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4th IVPN SYMPOSIUM
PHARMACY: FROM EVIDENCE TO PRACTICE

Modern Management of Perianal Fistulas in Crohn's Disease (PFCD): Future Directions

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Disclosure Information

- I have no financial relationship to disclose.

Learning objectives

- Explain the physiology, etiology, and anatomical classification of Perianal fistulas
- Discuss the clinical manifestations, prognosis, and diagnosis of perianal fistulas
- Discuss pharmacological and surgical treatment options for perianal fistulas in Crohn’s disease (PFCD)

What is a Perianal Fistula

- An epithelialized track that can form and connects the abscess in the anus or rectum with the perirectal skin
- Anal fistulas are sometimes also referred to as "fistula-in-ano

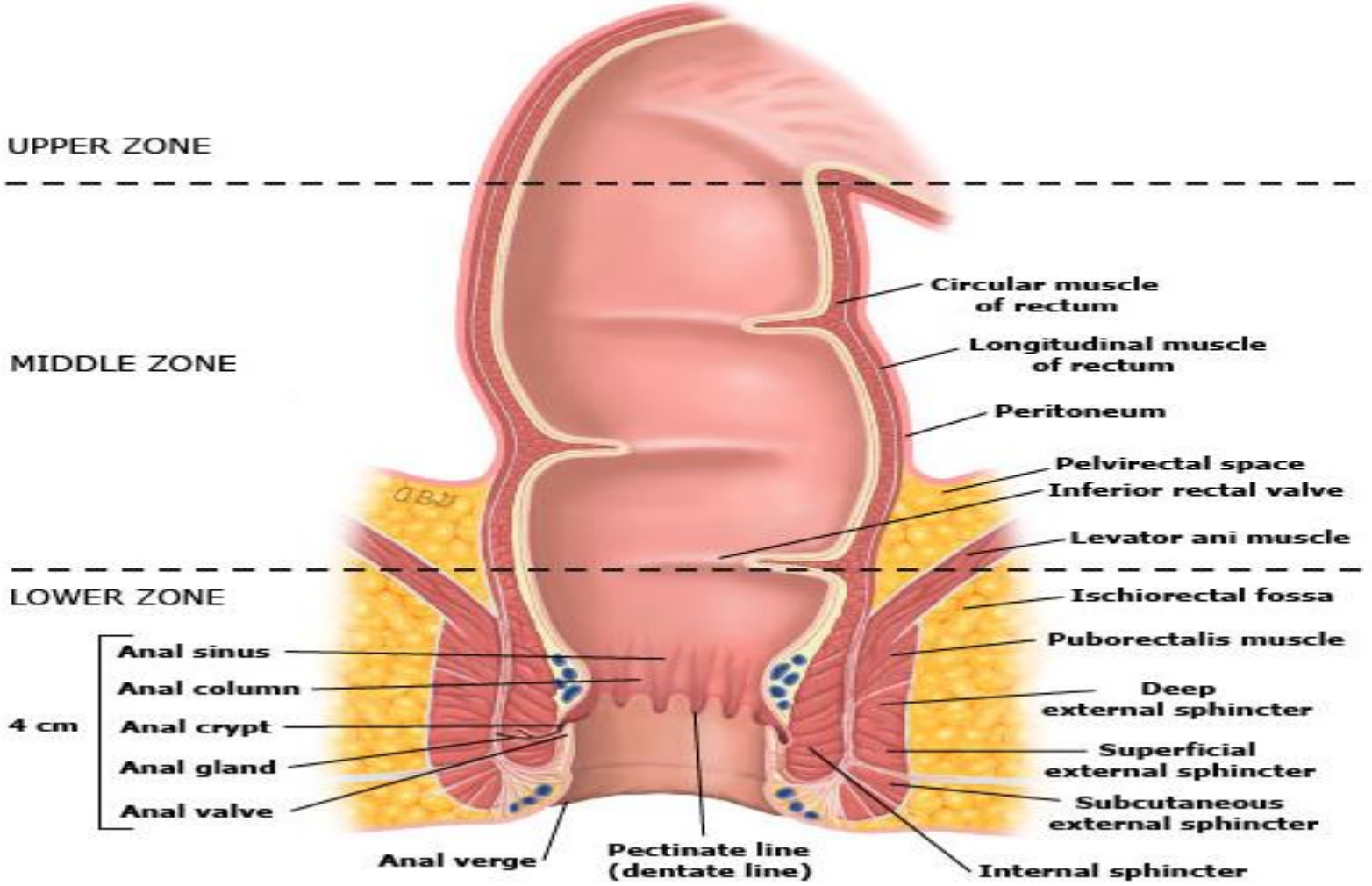
Epidemiology

- The incidence of an anal fistula developing from an anal abscess ranges from 26 to 38 percent
- The mean age for presentation of anal abscess and fistula disease is 40 years
- The presence of perianal fistulas can be the initial manifestation of CD in 10% of the patients
- PFCD tends to be more prevalent in colonic disease and rectal involvement than in those with isolated ileal disease
- Adult males are twice as likely to develop an abscess and/or fistula compared with women

Etiology

- An infected anal crypt gland
- Crohn disease
- Lymphogranuloma venereum: chronic infection in the lymphatic system caused by Chlamydia trachomatis
- Radiation proctitis: Pelvic radiation
- Actinomycosis: in immunocompromised patients
- Obstetric injury: prolonged labor
- Rectal foreign bodies

Pathogenesis

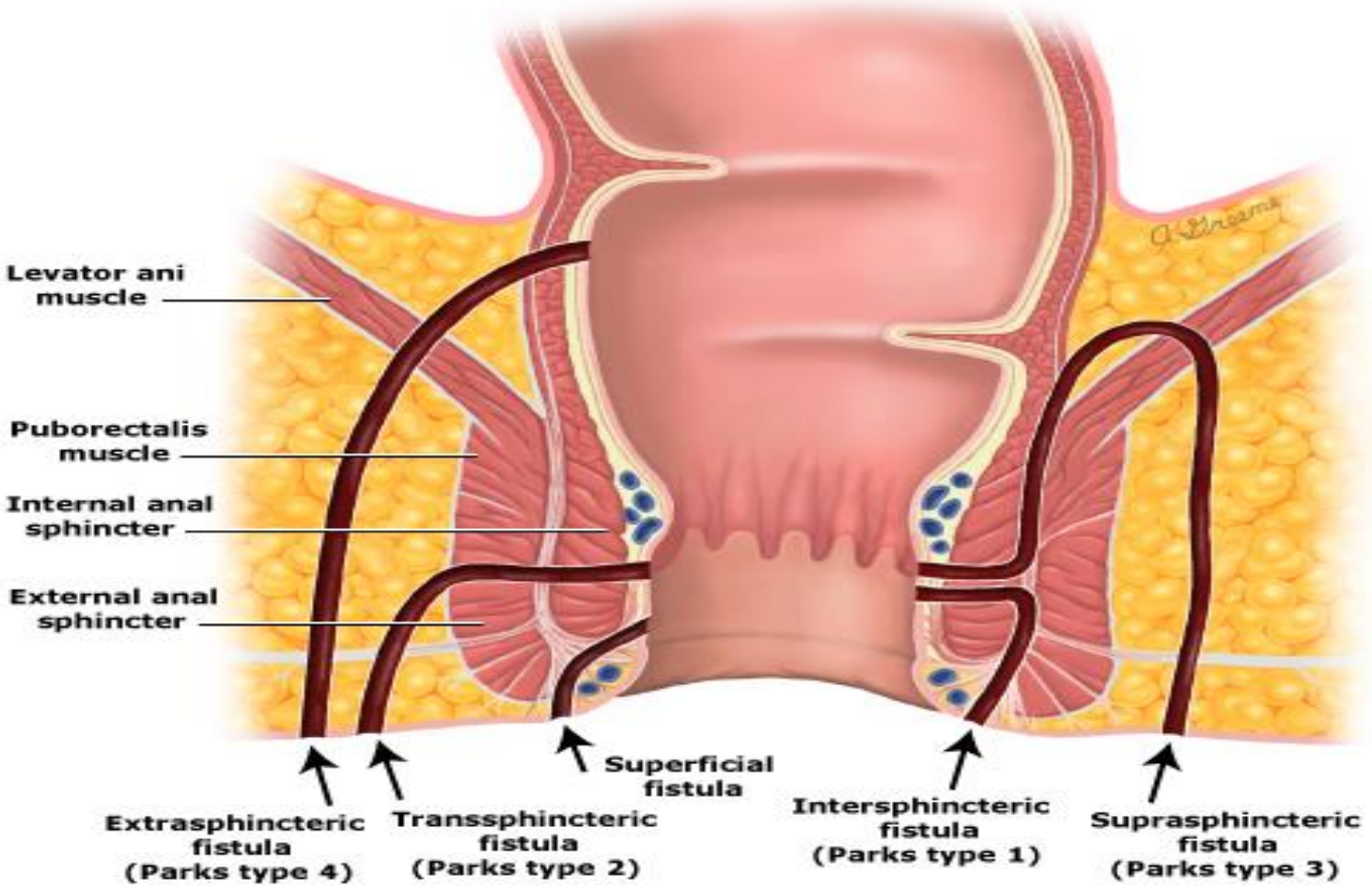


Classification

Relationship to the anal sphincter muscles:

- Intersphincteric
- Transsphincteric
- Suprasphincteric
- Extrasphincteric
- Superficial

Classification



Perianal complications in Crohns disease

- “Nonhealing" anorectal abscess following drainage
- Chronic purulent drainage and a pustule-like lesion
- Intermittent rectal pain and pruritis
- Bleeding

Prognosis

- Anorectal abscesses
- Anal stenosis
- Hemorrhoids
- Risk of Adenocarcinoma

Management principles

- Why is it challenging?

  - Active rectal inflammation
  - Persistence of inflammation
  - Mechanical abnormalities in the perineum

Management principles

- Combined medical-surgical management constitutes the best approach to achieve fistula healing
- 33 percent remained asymptomatic despite continued presence of the fistula
- 38 percent had spontaneous healing during 10 years of follow-up

- Symptomatic relief
  - Decrease fecal soilage by reducing diarrhea
  - Sitz baths
  - No excessive wiping or astringent use

Management principles

- Antibiotics
- Uncontrolled case series
- Only if symptomatic measures were not successful in 5 days
  - Metonidazole
  - Ciprofloxacin
  - Combination
- Topical nitroglycerin or calcium channel blockers

Severe/ Complex fistulizing disease

- Thiopurines (Conventional therapy)
  - **Azathioprine**
    - *Monotherapy:* 2 to 2.5 mg/kg/day; begin within 2 to 4 weeks after surgery and continue for 12 to 24 months
    - *Combination therapy (in combination with metronidazole):* 100 mg daily (<60 kg) **or** 150 mg daily (≥60 kg) for up to 52 weeks
    - Oral: 1.5 to 2.5 mg/kg/day in combination with an anti-TNF agent (eg, adalimumab, infliximab)
  - **6-Mercaptopurine**
    - 1.5 mg/kg/day (in combination with metronidazole) for ~18 months after surgery
    - Oral: 0.75 to 1.5 mg/kg/day in combination with an anti-TNF agent

Severe/ Complex fistulizing disease

- Anti-TNF agents

  - **Infliximab (IFX)**
    - IV: 5 mg/kg at 0, 2, and 6 weeks, followed by 5 mg/kg every 8 weeks thereafter; dose may be increased to 10 mg/kg in patients who respond but then lose their response.
    - If no response by week 14, consider discontinuing therapy

  - **Adalimumab (ADA)**
    - SQ: Initial: 80 mg (given on day 1), then 40 mg 2 weeks later (day 15)
    - Maintenance: 40 mg every week **or** 40 mg every other week beginning day 29

Severe/ Complex fistulizing disease

- Alpha-4-beta-7 integrin monoclonal antibody

  - **Vidolizumab (VDZ)**
    - selectively modulating leucocyte trafficking to the bowel
    - IV: 300 mg at 0, 2, and 6 weeks and then every 8 weeks thereafter
    - Discontinue therapy in patients who show no evidence of therapeutic benefit by week 14.
    - (GEMINI) 2 trial, (OBSERV-IBD), (ENTERPRISE) trial

  - **Certolizumab pegol (CZP)**
    - SubQ: Initial: 400 mg, repeat dose 2 and 4 weeks after initial dose
    - Maintenance: 400 mg every 4 weeks

Severe/ Complex fistulizing disease

- **<u>Ustekinumab (UST)</u>**
  - blocks the p40 subunit shared by both interleukins (IL-12 and IL-23)
  - Inhibition of the inflammatory cascade through multiple pathways and consequently reduces systemic inflammation
  - Induction: IV: (weight- based) 260-520 mg
  - Maintenance: SubQ: 90 mg every 8 weeks; begin maintenance dosing 8 weeks after the IV induction dose
  - (UNITI) trial, (IM-UNITI) trial, (CERTIFI)

Severe/ Complex fistulizing disease

Main studies with efficacy data from biological agents in PFCD					
Agent	Author (YOP)	Type of study	Fistula closure as primary endpoint	Number of patients	Fistula closure (%)
IFX	Present et al (1999)	Randomized controlled trial	Yes	94	55%
IFX	Sands et al (2004)	Randomized controlled trial	No	282	36%
ADA	Colombel et al (2009)	Post hoc analysis	No	70	60%
CZP	Schreiber et al (2011)	Post hoc analysis	No	28	36%
VDZ	Sandborn et al (2013)	Post hoc analysis	No	17	41.2%
UST	Sands et al (2017)	Post hoc analysis	No	37	24.7%

Keeping in mind

- Optimized dosing of Anti-TNF therapy
- Combination of anti-TNF therapy and surgery
- Local injections of anti-TNF agents?
- Future strategies: cell-based therapy for PFCD
- The role of endoscopy in the management of PFCD: Endoscopic fistulotomy, Endoscopic drainage, clipping and suturing..etc
- Fibrin glue injections

Additional Literature/References

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