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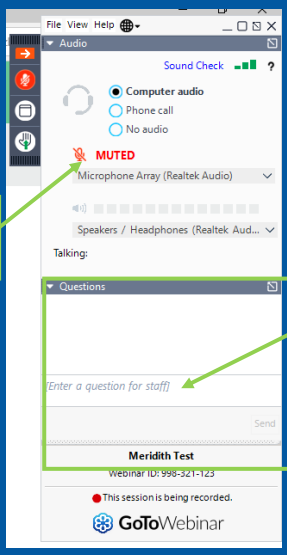
Participating in the Webinar



All attendees will be muted and will remain in Listen Only Mode.

Type your questions here so that the moderator can see them. Not all questions will be answered but we will get to as many as possible.

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How to Receive CME and MOC Points

LIVE VIRTUAL GRAND ROUNDS WEBINAR

ACG will send a link to a CME & MOC evaluation to all attendees on the live webinar.

ABIM Board Certified physicians need to complete their MOC activities by December 31, 2022 in order for the MOC points to count toward any MOC requirements that are due by the end of the year. No MOC credit may be awarded after March 1, 2023 for this activity.

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MOC QUESTION

If you plan to claim MOC Points for this activity, you will be asked to: Please list specific changes you will make in your practice as a result of the information you received from this activity.

Include specific strategies or changes that you plan to implement.
THESE ANSWERS WILL BE REVIEWED.

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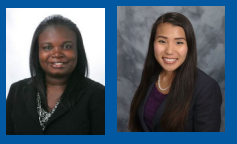
ACG Virtual Grand Rounds

Join us for upcoming Virtual Grand Rounds!

CAREER EDITION – Wednesday, September 14, 2022
How To Teach Endoscopy & Deal With Complications
Faculty: Nikiya O. Asamoah, MD, Keith L. Obstein, MD, FACG, Mohammad Bilal, MD
Moderators: Judy A. Trieu, MD, MPH, Paula G. Adamson, MD
Wednesday, September 14, 2022 from **8:30 – 9:30 PM Eastern**



Week 37 – Thursday, September 15, 2022
Pancreatic Cancer Palliation
Faculty: Nalini Guda, MD, FACG
Moderator: Prabhleen Chahal, MD, FACG
Thursday, September 15, 2022 at Noon Eastern and **NEW! 8pm Eastern!**

Visit **gi.org/ACGVGR** to Register

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Disclosures

Miguel D. Regueiro, MD, FACG
AbbVie, Janssen, UCB, Pfizer, Takeda, Celgene, Genentech, Gilead, BMS, Lilly: Unrestricted educational grants

Abbvie, Janssen, UCB, Takeda, Pfizer, Miraca Labs, Amgen, Celgene, Seres, Allergan, Genentech, Gilead, Salix, Prometheus, Lilly, TARGET Pharma Solutions, ALFASIGMA, S.p.A., BMS: Advisory Board, consultant

CME Outfitters, Imedex, GI Health Foundation (GiHF), Cornerstones, Remedy, MJH Life Sciences, Medscape, MDEducation, WebMD, HMPGlobal: CME Companies

Wolters Kluwer Health as Author/Editor of UpToDate, Crohn's and Colitis Foundation as Editor-in-Chief, CC360: Royalties and editorships

Jill K.J. Gaidos, MD, FACG
AbbVie: Speakers' bureau
BMS: Advisory board

**All of the relevant financial relationships listed for these individuals have been mitigated*

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Perianal Crohn's Disease – Evolutions in Management

Miguel Regueiro, MD, FACG
Chair, Department of Gastroenterology, Hepatology, & Nutrition
Vice Chair, Digestive Diseases and Surgery Institute
Professor of Medicine, Lerner College of Medicine
Cleveland Clinic

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Newly Diagnosed Crohn's disease with fistula

- 30-year-old female presents with a 3-month history of perianal pain and drainage. No change in stool habits.
  - Treated empirically with metronidazole with only minimal improvement
  - Colonoscopy with TI intubation and bx are normal
- FH: positive for Crohn's
- PE: Normal except rectal exam which showed…

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Patient asks you if she could have Crohn's disease and does this happen frequently to CD patients or is she just the unlucky one?

She also wants to know what to expect over her lifetime if this is from Crohn's disease?

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Epidemiology / Morbidity

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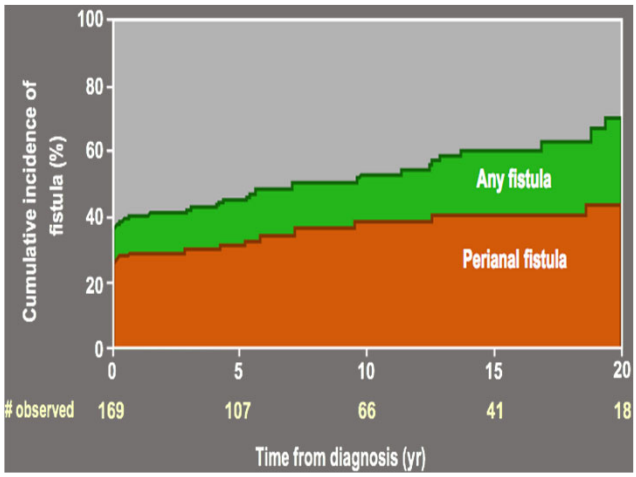
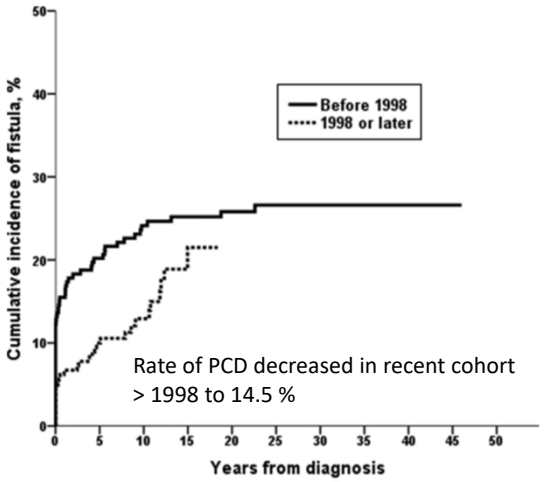
Cumulative Incidence of Crohn's Fistulas





Schwartz et al, Gastro 2002
Park et al., IBD 2019

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Durable Fistula Healing Rates are Disappointing

- Retrospective study from Leiden of 232 patients with CD fistulas - ~ 10 years follow-up
- 78% had complex fistulas
- Long –term fistula healing was seen in only 37% of patients with complex fistulas
  - 66.7 % of simple fistulas
  - 53 % of patients required surgery (colectomy, etc.)
- Proctectomy Rate in recent Mayo cohort was largely unchanged at 19%

Molendijk et al. IBD 2014
Park et al., IBD 2019

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Perianal Anatomy

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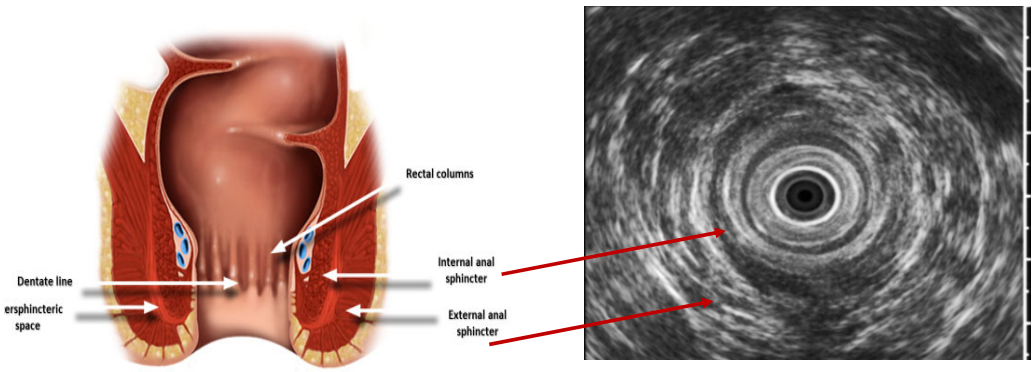
Normal Radial EUS Anatomy



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Classification System

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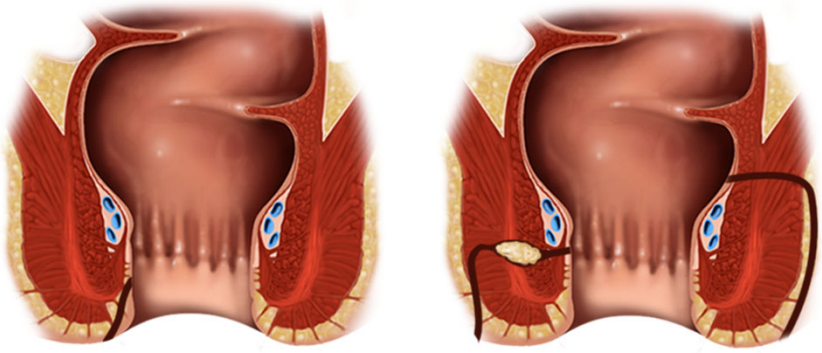
Simple vs. Complex Fistulas



Simple **Complex**

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- 50-year-old male presents with long history of perianal pain and drainage. Recently started passing air and stool when he urinates. No change in stool habits.
  - Treated in past with antibiotics, immunomodulators and infliximab
  - Several attempts at surgical treatment without success
  - Colonoscopy with TI intubation and biopsies are normal
- FH: positive for Crohn's
- PE: Normal except rectal exam which showed…

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What is the best approach to this problem?

What are his treatment options (medical and surgical)?

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Approach to Initial Diagnosis and Assessment

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Why is a precise evaluation important?

The key to successful management is to establish adequate drainage of all abscesses and to control fistula healing. An imaging modality should provide a virtual road map for this purpose.

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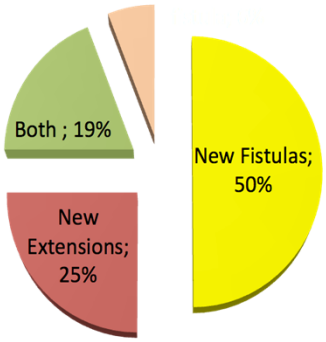
What Happens When Fistulas are Missed at Time of EUA?



In 52% of patients needed repeat surgery in cases where surgery and MRI disagreed

-Fistula recurrence was always at site predicted by MRI

Buchanan et al, Lancet 2002

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Study Results

- A prospective triple blinded study compared EUS, MRI and EUA in 32 patients with suspect perianal Crohn's disease.[1]
- All three methods showed excellent accuracy in assessing these patients
  - EUS – 91% (95% CI 75% - 98%)
  - EUA – 91% (95% CI 75% - 98%)
  - MRI – 87% (95% CI 69% - 96%)
- Combining either of the imaging modalities with EUA increased the accuracy to 100%

1- Schwartz et al., Gastro 2001

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Perianal Crohn's Disease

…notoriously difficult to treat

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Options for Therapy

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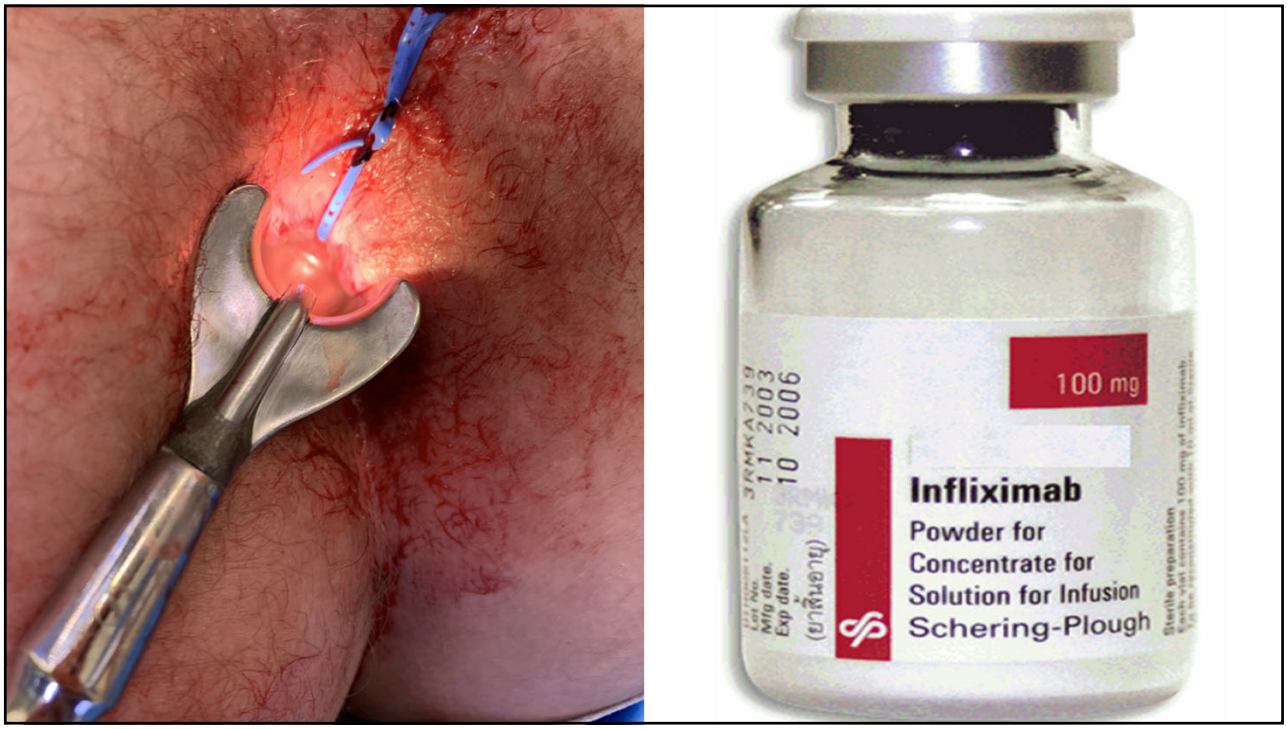

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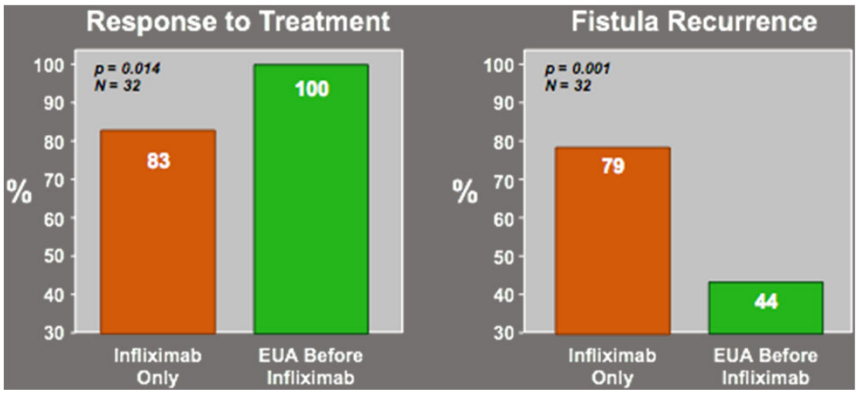
Does Controlling Fistula Healing Make a Difference?



Regueiro et al, IBD 2003

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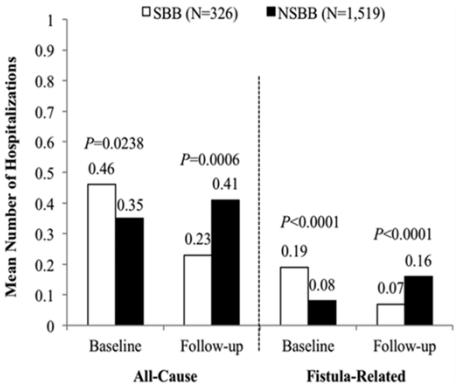
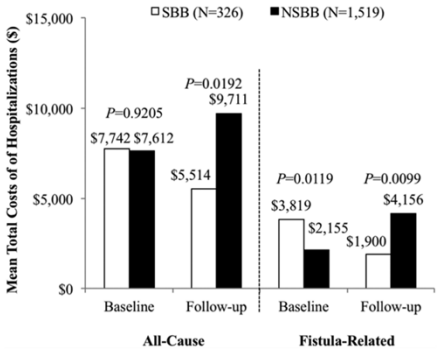
Comparison of Healthcare Utilization in Patients with CD Perianal Fistulas Treated with Biologics with or without Setons





Schwartz, IBD 2017

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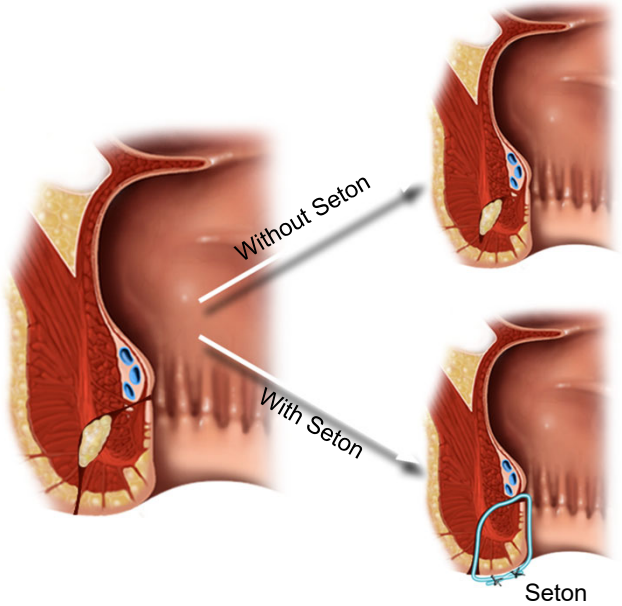
Setons Prevent Premature Closure of Fistula Openings



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Surgical Treatment

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Fistulas

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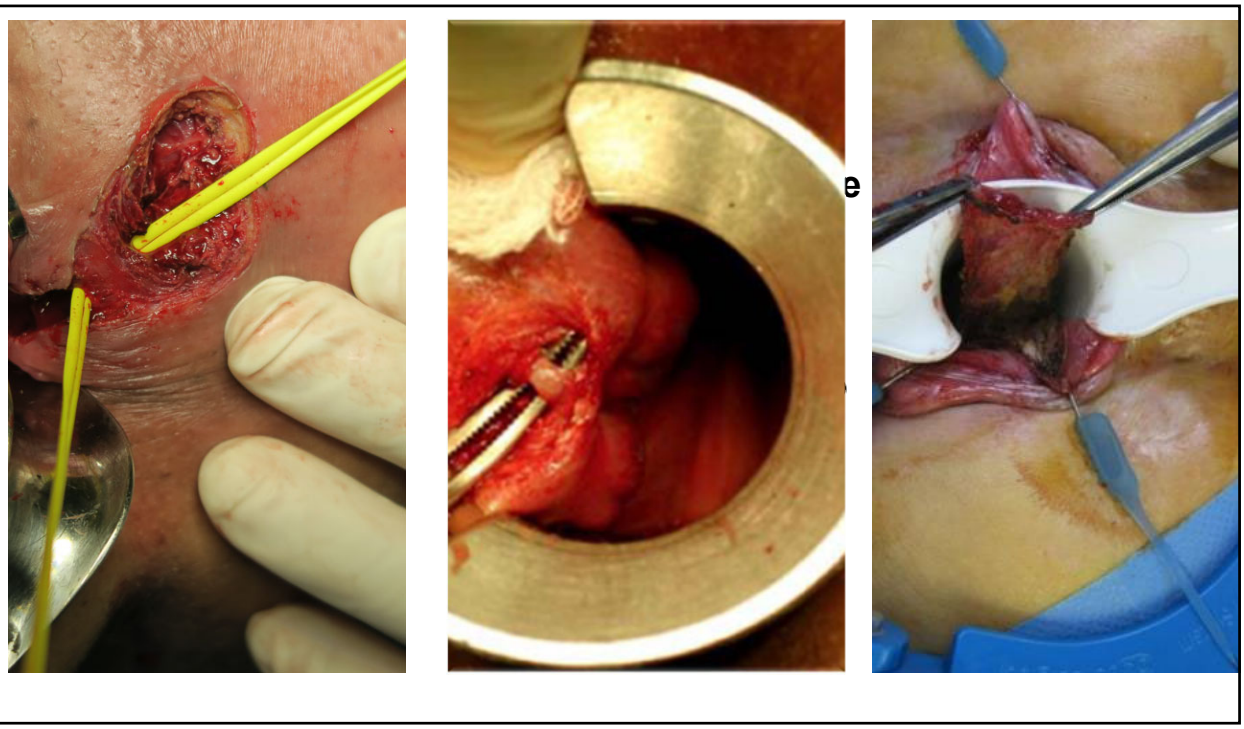

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Setons

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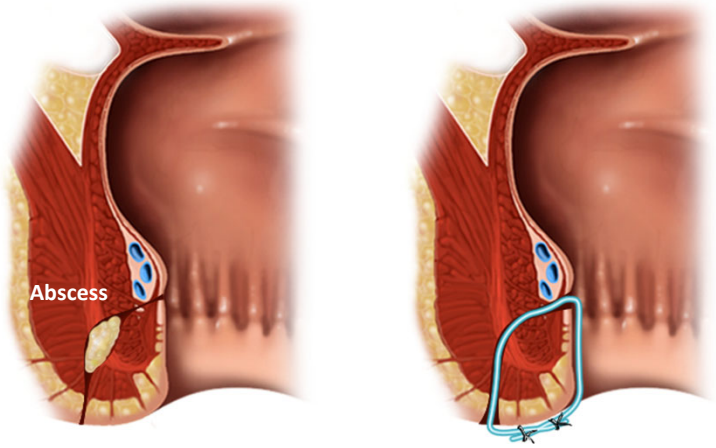
How Setons Help



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Medical Therapies

- Antibiotics (metronidazole, ciprofloxacin)
- Immunosuppressives
  - Azathioprine
  - 6-mercaptopurine
  - Cyclosporine
  - Tacrolimus
- Biologic Agents
  - Infliximab
  - Adalimumab
  - Certolizumab
  - Vedolizumab ?
  - Ustekinumab?
- Novel Agents
  - Adipose Derive Stem Cells

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Antibiotics

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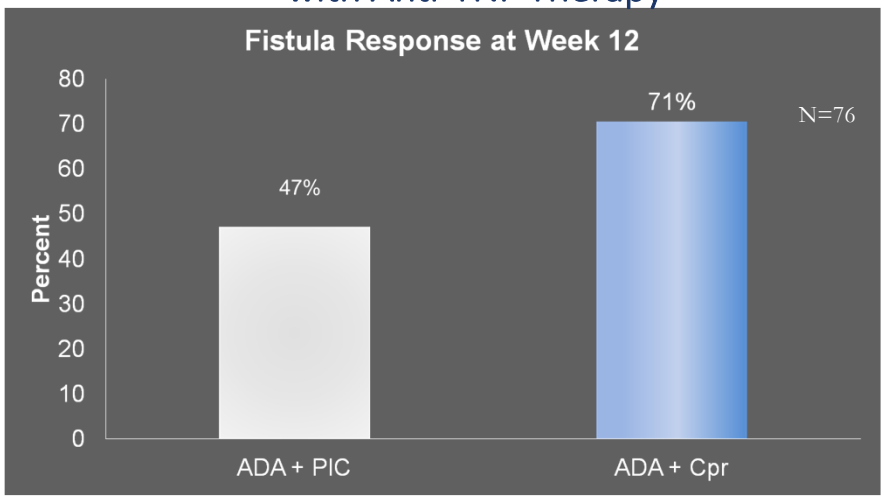
Antibiotics Improve Fistula healing in Combination with Anti-TNF Therapy



All patients received adalimumab 160 mg at wk 0, 80 mg at wk 2 and then 40 mg qow. Patients were then randomized to Ciprofloxacin 500 mg bid or placebo.

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Azathioprine / 6 - MP

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Azathioprine / 6 - MP

- The 5 Controlled trials were summarized in a meta-analysis[1]
  - 22 / 41 (54%) of patients who received AZA /6-MP responded vs. 6 / 29 (21%) who received placebo.
  - Pooled odds ratio was 4.44 in favor of fistula healing

1-Pearson et al. *Ann Intern Med*. 1995

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Cyclosporine & Tacrolimus (FK-506)

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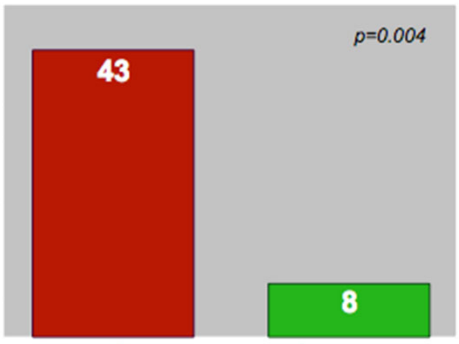
Tacrolimus (FK-506)

The double blinded placebo study of 48 patients randomized to receive 0.20mg/kg/day for 10 weeks. Primary endpoint was improvement defined as closure of ≥ 50% fistulas and maintenance of closure for ≥ 4 weeks.

Week 10 Results



Only 10% had closure of all fistulas

Sandborn et al. , Gastro 2003

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Anti-TNF α Antibody

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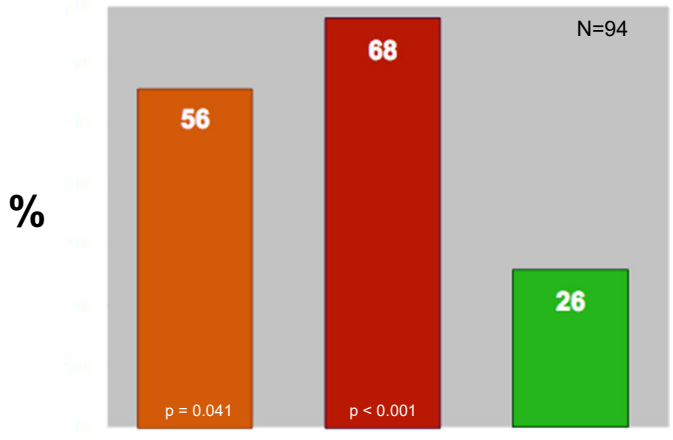
Infliximab for Crohn's Perianal Fistulas

Primary endpoint; > 50% reduction in open fistulas

Initial Fistula Response to Infliximab



Present et al. , NEJM 1999

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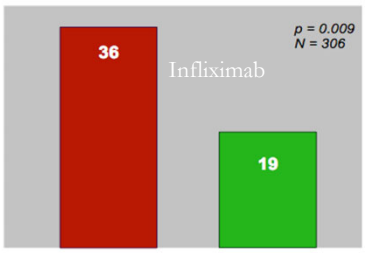
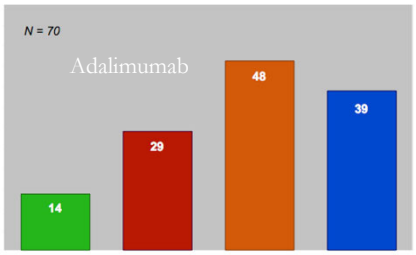
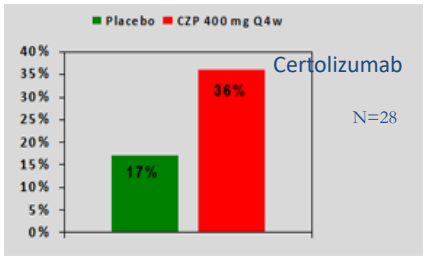
Anti-TNF Maintenance Therapy for CD Related Fistulas







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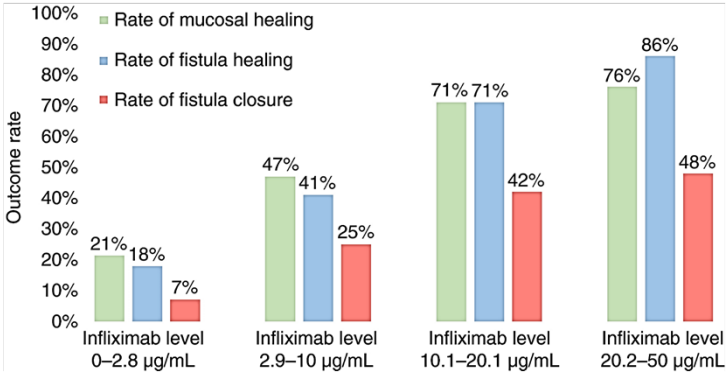
Higher Infliximab Trough Levels are Associated with a Higher Rate of Perianal Fistula Healing



Yarur A., APT 2017

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How Can We Improve Outcomes for Patients with Crohn's Perianal Fistulas?

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Recurrent Fistula Patient

- 45 year-old female presents with 5-year history of Crohn's disease. Has had perianal fistula that has drain intermittently for 4 years.
- Presents with 2-month history of perianal pain and drainage.
  - Currently on infliximab monotherapy
  - Colonoscopy with TI intubation and biopsies are shows active proctitis
- PE: Normal except rectal exam which showed…

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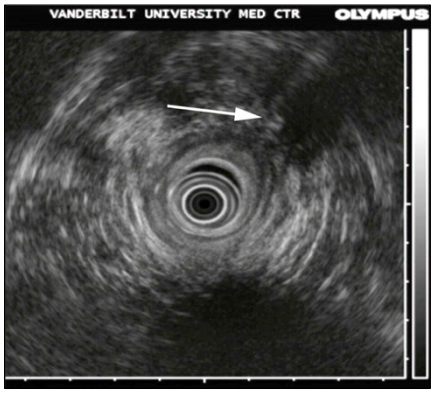

She asks what can be done to get increase her chances of healing and get her fistula to stop draining for good?

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The Use of Imaging to Guide Therapy

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MRI to Guide Therapy with Infliximab or Adalimumab

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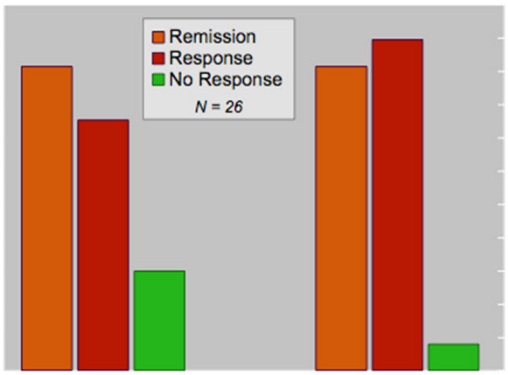

Medical therapy was increased if no or partial response seen on MRI

Ng et al. Am J Gastro 2009

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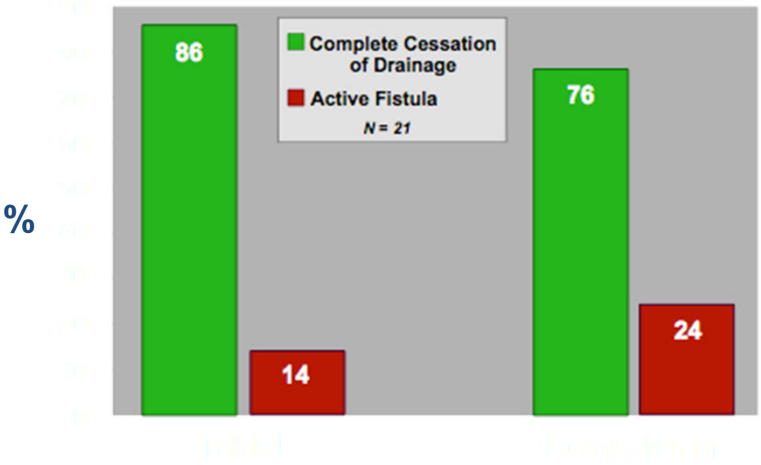
Utilizing EUS to Improve Fistula Healing



Schwartz et al, IBD 2005

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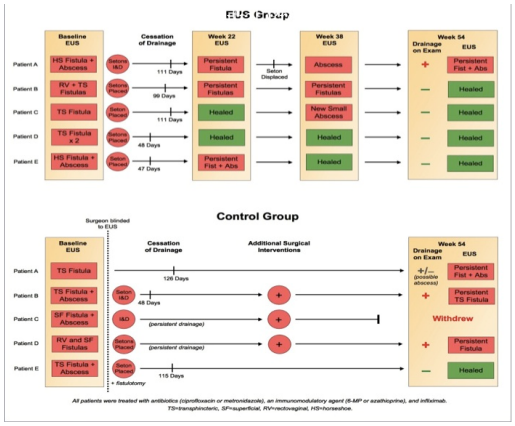
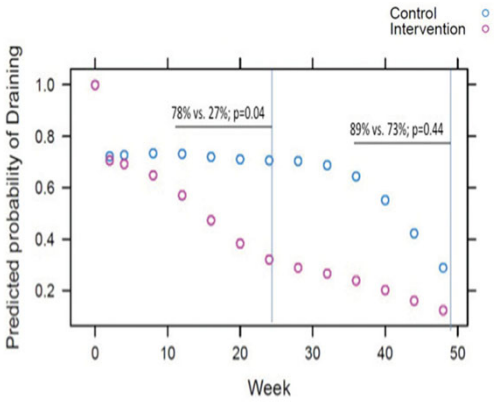
Two Randomized Prospective Studies Looking at EUS to Improve Outcomes





1-Spradlin, Schwartz Am J Gatro 2008
2- Wiese,Schwartz Am J Gastro 2011 (ab)

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Future Options ?

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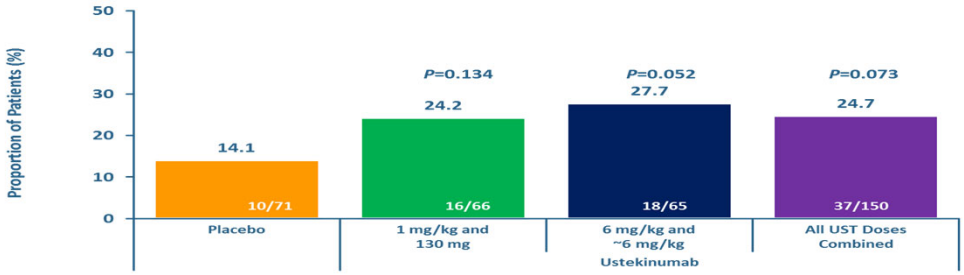
Post Hoc Analysis Suggests Ustekinumab Effective for Perianal Disease in Crohn's

Fistula Resolution at Week 8 - Pooled Data from CERTIFI, UNITI-1 and UNITI-2



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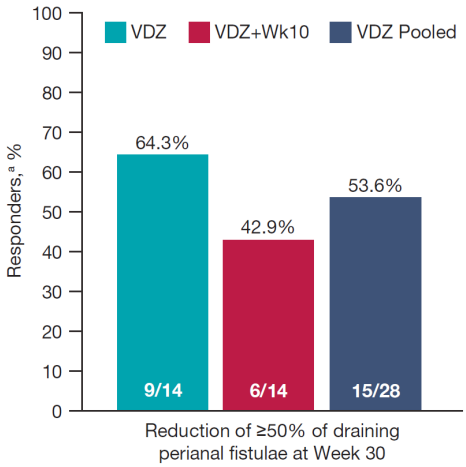
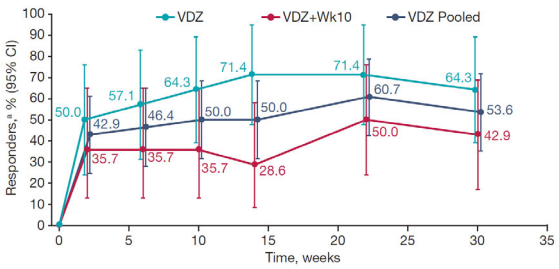
Enterprise- Vedolizumab for CD Perianal Fistulas





Schwartz et al. DDW 2020

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Non-healing Fistula despite Infliximab

- 37 year-old female presents with 3-year history of Crohn's disease. Has had perianal fistula that has drain intermittently for 2 years.
- Presents with 6-month history of anal fistula drainage.
  - Currently on infliximab monotherapy
  - Colonoscopy with TI intubation and biopsies shows NO active Crohn's – the rectal and colonic Crohn's disease is now in remission
- PE: Normal except rectal exam which showed…

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What next? The Infliximab is "working" and the Crohn's is in remission

- But there is a persistent fistula tract that is draining – pelvic MRI shows the fistula, but no inflammation, no abscess, otherwise normal

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Int J Colorectal Dis (2003) 18:451–454
DOI 10.1007/s00384-003-0490-3

CASE REPORT

Damian García-Olmo
Mariano García-Arranz
Lourdes Gómez García
Eduardo Serna Cuellar
Ignacio Fernández Blanco
Luis Asensio Prianes
José Antonio Rodríguez Montes
Francisca Lima Pinto
Dolores Herreros Marcos
Luis García-Sancho

Autologous stem cell transplantation for treatment of rectovaginal fistula in perianal Crohn's disease: a new cell-based therapy

- 33-year-old female
- Complex fistula with 5 perianal tracts which converged into rectovaginal fistula
- Infliximab
- Gracilis flap
- ***Injection of 9×10⁶ MSCs → healed within 3 months***

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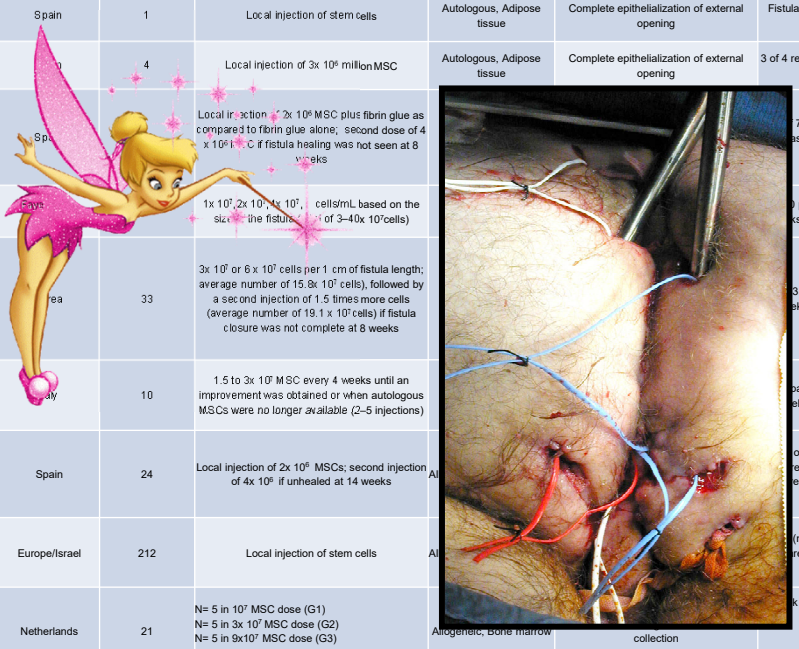
Name of Study	Type of Study	Location	# patients with CD	Intervention	Type and source of Stem Cells	Outcome	Results	Use of MRI
García-Olmo et al 2003[40]	Case report	Spain	1	Local injection of stem cells	Autologous, Adipose tissue	Complete epithelialization of external opening	Fistula healed in 1 week, No recurrence till 3 months post treatment	No
García-Olmo et al 2005[41]	Phase I, open label, single arm		4	Local injection of 3x 10⁶ millon MSC	Autologous, Adipose tissue	Complete epithelialization of external opening	3 of 4 rectovaginal or perianal fistula (75%) at 8 weeks	No
García-Olmo et al 2009[42,70]	Phase IIb, open label, double arm, randomized	Sp		Local injection of 2x 10⁶ MSC plus fibrin glue as compared to fibrin glue alone; second dose of 4 x 10⁶ if fistula healing was not seen at 8 weeks			7 fistulas (71%) in MSC versus 1 of 7 (14%) healed in fibrin glue alone at 8 weeks	No
Cho et al 2013[43]	Phase I, open label, single arm	Korea		1x 10⁷, 2x 10⁷, 4x 10⁷, cells/mL based on the size of the fistula (range of 3–40x 10⁷cells)			patients (30%) had complete healing at s post treatment; sustained at 8 months	No
Lee et al 2013[44]	Phase II, open label, single arm	Korea	33	3x 10⁷ or 6 x 10⁷ cells per 1 cm of fistula length; average number of 15.8x 10⁷ cells), followed by a second injection of 1.5 times more cells (average number of 19.1 x 10⁷ cells) if fistula closure was not complete at 8 weeks			3 patients (82%) had complete healing at eks; 88% sustained closure at one year	No
Ciccocioppo et al 2011[45]	Open label, single arm	Italy	10	1.5 to 3x 10⁷ MSC every 4 weeks until an improvement was obtained or when autologous MSCs were no longer available (2–5 injections)			patients (67%) with complete closure at 8 eks; all sustained closure at one year	Yes
de la Portilla et al 2013[46]	Phase I/IIa open label, single arm	Spain	24	Local injection of 2x 10⁶ MSCs; second injection of 4x 10⁶ if unhealed at 14 weeks	Al		of 18 fistulas (28%) closed at 24 weeks eatment. 7 out of 18 patients (47%) had e of external openings at 24 weeks post treatment.	Yes
Panes J et al 2016[71]	Phase III, RCT	Europe/Israel	212	Local injection of stem cells	Al		(n=53 of 107) healed in the MSC group ed with 34% (n=36 of 105, p = 0.024) at 24 weeks	Yes
Molenkijk et al 2015[47]	Open label, 4 arms	Netherlands	21	N= 5 in 10⁷ MSC dose (G1) N= 5 in 3x 10⁷ MSC dose (G2) N= 5 in 9x10⁷ MSC dose (G3) N= 6 in placebo (G4)	Allogeneic, Bone marrow	collection	k fistula healing: G1:2/5 G2:4/5 G3:1/5 G4:2/6	Yes



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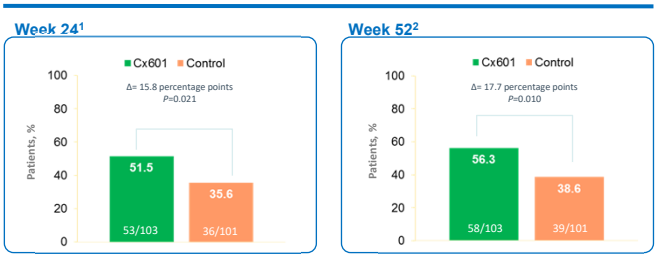
Adipose Derived Stem Cells – Fistula Healing at Week 24 and Week 52 (n=204)



- Remission and Response rates higher in TNF/Immunomod pts - 67% v. 47%
- 75% of those who healed by wk 24 maintained remission out to week 52

Panes et al, Lancet 2016

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Mesenchymal Stem Cells (MSCs) are safe

- No trial has reported systemic complications
- No trial has reported systemic infections
- Most frequent AE = pain at site of injection (12-15%)
- 2nd most frequent AE = perianal abscess at injection site (5-13%)
  - **same frequency in treatment and control*
- Drop out rate of study due to AE ~5%

	Cx601 (n=103)	Placebo (n=102)
Overall	68 (66%)	66 (65%)
TEAEs leading to study withdrawal	5 (5%)	6 (6%)
TEAEs in ≥5·0% of patients*		
Proctalgia	13 (13%)	11 (11%)
Anal abscess	12 (12%)	13 (13%)
Nasopharyngitis	10 (10%)	5 (5%)
Diarrhoea	7 (7%)	3 (3%)
Abdominal pain	4 (4%)	6 (6%)
Fistula†	3 (3%)	6 (6%)
Treatment-related adverse events	18 (17%)	30 (29%)
Treatment-related adverse events in ≥2·0% of patients*		
Anal abscess	6 (6%)	9 (9%)
Proctalgia	5 (5%)	9 (9%)
Procedural pain	1 (1%)	2 (2%)
Fistula discharge‡	1 (1%)	2 (2%)
Induration	0	2 (2%)
Serious TEAEs§	18 (17%)	14 (14%)
Serious TEAEs in ≥2·0% of patients*		
Anal abscess	9 (9%)	7 (7%)
Serious treatment-related adverse events	5 (5%)	7 (7%)
Anal abscess	5 (5%)	5 (5%)
Proctalgia	0	1 (1%)
Anal inflammation	0	1 (1%)
Liver abscess	0	1 (1%)

Cx601=allogeneic, expanded, adipose-derived stem cells. TEAE=treatment-emergent adverse event (MedDRA, version 17.0). *In either treatment group. †New fistula, reopening of closed fistula. ‡Fistula discharge in a closed fistula. §Defined as any adverse event that at any dose resulted in death, was life-threatening, caused permanent incapacity or disability, resulted in hospital admission or prolonged a hospital stay, was a medically significant event, or was a suspected transmission of an infectious drug.

Table 3: **Treatment-emergent adverse events up to week 24 in the safety population**

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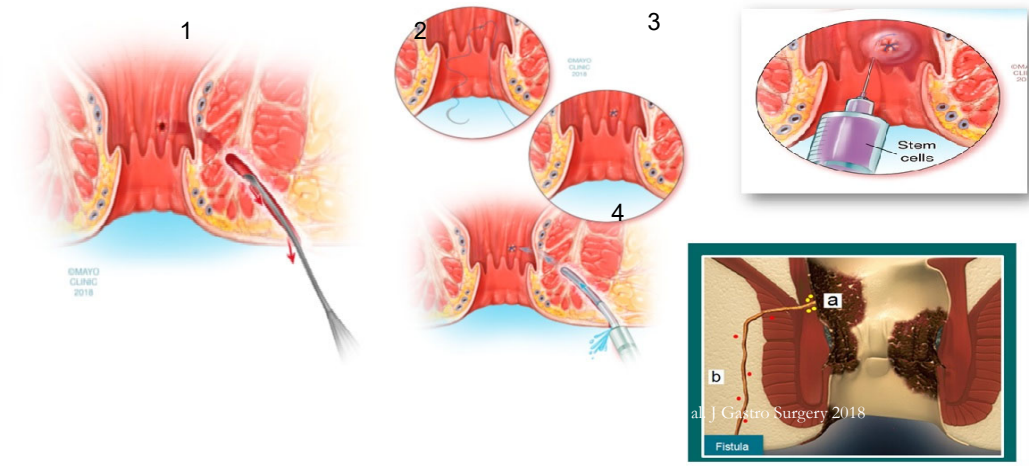
Steps for Administering Stem Cells



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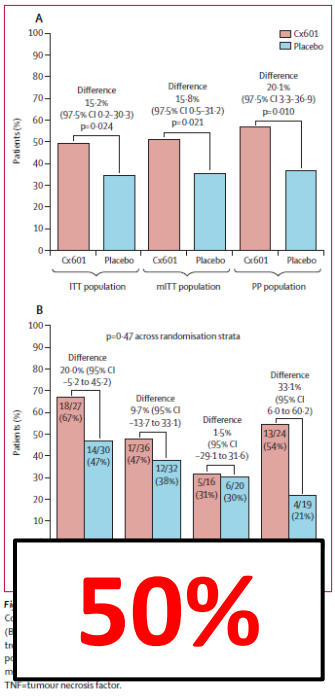
MSCs are effective



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"Con's" to stem cell therapy

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#1: GMP grade labs at multiple sites is not realistic

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#2: Shelf life is *hours*

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Conclusions

- Crohn's fistulas are notoriously difficult to treat
- Most require surgery at some point
- Seton + biologic = most effective place to start
- Proctitis and number of tracts prohibits the limit of local surgical intervention
- 20% will have proctectomy
- Stem cell therapy may offer novel approach

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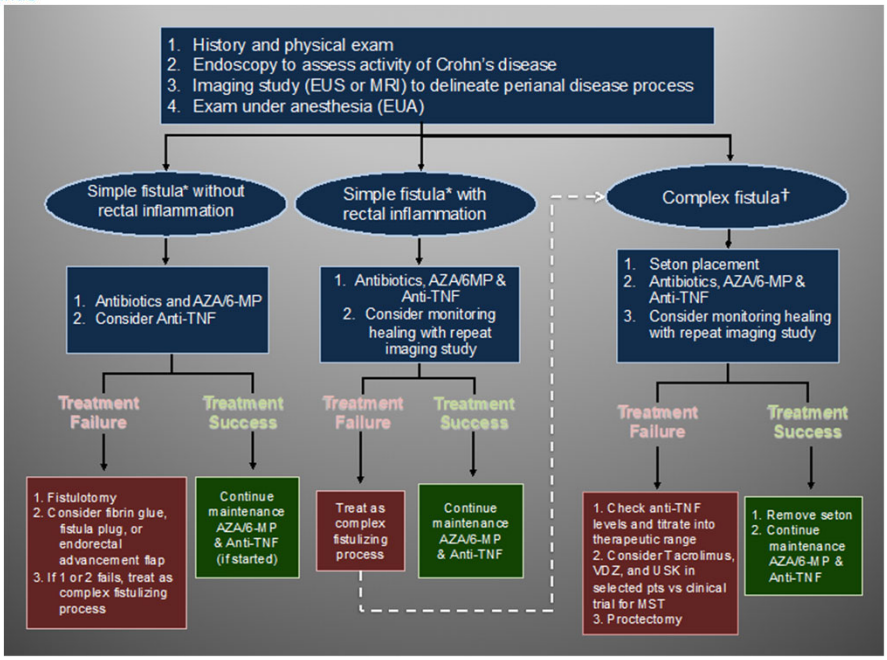

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Questions and Answers

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