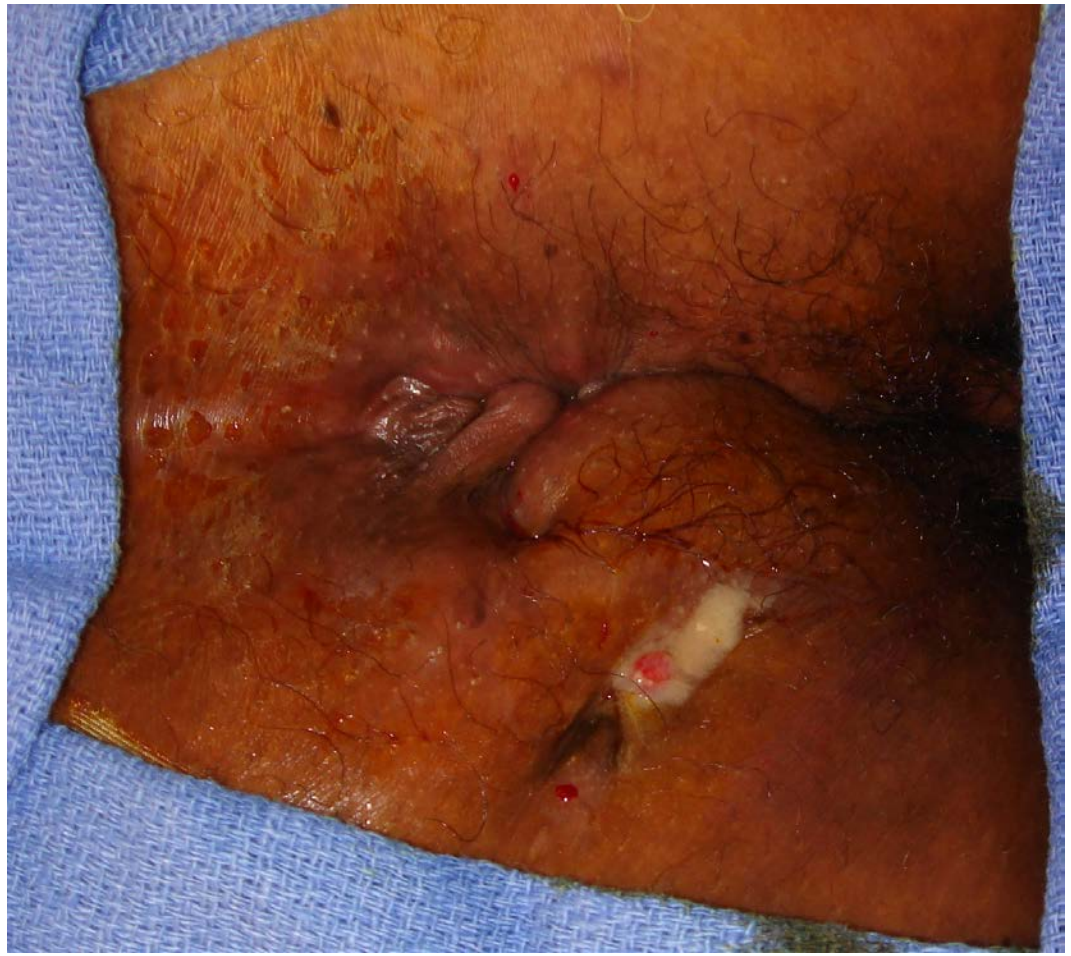
Case Presentation

- 50 y/o female with a history of Crohn's disease presents to the outpatient clinic with complaint of soiling her underwear
- She states 4 months ago she developed a perianal boil that ruptured
- She now has a chronic draining wound and persistent perianal itching

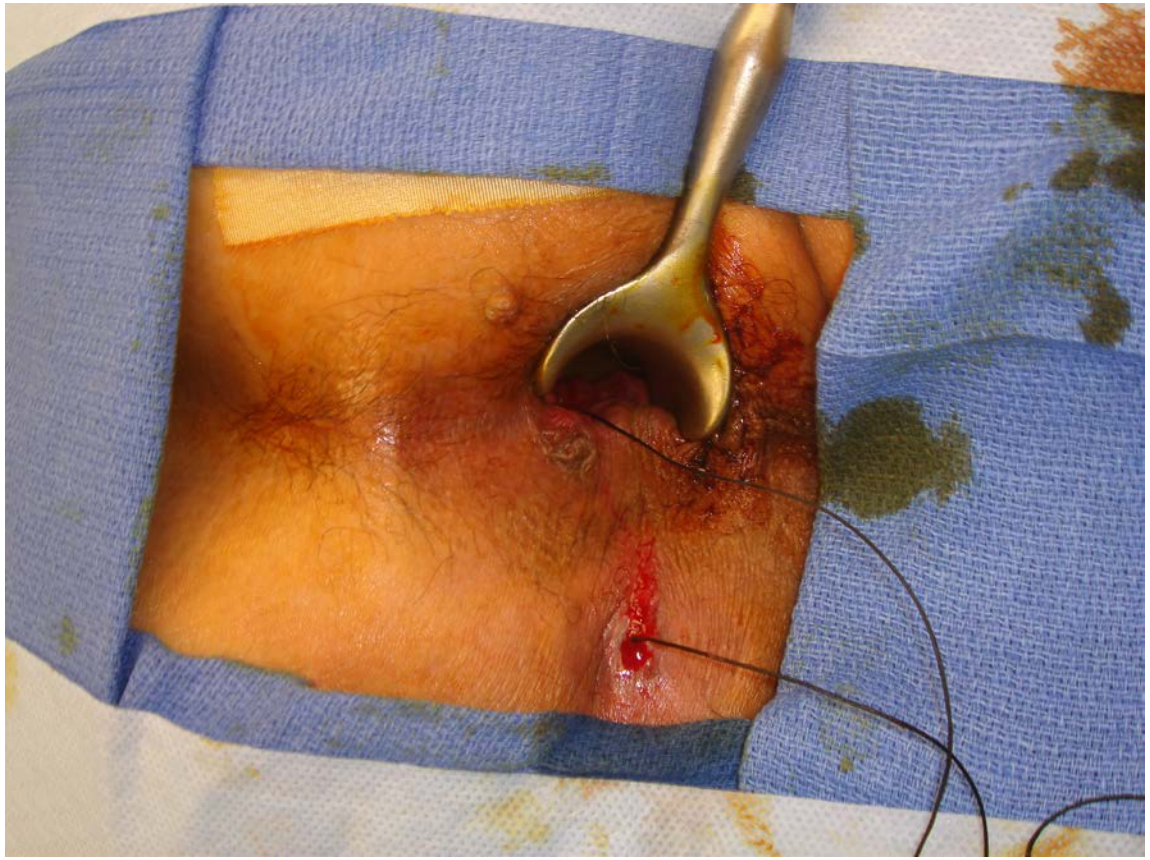
Physical Exam



Physical Exam



Exam Under Anesthesia



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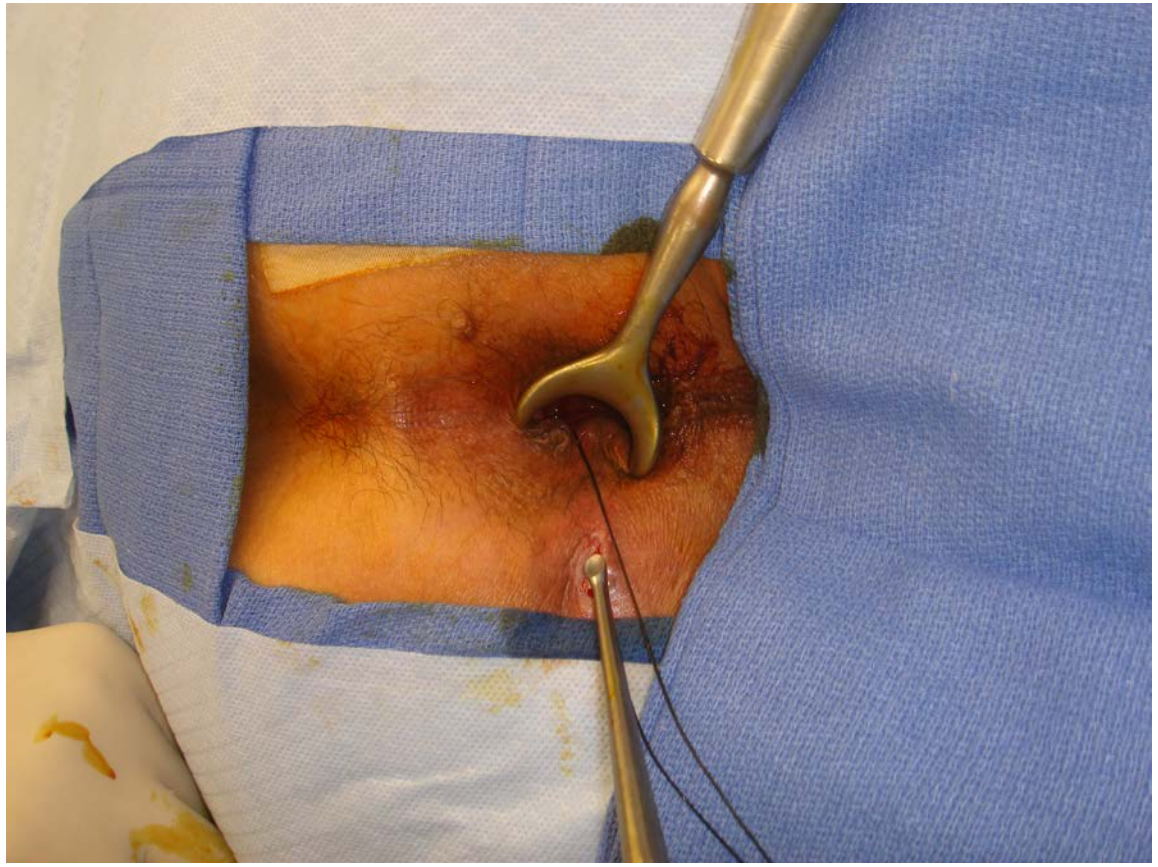

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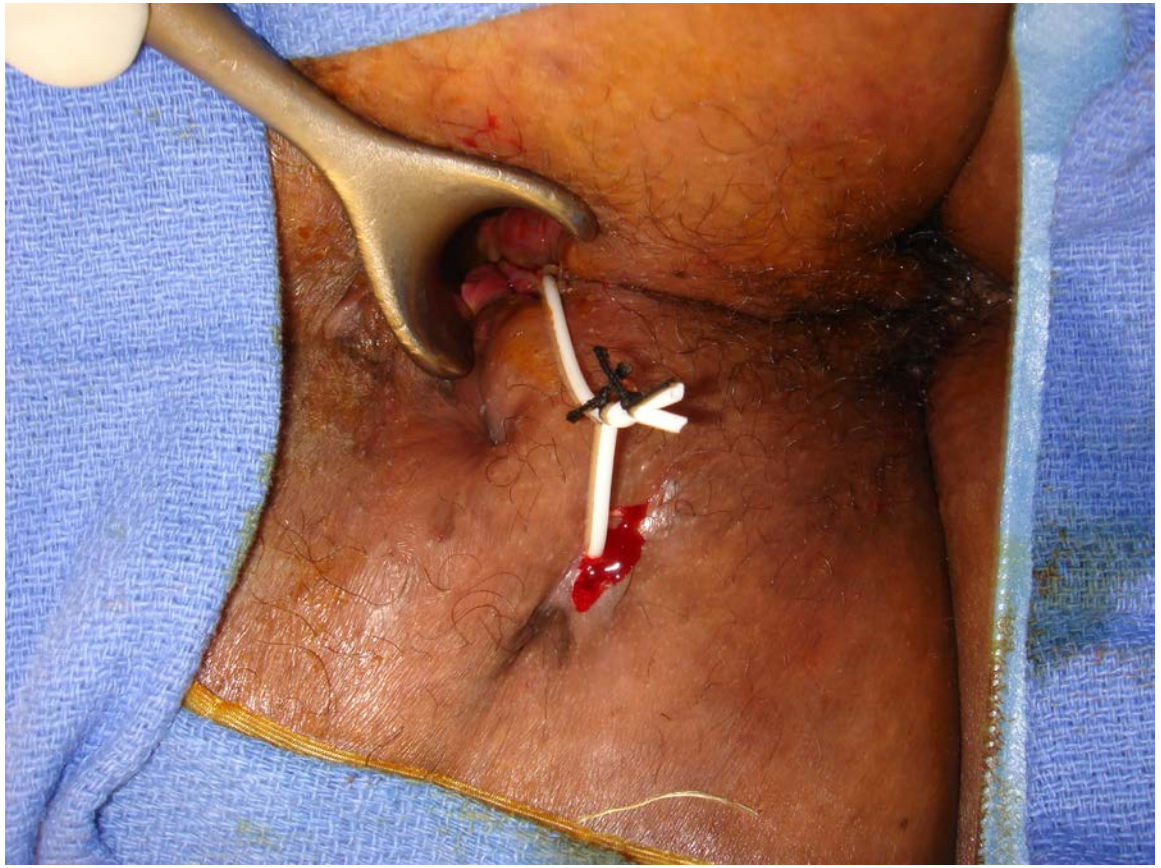

History of Anal Fistula

- Hippocrates (460-357 BC) made reference to surgical treatment of anal fistula

History of Anal Fistula

- William Shakespeare's comedy *All's Well That Ends Well* (written circa 1603) uses a cure for fistula as a central plot device

Cosman BC. DCR 1998;41:914-924.

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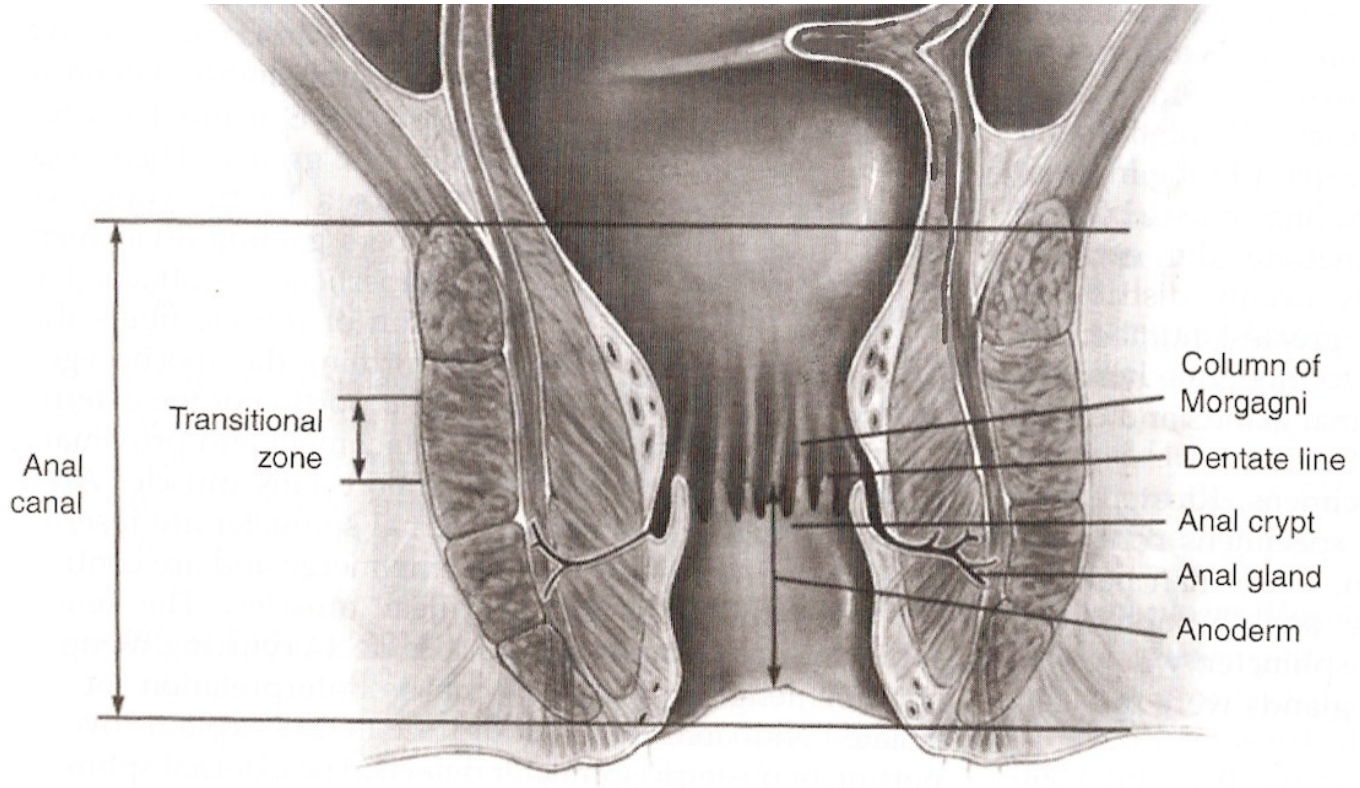
Cryptoglandular Theory

- Sir Alan Parks: Duct obstruction leads to stasis and gland infection
- Crohn's fistulas frequently do not have an internal opening at the dentate line and it is unclear if this theory applies



Parks AG. Br. Med J 1961;1:463-469.

Background

- Optimal multimodal therapy for Crohn's Disease (CD) including antibiotics, steroids, immunosuppressants, anti-TNF therapy and surgery can show initial promising healing rates:
  - Simple fistula healing rate: 88.2%
  - Complex fistula healing rate: 64.6%

- However, initially healed fistulas have significant rates of recurrence:
  - Simple fistula recurrence rate: 26.7%
  - Complex fistula recurrence rate: 41.9%

*Findings in 232 patients in the Netherlands followed for a median of 10 years.

Molendijk I et al. Inflamm Bowel Dis 2014.

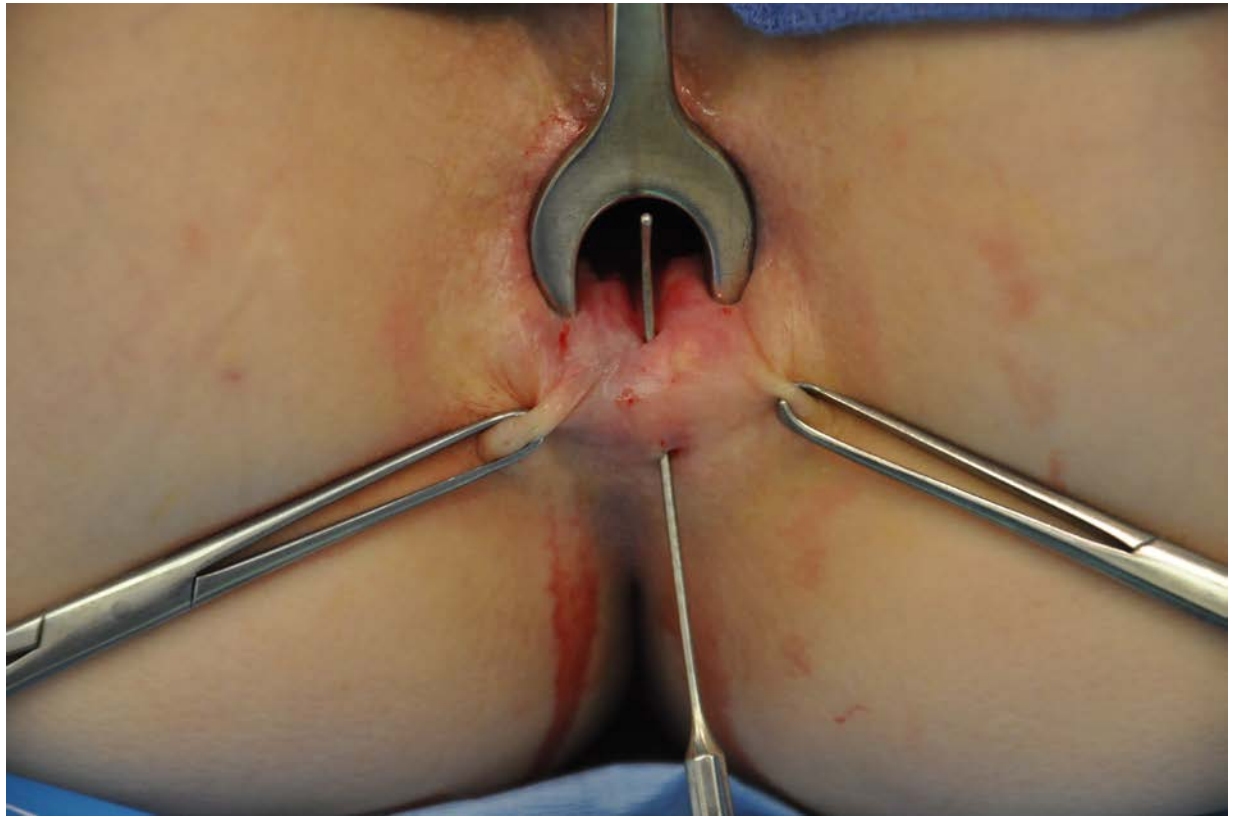
Background

- Hong Kong Registry data
- 981 patients with CD
  - 283 (28.8%) had perianal involvement (fistula or abscess)
  - 120 (12.2%) had perianal involvement as their first sign of CD
- Perianal CD patients were more likely to be male and younger at time of diagnosis
- 40.5% of patients with perianal CD required 2 or more surgical procedures

Mak WY et al. Journal of Crohn's and Colitis 2018.

Anal Fistulotomy

- This is an acceptable treatment for simple Crohn's anal fistulas



Fibrin Glue

- Success rates in Non-Crohn's patients: 14-60%
  - Addition of antibiotics to glue solution is not beneficial
  - Addition of closure of internal opening does not show statistical benefit

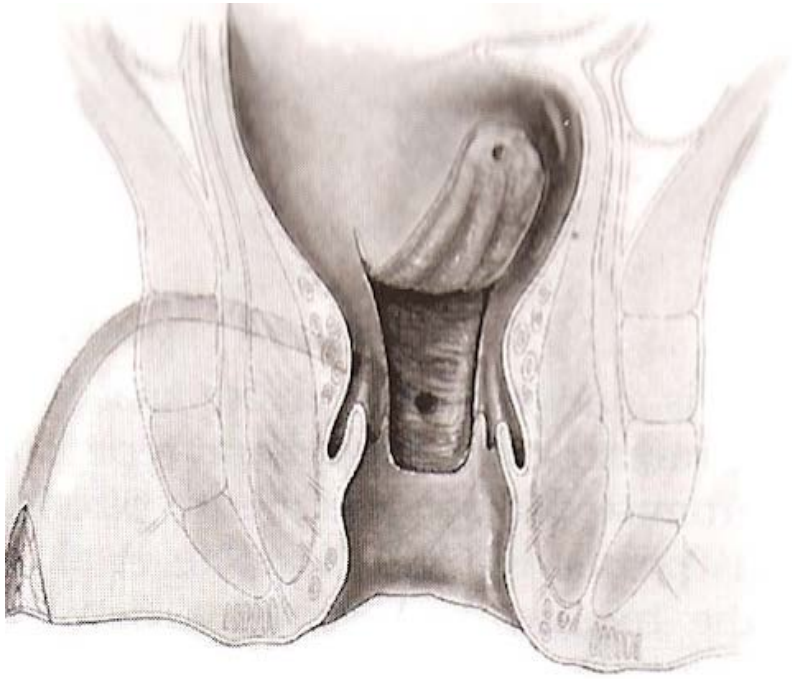
- Success rate in Crohn's disease:
  - RCT of 77 patients treated with glue or observed after seton removal
  - Clinical remission at 8 weeks:
    - Glue: 38%
    - No Glue: 16% (odds ratio, 3.2; 95% confidence interval: 1.1-9.8; P = .04)

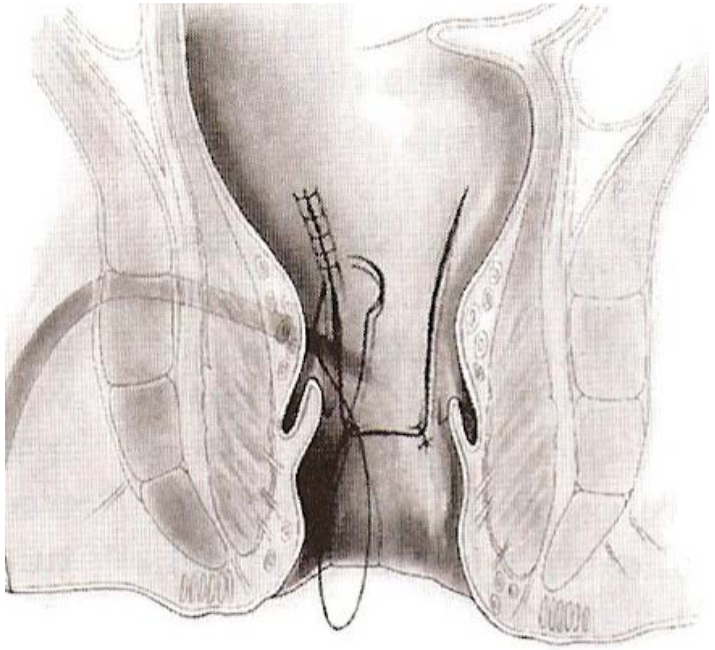
Whiteford MH et al DCR 2005;48:1337-42.

Singer et al DCR 2005;48:799-808.

Grimaud JC et al Gastroenterology 2010.

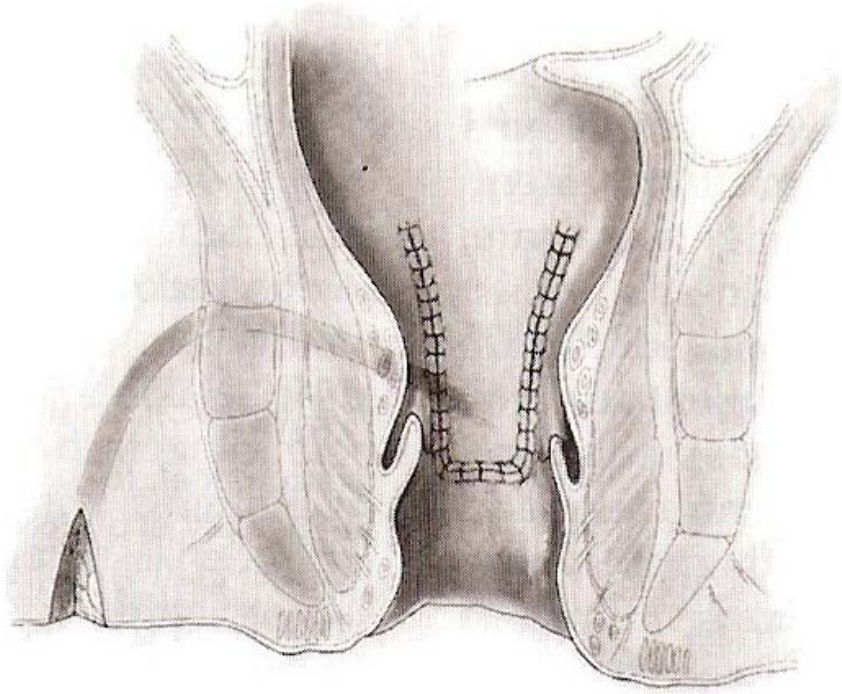
Endorectal Advancement Flap





Endorectal Advancement Flap

- Literature search of endorectal advancement flaps to treat Crohn's and non-Crohn's fistulas
- 35 studies with 2065 patients
- Non-Crohn's Fistulas:
  - Success Rate: 80.8%
  - Incontinence Rate: 13.2%
- Crohn's Fistulas:
  - Success Rate: 64%
  - Incontinence Rate: 9.4%



*Authors noted that overall quality of evidence was poor.

Soltani A et al. DCR 2010.

Infliximab Therapy

- Retrospective Review of 156 patients, median followup of 250 weeks
  - 17.9% had a simple fistula
  - 62% had a seton placed
  - 56% were given concomitant immunosuppressants
- 108 pts (69%) had at least one fistula close
- Probability of fistula recurrence increased over time:
  - 16.5% at 1 year
  - 40.1% at 5 years

Bouguen G et al Clin Gastroenterol Hepatol 2013.

Infliximab Therapy

- Factors that predicted fistula closure:
  - Concomitant Immunosuppressants (HR = 2.58)
  - Duration of seton drainage <34 weeks (HR = 2.31)
  - Ileocolonic disease (HR = 1.88)
  - Long-term duration of infliximab treatment (HR = 1.76)

Bouguen G et al Clin Gastroenterol Hepatol 2013.

Anti-TNF + Antibiotics

- Adalimumab combined with Ciprofloxacin is Superior to Adalimumab alone
- Randomized, double blinded, placebo-controlled trial of 76 patients
- After adalimumab induction therapy (160/80 mg week 0, 2), patients received 40 mg every other week together with ciprofloxacin 500 mg or placebo twice daily for 12 weeks. After 12 weeks, adalimumab was continued.
- Follow-up was 24 weeks.
- Clinical response rate = 50% reduction of fistulas from baseline to week 12
- Remission rate = 100% reduction of fistulas from baseline (closure of all fistulas)

Dewint P et al. Gut 2014.

Anti-TNF + Antibiotics

- Clinical response at week 12:
  - Adalimumab plus Cipro: 71%
  - Adalimumab alone: 47% (p=0.047)

- Remission rate at week 12:
  - Adalimumab plus Cipro: 65%
  - Adalimumab alone: 33% (p=0.009)

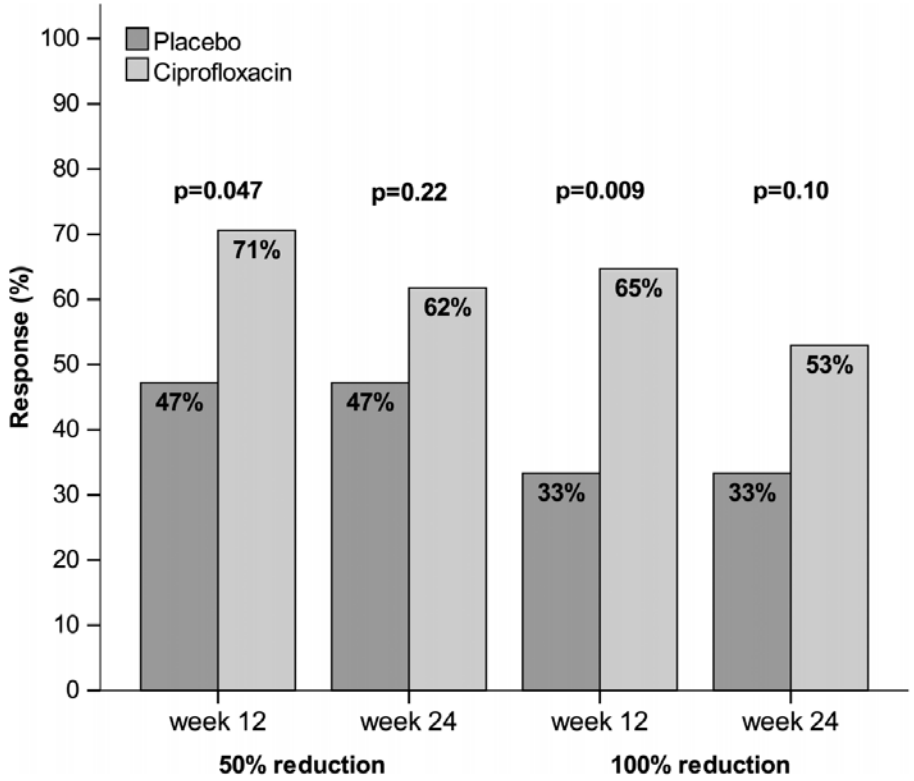
- Combination treatment was associated with a higher mean CDAI change and mean IBDQ change at week 12 (p=0.005 and p=0.009, respectively).

- Remission rate at week 24:
  - Adalimumab plus Cipro: 53%
  - Adalimumab alone: 33% (p=0.098) **NS**
  - No safety issues were observed

Dewint P et al. Gut 2014.

Anti-TNF + Antibiotics

- Combination therapy of adalimumab and ciprofloxacin results in a higher fistula closure rate and results in a better quality of life than adalimumab therapy alone.
- After discontinuation of ciprofloxacin the initial beneficial effect on fistula closure is not sustained.
- Previous administration of infliximab does not influence the effect of adalimumab to induce fistula closure.
- To induce fistula closure in patients with perianal fistulising Crohn's disease the association of ciprofloxacin with adalimumab is preferred over adalimumab alone.



Dewint P et al. Gut 2014.

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Local Injection of Anti-TNF Agents

- Pilot study of 12 patients
- Seton was placed. Later (depending on response to seton) adalimumab was given under local anesthetic in the clinic.
- Adalimumab (20mg in 20ml) was injected with a spinal needle along the fistula tract and around the internal orifice every 2 weeks with a median number of injection of 7 (range 4-16). The seton was removed at the time of the third injection.
- Median followup: 17.5 months. Median number of injections: 7 (range: 4-16)
- 9 of 12 patients (75%) reached complete cessation of fistula drainage. All patients showed improvement
- Perianal Crohn's Disease Activity Index significantly improved in all patients

Tonelli F et al Dis Colon Rectum 2012.

Mesenchymal Stromal Cells (MSCs)

- 300 patients with published results in 23 published articles
  - N=1 to 212, Success Rates 30-83%
- Derived from bone marrow aspiration or liposuction
- There is debate whether **allogenic** or **autologous** MSCs are the ideal cellular product
- Some investigators support the use of autologous MSCs given some patients may conceptually want to receive their own cells rather than cells from another human being
- There is substantial evidence that not all donor MSCs are equivalent with regards to their proliferative and functional properties
  - Older age sig impacts cell proliferation and viability
  - Female gender may improve therapeutic effect of bone marrow-derived MSCs
  - MSCs harvested from adipose tissue in pts with CD exhibit reduced immunosuppressive capability

Kotze PG et al Current Pharmaceutical Design 2019.

Mesenchymal Stromal Cells (MSCs)

- Some investigators support the use of autologous MSCs given the concern for alloimmunity following the delivery of allogeneic MSCs
- **Alloimmunity** (sometimes called isoimmunity) is an immune response to nonself antigens from members of the same species, which are called alloantigens or isoantigens
  - Could be a problem which would prohibit retreatment
- Alloimmunity has not been previously investigated in clinical trials utilizing MSCs for local injection in CD patients
- Previous trials investigating systemic delivery of MSCs for non-Crohn's indications have not demonstrated significant alloimmunity
  - MSCs have low levels of Major Histocompatibility Complex (MHC) Class I receptors and no surface MHC Class II receptors

Kotze PG et al Current Pharmaceutical Design 2019.

Mesenchymal Stromal Cells (MSCs)

- Advantages of allogenic MSCs
  - In the clinical trial setting, using MSCs from one donor reduces variability
  - Provides an ‘off the shelf’ product, available to deliver at the point of patient care
  - Allows for MSCs from the ideal donor
  - Does not require the patient to have bone marrow aspiration or liposuction
  - Avoids delays in care after harvesting while cells are expanded in cell culture

- The efficacy of MSCs appears to be related to their anti-inflammatory effects

Kotze PG et al Current Pharmaceutical Design 2019.

Mesenchymal Stromal Cells (MSCs): Scaffolding

- Combination of autologous, adipose-derived MSCs and fibrin glue has shown increased efficacy a small study
  - MSCs + Glue: 17 of 24 patients (**71 %**) healed
  - Glue alone: 4 of 25 (**16 %**) healed (RR, 4.43; confidence interval, 1.74-11.27); P < 0.001).

- Combination of autologous MSCs and and the the GoreBio-A Fistula Plug demonstrated good efficacy in a small study
  - At 6 months, 10 of 12 patients (**83%**) demonstrated healing

Garcia-Olmo D et al. DCR 2009.

Dietz AB et al. Gastroenterology 2017.

MSCs: A Phase 3 Randomised, Double-Blind Controlled Trial

- Largest phase III study ever published in MSCs for Crohn's-related anal fistula
- ADMIRE-CD (Adipose-Derived Mesenchymal Stem Cells for Induction of Remission in Perianal Fistulizing Crohn's Disease) trial
- Allogenic stem cells were utilized
- 49 different hospitals in Europe and Israel
- Inclusion Criteria:
  - Age > 18
  - Non-active or mildly active luminal Crohn's disease for at least 6 months with CDAI of ≤ 220
  - Complex perianal fistula
  - Maximum of 2 internal openings and 3 external openings
  - Fistula had to have been draining for at least 6 weeks

Panes J et al. Lancet 2016.

MSCs: A Phase 3 Randomised, Double-Blind Controlled Trial

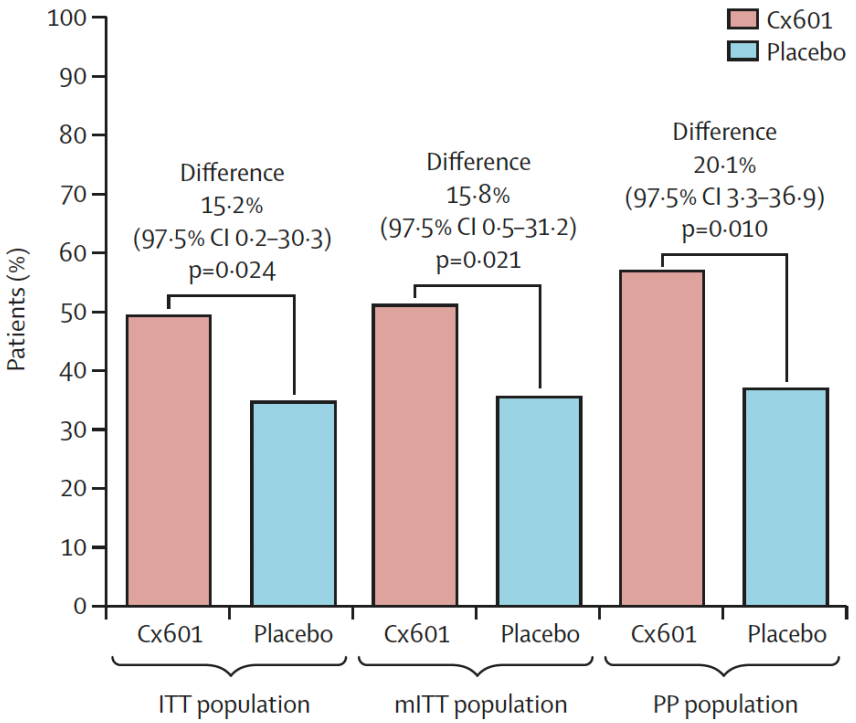
- Exclusion Criteria:
  - Rectovaginal fistulas
  - Rectal/Anal Stenosis
  - Active severe proctitis (presence of superficial or deep ulcers)
  - Diverting stoma
  - Presence of abscess > 2cm

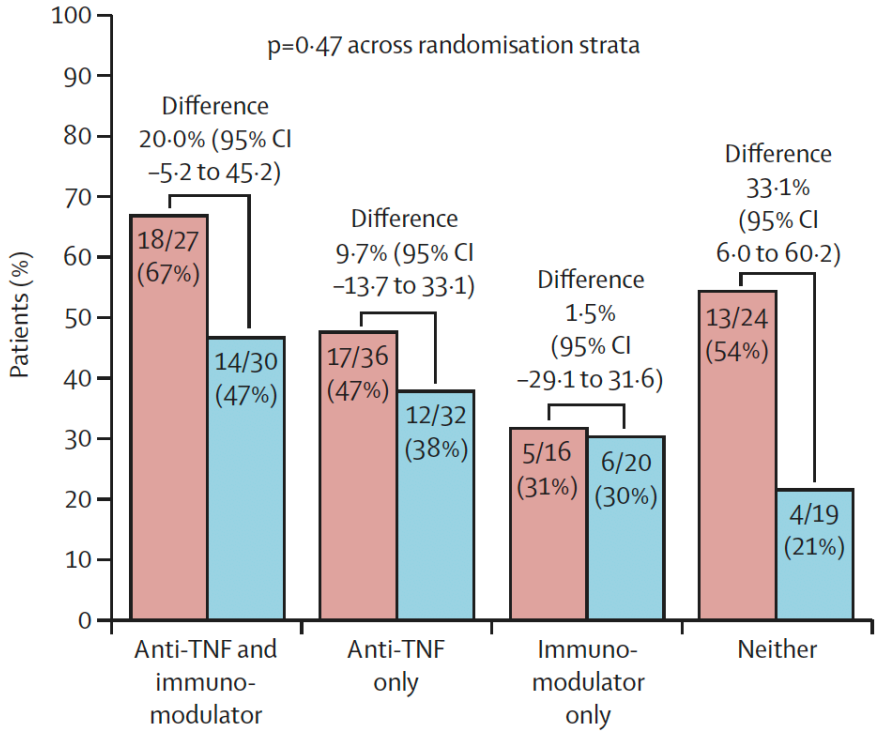
- Procedures:
  - Pelvic MRI done preop
  - Exam under anesthesia and seton placement if “clinically indicated” at least 2 weeks prior to MSCs
  - During treatment, seton was removed. Internal fistula opening closed with 2-0 PDS suture
  - 24 ml solution of 120 million expanded adipose-derived MSCs was injected around all fistula tracts and internal openings

Panes J et al. Lancet 2016.

MSCs: A Phase 3 Randomised, Double-Blind Controlled Trial

- 212 patients were randomly assigned 107 to MSCs and 105 to placebo
  - MSC success rate: 53 of 107 (**50%**)
  - Placebo success rate: 36 of 105 (**34%**) (P=0.024)





Panes J et al. Lancet 2016.

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MSCs: A Phase 3 Randomised, Double-Blind Controlled Trial

- This was a commercialized product produced by TiGenix and (Belgium) later designated as Alofisel (darvadstrocel)
- Alofisel was the first stem cell therapy made out of donor stem cells to receive a marketing authorization in Europe March 2018
- TiGenix was purchased by Takeda in July 2018

Panes J et al. Lancet 2016.

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Conclusions

- Primary healing of Crohn's related anal fistulas is lower than non-Crohn's related anal fistulas
- Recurrence of anal fistula disease is increased with time
- Anti-TNF therapy + ABX has a higher initial healing rate
- Local injection of Anti-TNF agents has not been widely study
- Mesenchymal stromal cells (MSCs) appear promising
- Addition of a scaffold to MSCs may improve efficacy
- An approved allogenic MSC is now commercially available in Europe

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