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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.

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.
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.

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: Nikki O. Asamoah, MD, Keith L. Obstein, MD, FACP, Mohammad Bilal, MD
Moderators: Judy A. Trieu, MD, MPH, Paula G. Adamson, MD
Wednesday, September 14, 2022 from 8:30 – 9:30 PM Eastern

Pancreatic Cancer Palliation
Faculty: Nalini Guda, MD, FACP
Moderator: Prabhleen Chahal, MD, FACP
Thursday, September 15, 2022 at Noon Eastern and 8pm Eastern!

Visit gi.org/ACGVGR to Register
Disclosures

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

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...
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?

Epidemiology / Morbidity
**Cumulative Incidence of Crohn’s Fistulas**

![Graph showing cumulative incidence of Crohn’s Fistulas](image)

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

**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**
Perianal Anatomy

Normal Radial EUS Anatomy
Classification System

Simple vs. Complex Fistulas

Simple

Complex
• 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...

What is the best approach to this problem?

What are his treatment options (medical and surgical)?
Approach to Initial Diagnosis and Assessment

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.
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

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
Perianal Crohn’s Disease

...notoriously difficult to treat

Options for Therapy
Does Controlling Fistula Healing Make a Difference?

Response to Treatment

<table>
<thead>
<tr>
<th></th>
<th>Infliximab Only</th>
<th>EUA Before Infliximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>(%)</td>
<td>83</td>
<td>100</td>
</tr>
</tbody>
</table>

Fistula Recurrence

<table>
<thead>
<tr>
<th></th>
<th>Infliximab Only</th>
<th>EUA Before Infliximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>(%)</td>
<td>79</td>
<td>44</td>
</tr>
</tbody>
</table>

Regueiro et al, IBD 2003
Comparison of Healthcare Utilization in Patients with CD Perianal Fistulas Treated with Biologics with or without Setons

Setons Prevent Premature Closure of Fistula Openings
Surgical Treatment

Fistulas
Setons
How Setons Help

Medical Therapies

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

• The 5 Controlled trials were summarized in a meta-analysis¹
  • 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

Cyclosporine & 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

43

8

$p=0.004$

Anti-TNF α Antibody

Infliximab for Crohn’s Perianal Fistulas

Primary endpoint; > 50% reduction in open fistulas

Initial Fistula Response to Infliximab

- 56
- 68
- 26

N=94

p = 0.041

p < 0.001

Present et al., NEJM 1999
Anti-TNF Maintenance Therapy for CD Related Fistulas

- Infliximab
  - 36
  - 19
- Adalimumab
  - 46
  - 39
- Certolizumab
  - N=28
  - 17%

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

- Infliximab level 0-2.8 μg/mL
  - Rate of mucosal healing: 21%, 18%
  - Rate of fistula healing: 47%, 41%
  - Rate of fistula closure: 25%
- Infliximab level 2.9-10 μg/mL
  - Rate of mucosal healing: 7%
  - Rate of fistula healing: 42%
  - Rate of fistula closure: 48%
- Infliximab level 10.1-20.1 μg/mL
  - Rate of mucosal healing: 71%, 71%
  - Rate of fistula healing: 76%
  - Rate of fistula closure: 86%

Vasut A., APT 2017
How Can We Improve Outcomes for Patients with Crohn’s Perianal Fistulas?

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

The Use of Imaging to Guide Therapy
MRI to Guide Therapy with Infliximab or Adalimumab

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

Ng et al. Am J Gastro 2009

Utilizing EUS to Improve Fistula Healing

Schwartz et al. IBD 2005
Two Randomized Prospective Studies Looking at EUS to Improve Outcomes

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

Future Options?
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

Enterprise- Vedolizumab for CD Perianal Fistulas

Schwartz et al. DDW 2020
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...

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
### CASE REPORT

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

#### Description
- **33-year-old female**
- Complex fistula with 5 perianal tracts which converged into rectovaginal fistula
- Infliximab
- Gracilis flap
- Injection of $9 \times 10^6$ MSCs → healed within 3 months

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### Table: Study Findings

<table>
<thead>
<tr>
<th>Name of Study</th>
<th>Type of Study</th>
<th>Location</th>
<th># patients with CD</th>
<th>Intervention</th>
<th>Type and source of Stem Cells</th>
<th>Outcome</th>
<th>Results</th>
<th>Use of MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>García-Olmo et al 2003</td>
<td>Case report</td>
<td>Spain</td>
<td>1</td>
<td>Local injection of 200 cells</td>
<td>Autologous, Adipose tissue</td>
<td>Fistula healed in 1 week. No recurrence till 3 months post treatment.</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>García-Olmo et al 2005</td>
<td>Phase I, open label, single arm</td>
<td>Spain</td>
<td>4</td>
<td>Local injection of $3 \times 10^6$ million MSC</td>
<td>Autologous, Adipose tissue</td>
<td>3 of 4 rectovaginal or perianal fistulas (75%) healed at 8 weeks.</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>García-Olmo et al 2009</td>
<td>Phase IIb, open label, double arm, randomized</td>
<td>Spain</td>
<td>14</td>
<td>Local injection of 2x $10^6$ MSC plus fibrin glue if fistula healing was not seen at 8 weeks</td>
<td>Autologous, Adipose tissue</td>
<td>5 of 7 fistulas (71%) in MSC versus 1 of 7 (14%) healed at 8 weeks post treatment.</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Cho et al 2013</td>
<td>Phase I, open label, single arm</td>
<td>Korea</td>
<td>10</td>
<td>$1x 10^7, 2x 10^7, 4x 10^7$ cells/mL based on the size of the fistula (total of 3–40 $10^7$ cells)</td>
<td>Autologous, Adipose tissue</td>
<td>3 of 10 patients (30%) had complete healing at 8 weeks post treatment; sustained at 8 months.</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Lee et al 2013</td>
<td>Phase II, open label, single arm</td>
<td>Korea</td>
<td>33</td>
<td>$3x 10^7$ or $6x 10^7$ cells, 1 cm/tract (length = average number of 18 fistulas / 1 tract). Followed by 1-2x of above. If no improvement: Local injection of 2x $10^6$ MSCs 2 weeks later.</td>
<td>Autologous, Adipose tissue</td>
<td>27 of 33 patients (82%) had complete healing at 8 weeks; 88% sustained closure at one year.</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Ciccocioppo et al 2011</td>
<td>Open label, single arm</td>
<td>Italy</td>
<td>10</td>
<td>1.5 to 3 $10^6$ MSC every 4 weeks until an improvement was obtained or when autologous MSCs were no longer available (2 to 5 injections)</td>
<td>Autologous, Bone marrow</td>
<td>6 of 9 patients (67%) with complete closure at 8 weeks.</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>de la Portilla et al 2013</td>
<td>Phase I/IIa open label, single arm</td>
<td>Spain</td>
<td>24</td>
<td>Local injection of 2x $10^6$ MSCs, second injection of 4x $10^6$ if unhealed at 14 weeks.</td>
<td>Autologous, Adipose tissue</td>
<td>24 of 16 fistulas (28%) closed at 24 weeks post treatment. 7 out of 16 patients (43%) had closure of external openings at 24 weeks post treatment.</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Panes J et al 2016</td>
<td>Phase II, RCT</td>
<td>Europe-Israel</td>
<td>211</td>
<td>Local injection of stem cells.</td>
<td>Autologous, Adipose tissue</td>
<td>195 of 211 fistulas (91%) healed in the MSC group and with 54% (p = 0.024) at 24 weeks post treatment.</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>

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### Additional Information
- **American College of Gastroenterology**
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%
Steps for Administering Stem Cells

1. Patient 1: MSCs are effective 83% at 24 weeks.
2. Patient 2: MSCs are effective 50% at 24 weeks.

American College of Gastroenterology
“Con’s” to stem cell therapy

#1: GMP grade labs at multiple sites is not realistic
#2: Shelf life is *hours*

#3: Cost is prohibitive
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
Questions and Answers

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