ANAL FISSURE

CHI Formulary Development Project

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- IDF-FR-WI-01-01SearchMethodologyGuideForNewIndications

Abbreviations

ACG	American College of Gastroenterology
AF	Anal Fissure
ASCRS	American Society of Colon and Rectal Surgeons
ATC	Anatomical Therapeutic Chemical
CADTH	Canadian Agency for Drugs and Technologies in Health
CCB	Calcium Channel Blocker
CHI	Council of Health Insurance
EMA	European Medicines Agency
FDA	Food and Drug Administration
FI	Fecal Incontinence
GI	Gastrointestinal
HAS	Haute Autorite de Sante
HIV	Human Immunodeficiency Virus
HTA	Health Technology Assessment
IBD	Inflammatory Bowel Disease
ICD	International Classification of Diseases
IDF	CHI Drug Formulary
IQWIG	Institute for Quality and Efficiency in Health Care
KSA	Kingdom of Saudi Arabia
LIS	Lateral Internal Sphincterotomy
MHRA	Medicines and Healthcare products Regulatory Agency
N/A	Not Applicable
NICE	National Institute for Health and Care Excellence
PBAC	Pharmaceutical Benefits Advisory Committee
PMDA	Pharmaceuticals and Medical Devices Agency
RAC	Russian Association of Coloproctologists
REMS	Risk Evaluation and Mitigation Strategies
SFDA	Saudi Food and Drug Authority

Executive Summary

The term **anal fissure** (AF) refers to a linear tear within the anal canal that usually extends from the dentate line toward the anal verge. Although this **benign anorectal condition** is commonly encountered in practice, there is a paucity of population-level data describing its incidence[1].

Trauma and irritation to the anal canal, often precipitated by either constipation or diarrhea, can lead to development of anal fissure. The primary **symptom** associated with anal fissures is anal pain, provoked by defecation, and may last for several hours after defecation. The pain is usually sharp, feels like a tearing sensation or "passing glass", and can be debilitating because of its intensity. Anorectal bleeding may also be present, typically bright red when wiping. An anal fissure is a clinical **diagnosis** made essentially by physical exam alone, which must be done to rule out other possible causes of rectal pain.

Anal fissures are most commonly located in the posterior midline (73%) but can be found in the anterior midline in 13% of women and 8% of men, with 2.6% occurring both anteriorly and posteriorly simultaneously[2]. It is one of the most common diseases. It accounts for 10–15% of all coloproctological diseases, the incidence ranges from 20 to 23 per 1,000 in 2018 adult population[3]. The disease most often develops between the ages of 30 to 50 years, which determines its social significance[4]. The incidence among males and females is comparable. According to literature, the incidence of anorectal diseases including anal fissures in the general population in the **Kingdom of Saudi Arabia (KSA) is 5-15%[5].**

Lateral fissures or multiple fissures are considered to be an **atypical presentation** and require a more comprehensive evaluation because of the association with HIV infection, Crohn's disease, syphilis, tuberculosis, and hematologic malignancies.

Anal fissure can be classified:

1. **By the disease time**:
   - Acute
   - Chronic
2. **By site of the tear in the anal canal**:
   - Posterior
   - Anterior
   - Lateral
3. **By the spasming of the internal sphincter**:
   - With spasming
   - Without spasming (most often occur due to the complications or are secondary manifestations of another disease).

Acute fissures, defined as symptoms present for **< 6 weeks**, will appear as a longitudinal tear. **Fissures of a longer duration** will often manifest 1 or more stigmata of chronicity, including a hypertrophied anal papilla at the proximal aspect of the fissure, a sentinel tag at the distal aspect of the fissure, and/or exposed internal anal sphincter muscle within the base of the fissure. The **pathogenesis** of chronic fissures arises from underlying hypertonicity of the internal anal sphincter, leading to local ischemia and impaired wound healing[6].

A **study** investigating the prevalence of anal fissure and its manifestations and causes among young general population of **Eastern Governorate in KSA** has shown that AF is a common clinical problem, more common in males. Constipation is the most commonly associated comorbidity. Herbal remedies were the most common method for treatment followed by laxatives, topical ointments, analgesics and topical anesthetics[7].

This report compiles all clinical and economic evidence related to anal fissure according to the relevant sources. The ultimate objective of issuing AF guidelines by the Council of Health Insurance is to update the IDF (CHI Drug Formulary) with the **best available clinical and economic evidence related to drug therapies, ensuring timely and safe access to AF patients in Saudi Arabia**. The main focus of the review was on North American, European, and international guidelines (World Society of Emergency Surgery) issued within the last five years.

While some guidelines are more general and describe only AF management, some other are mainly related to the clinical examination; diagnosis; prevention and rehabilitation post-surgery with specific therapeutic management. To elaborate, **North American guidelines** included the American Society of Colon and Rectal Surgeons (ASCRS) recommendations and the American College of Gastroenterology (ACG) guidelines. ASCRS recommendations further elaborated on the initial management of acute anal fissure and the protocol to adopt for chronic ones. The ACG recommendations provided insight on the treatment of acute AF and the management of chronic AF with topical therapies, minimally invasive procedures and surgical interventions. The **European guideline** published by the Russian association of coloproctologists has focused on the clinical examination, instrumental diagnosis tests, treatment of acute and chronic anal fissures and the medical rehabilitation post-surgery. **International guideline** drew focus on the management of acute anal fissure in an emergency context.

Main recommendations issued by different **Health Technology Assessment** (HTA) bodies on the use of the current medications in AF were reviewed and summarized. These include the National Institute for Health and Care Excellence (NICE), the Canadian Agency for Drugs and Technologies in Health, Haute Autorité de Santé (HAS), the Institute for Quality and Efficiency in Healthcare (IQWIG), and the

Pharmaceutical Benefits Advisory Committee (PBAC). Section 3 lists the key recommendations synthesis for AF treatment.

The management of AF involves a **multidisciplinary approach** and greatly differs based on the type of AF (acute or chronic). The number of drugs that are sFDA approved for the management of anal fissure is still **limited**. KSA has access to 4 approved treatments only (Botulinum toxin A; Psyllium; topical anesthetic and topical Metronidazole). Section 2 provides a full description of each with final statements on the placement of therapy. All recommendations are well supported by reference guidelines, Grade of Recommendation (GoR), Level of Evidence (LoE) and Strength of Agreement (SoA) reflecting specific drug class role in the management of PE.

The goal of the treatment of anal fissure is to break the cyclic anal sphincter spasm, prevent tearing of the anal mucosa, and promote healing of the fissure[8].

The strongest recommendations include:

- As the first step in therapy, sitz baths and fiber supplements such as psyllium will heal about half of all patients with acute anal fissure, with or without the use of topical anesthetics or anti-inflammatory ointments. In addition to fissure repair, symptomatic pain and bleeding alleviation can be accomplished with almost no adverse effects.
- Local application of a calcium channel blocker should be the initial medical treatment of chronic anal fissure.
- Botulinum toxin A injections may be attempted in patients in whom calcium channel blocker (CCB) therapy fails or as an alternative option to CCB.
- Lateral internal sphincterotomy (LIS) is the surgical treatment of choice for chronic anal fissures that do not heal with nonsurgical measures.

Major recommendations for suggested **SFDA-registered** drug therapies are summarized in table 1 below:

Table 1. Major Recommendations for the Management of Anal Fissure

Medication	Indication	Level of Evidence/ Recommendation	HTA Recommendations
Botulinum Toxin A	In patients in whom CCB fails or as an alternative option to CCB	Conditional recommendation; quality of evidence: low).	No cost-effectiveness studies were identified. Botulinum toxin type A injection is less

			effective than surgery, no better or worse than topical nitrates and no better than placebo or lidocaine at healing anal fissure.
Psyllium	Stool softener for acute AF. First line treatment after diet management for acute AF.	Strong recommendation based on moderate-quality evidence, 1B	No HTA analysis was conducted for psyllium by the concerned HTA bodies.
Topical Lidocaine	First line treatment for acute AF alone or in addition to a bulking laxative	Strong recommendation based on moderate-quality evidence, 1B	No evidence was identified regarding the cost-effectiveness of topical anesthetics for patients undergoing dermatological procedures.
Topical Metronidazole	Used if there is a risk of poor medication compliance or poor genital cleanliness	Weak recommendation based on very low-quality evidence, 2D	The HTA bodies did not issue any recommendation on the cost effectiveness of Metronidazole

Section 1.0 Summary of Reviewed Clinical Guidelines and Evidence

1.1 KSA Guidelines

To date, there are no guidelines published by Saudi medical bodies on the management of anal fissures.

1.2 North American Guidelines

Multiple organizations have published guidelines for the management of Anal Fissure, most notably the American Society of Colon and Rectal Surgeons (ASCRS) in 2022 and the American College of Gastroenterology (ACG) in 2021. Recommendations of those guidelines are detailed in the following section.

1.2.1 American Society of Colon and Rectal Surgeons (ASCRS) Clinical Practice Guidelines for the Management of Anal Fissures (2023)

The main recommendations included in the ASCRS clinical practice guidelines are detailed below [9].

Table 2 details the recommendations that have been updated by ASCRS in comparison to the 2017 guidelines.

Table 2. Updated Recommendations in the 2023 ASCRS Anal Fissure Clinical Practice Guideline *(Adapted from ASCRS Guidelines)*

2022 Updated Recommendations
2. Anal fissures may be treated with topical nitrates, although headache symptoms may limit their efficacy (strong recommendation based on moderate-quality evidence, 1B)
3. Compared with topical nitrates, the use of calcium channel blockers for chronic anal fissures has a similar efficacy, with a superior side-effect profile, and can be used as first-line treatment (strong recommendation based on moderate-quality evidence, 1B)
4. Botulinum toxin has similar results compared with topical therapies as first-line therapy for chronic anal fissures and modest improvement in healing rates as second-line therapy following failed treatment with topical therapies (strong recommendation based on moderate-quality evidence, 1B)

8. Lateral internal sphincterotomy tailored to the length of the fissure yields similar healing rates but decreased fecal incontinence rates compared with traditional lateral internal sphincterotomy extending to the dentate line (strong recommendation based on high-quality evidence, 1A)

Management of Acute Anal Fissure

- **Nonoperative therapy** of acute anal fissures is safe and should usually be used initially: Nonoperative methods such as **sitz baths** and the use of **laxatives** such as psyllium fiber or other bulking agents, with or without the addition of topical **anesthetics** or topical **steroids**, relieved the symptoms of nearly half of all patients with an acute anal fissure (strong recommendation based on moderate-quality evidence, 1B).

Management of Chronic Anal Fissure

- Chronic anal fissures necessitate a **customized strategy** since long-term effects of surgical treatment, such as **fecal incontinence** (FI), may not be apparent for several years (strong recommendation based on moderate-quality evidence, 1B).
- **Topical nitrates** can be used to treat anal fissures, albeit **headache** symptoms may restrict its effectiveness: Topical nitroglycerin has been linked to healing in around 50% of chronic anal fissures. Headache affects at least 30% of treated patients, is practically universal in some reports, and causes up to 20% of patients to discontinue medication. Higher doses were not connected with faster healing rates (strong recommendation based on moderate-quality evidence, 1B).
- When compared to topical nitrates, **calcium channel blockers** have comparable efficacy, a better side-effect profile, and can be used as **first-line** treatment for chronic anal fissures. Because topical calcium channel blockers have fewer systemic side effects, they are preferable. In terms of headache occurrence, **diltiazem** was better tolerated than glyceryl trinitrate (strong recommendation based on moderate-quality evidence, 1B).
- **Botulinum toxin A** provides similar results to topical therapies as first-line therapy for chronic anal fissures and a small improvement in healing rates as second-line therapy after topical therapies fail. There is no agreed-upon procedure for botulinum toxin dose or injection techniques (strong recommendation based on moderate-quality evidence, 1B).
- The use of **topical nitroglycerin in conjunction with botulinum toxin** has been recommended to promote healing and symptoms in people suffering from chronic anal fissure (strong recommendation based on moderate-quality evidence, 1B).

- In chosen **pharmacologically naive patients with persistent anal fissure**, **lateral internal sphincterotomy** (LIS) may be provided. Patients who have had their symptoms for more than a year are less likely to react to medical treatment. Given poor compliance and higher rates of persistent fissures with nonoperative management, as well as evidence of long-term fecal continence and quality of life preservation in the vast majority of patients after LIS, LIS can be safely offered as **first-line therapy for chronic anal fissures in patients without underlying FI** (strong recommendation based on high-quality evidence, 1A).
- Women with prior obstetrical injuries, patients with IBD, patients who have had previous anorectal procedures, and patients with a documented anal sphincter injury may be **excluded** from receiving LIS as first-line therapy (strong recommendation based on high-quality evidence, 1A).
- In selected patients **without baseline FI**, LIS is the treatment of choice for chronic anal fissures: In patients who do not have preoperative incontinence to gas or stool, it remains the most effective surgical technique (strong recommendation based on high-quality evidence, 1A).
- An advancement **flap** may be considered as an alternate surgical treatment for patients with **baseline preoperative FI and insufficient response to previous treatment** (strong recommendation based on high-quality evidence, 1A)
- Both **open and closed LIS approaches** produce comparable results, and any technique can be employed: open sphincterotomy can be linked with significantly higher postoperative pain scores and a 4.4% delayed healing rate of the surgical site at 1-year follow-up (strong recommendation based on high-quality evidence, 1A).
- When compared to typical LIS that extends to the dentate line, LIS customized to the length of the fissure offers equivalent healing rates but lower FI rates: **Tailored sphincterotomy** was proposed to lower the rate of FI after traditional LIS, which was defined as transecting internal sphincter muscle as far proximally as the dentate line (strong recommendation based on high-quality evidence, 1B)
- **Anocutaneous flap** is a safe surgical option for treating chronic anal fissures, with a lower risk of FI than LIS and comparable healing rates: An anocutaneous flap is an **alternate sphincter-preserving surgical technique** for patients with chronic anal fissure who are at higher risk of FI after LIS (weak recommendation based on moderate-quality evidence, 2B).

- An **anocutaneous flap added to botulinum toxin injection or LIS** may reduce postoperative pain and allow for primary wound healing (weak recommendation based on low-quality evidence, 2C).

1.2.2 American College of Gastroenterology (ACG) Clinical Guidelines for the Management of Benign Anorectal Disorders (2021)

The American College of Gastroenterology (ACG) published in 2021 its clinical guideline for the management of benign anorectal disorders where anal fissure was one of the diseases that were tackled, explaining the management of acute anal fissure, chronic anal fissure, minimally invasive procedures, and surgical intervention[10].

Table 3. Current Concepts of Chronic Anal Fissures

Chronic anal fissures are defined as lasting more than 8-12 week and are characterized by edema and fibrosis
Chronic anal fissures persist as nonhealing ulcers by anal sphincter spasm and consequent ischemia. Treatment is typically directed toward softening stool and reducing spasm to improve perfusion to this area.

Management of Acute Anal Fissure

- As the first step in therapy, **sitz baths** and **fiber supplements** such as psyllium will heal about half of all patients with **acute anal fissure**, with or without the use of **topical anesthetics** or **anti-inflammatory ointments**. In addition to fissure repair, symptomatic pain and bleeding alleviation can be accomplished with almost no adverse effects (Strong recommendation; quality of evidence: high).

Management of Chronic Anal Fissure

- Treatment with **topical nitrates** is marginally superior to placebo in the repair of chronic anal fissure with a short-term decrease in anal pressures (Strong recommendation; quality of evidence: low).
- The initial medical treatment for persistent anal fissures should be local administration of a **calcium channel blocker** (such as nifedipine or diltiazem). Side effects such as headache occur less frequently than with topical nitrates (Strong recommendation; quality of evidence: low).
- **Oral calcium channel blockers** may be as effective as topical ones, implying that it is the drug rather than the route of administration that is important; topical healing rates were 90%, while oral healing rates were 76% and side

effects were not significantly increased with the oral route (Strong recommendation; quality of evidence: low).

- **Diltiazem cream** 2% had less side effects than topical nitroglycerin and was favored over nitroglycerin (Strong recommendation; quality of evidence: low).

Minimally Invasive Procedures

- **Botulinum toxin A** injections should be tried in individuals **who fail CCB or as an alternative to CCB**: Doses of 5-100 units have been shown to have higher healing rates than placebo, despite the disadvantage of having a needle injection in a sensitive location. Temporary incontinence of flatus in up to 18% and of stool in 5% is the most common side effect (Conditional recommendation; quality of evidence: low).
- In patients with **refractory anal fissure**, topical nitrate treatments may enhance the benefits of botulinum toxin. Female sex, satisfaction with the first procedure, and a lower body mass index may all be predictors of efficacy (Conditional recommendation; quality of evidence: low)

Surgical Interventions

- **LIS** is the preferred surgical treatment for chronic anal fissures that do not heal with nonsurgical treatments: Patients who **do not respond to medicinal treatment or botulinum toxin** injection might be considered for LIS (Strong recommendation; quality of evidence: high)
- There is no difference in outcome between **open and closed sphincterotomy**, hence a minimal-incision method is likely to be favored. However, there is a small but real risk of FI from LIS (Strong recommendation; quality of evidence: high)
- When anal pressures are not high, LIS should be used with caution, however these assessments are normally made exclusively by digital examination. **Anal advancement flap repair or a V-Y plasty** would be advised in such circumstances (Strong recommendation; quality of evidence: high).
- Medical management is suggested in **Crohn's** disease patients, and LIS should be **used with extreme caution** (Strong recommendation; quality of evidence: high)
- **Refractory chronic anal fissures** should be treated with calcium channel blockers first; the significance of botulinum toxin is unknown. In individuals with rectal sparing disease and normal resting and squeeze pressures, LIS may be considered (Strong recommendation; quality of evidence: high).

Table 4. Treatment Recommendations for Chronic Anal Fissures

We recommend that local application of a calcium channel blocker should be the initial medical treatment of chronic anal fissure (strong recommendation; quality of evidence: low)
We suggest that botulinum toxin A injections may be attempted in patients in whom CCB fails or as an alternative option to CCB (Conditional recommendation; quality of evidence: low).
We recommend that LIS is the surgical treatment of choice for chronic anal fissures that do not heal with nonsurgical measures (strong recommendation; quality of evidence: high).

The ACG guidelines looked at multiple trials to assess the efficacy and reported adverse effects of various treatment options used for the management of chronic anal fissures. These are detailed in table 5, where the range encompasses data reported by the different studies.

Table 5. Summary of Treatment Options for Chronic Anal Fissures *(Adapted from the ACG 2021 Guideline)*

Management	Efficacy	Adverse effects
Nitroglycerine	50% with 0.1% GTN group 36% with 0.2% GTN group 57% with 0.4% GTN group	Headaches 6%-20%
Diltiazem	68%	Mild headache 20%
Botulinum toxin A	Healing 47%-67% <u>Recurrence</u>: 2 months 12% 6 months 16% 1 year 24% 2 years 1% 3 years 0%	• Incontinence 6%-7% • Hematoma and fistula 3% • Ecchymosis and itching
Lateral internal sphincterotomy (LIS)	Healing 94%-98%	• Urinary incontinence 4%-16% • Urinary retention 44% • Delayed wound healing 4%

GTN: Glyceryl Trinitrate

1.3 European Guidelines

1.3.1 The Russian Association of Coloproctologists (RAC) Clinical Guidelines for the Management of Anal Fissure (2021)

The Russian Association of Coloproctologists (RAC) guideline for the management of anal fissure explains in detail the clinical examination, diagnostic tests, the treatment of acute anal fissure and the management of chronic anal fissure[11].

Clinical Examination

- All patients with suspected anal fissures should have a **physical examination** to confirm the diagnosis: Visual inspection of the perianal skin and anus, as well as a **digital examination**: attention should be paid to changes in the perianal skin (wetness, rashes, etc.), the shape of the anus, its gap, the presence of scarring and deformities, as well as the condition of the inguinal lymph nodes (Grade of recommendation – C; Level of evidence - 4).
- It is necessary to determine the presence of clinical signs of spasming of the internal sphincter, characteristic of anal fissure (Grade of recommendation – C; Level of evidence - 4).

Instrumental Diagnostic Tests

- Because of the existence of severe pain syndrome, **anoscopy, proctoscopy, and colonoscopy** are not suggested for individuals with anal fissure: if necessary, these tests should be performed in the surgery room under anesthesia (Grade of recommendation – C; Level of evidence - 5).
- In patients with anal fissures who do not have apparent clinical indicators of internal sphincter spasming, it is recommended to research anal sphincter functions using **sphincterometry** to objectify the presence of internal sphincter spasming (Grade of recommendation - C; Level of evidence - 4).
- Spasming of the internal sphincter is confirmed in the presence of at least one of the following **manometric signs**: Increase of the mean pressure in the anal canal at rest or the presence of ultra-slow waves (Grade of recommendation – C; Level of evidence - 4).
- In patients with anal fissure, if there are no clear clinical signs of internal sphincter spasming based on clinical examination, it is recommended to check sphincter functions using **profilometry**, as this test is a more sensitive method for diagnosing the presence of internal sphincter spasming (Grade of recommendation - C; Level of evidence - 3).

- **Endoanal ultrasound and colonoscopy** are recommended for patients with anal fissure, in the absence of signs of the rectal internal sphincter spasming, according to physical and instrumental examination, and suspected presence of erosive and ulcerative lesions of the anal canal of specific etiology, as well as the development of complications (Grade of recommendation - C; Level of evidence - 5)

Treatment of Acute Anal Fissure

- All individuals with acute anal fissure should be treated **conservatively** (Grade of recommendation – A; Level of evidence - 1)
- **Diet therapy and normalization of the gastrointestinal tract** function with the use of laxatives should be preferred is patients with acute anal fissure: Consuming an adequate amount of **fluid** (liquids up to 1.5–2 liters per day) and dietary **fiber** (daily intake of 25 grams of dietary fiber) is indicated to restore gastrointestinal tract function and eliminate constipation. In cases where it is not possible to normalize the stool by food, **laxatives** (drugs containing the shell of plantain seeds or polyethylene glycol) should be used to help the patient generate a regular mushy stool (Grade of recommendations - C; Level of evidence - 5).
- Conservative therapy aimed at pain relief and healing the defect is recommended: both **systemic and topical agents** are used in the form of gels, creams, ointments, and suppositories (Grade of recommendation - C; Level of evidence - 5).
- Agents from the group of **propionic acid derivatives** or **local anesthetics** are used with severe pain syndrome (Grade of recommendation – C; Level of evidence - 5).
- It is recommended to inject **botulinum toxin type A** (total dosage from 10 units to 100 unit) into the spasming internal anal sphincter of patients with acute anal fissures: Clinical manifestations of anal incontinence are observed in 5.1%, they disappear within up to 8 weeks (Grade of recommendation – B; Level of evidence - 2).

Treatment of Chronic Anal Fissure

- **Conservative treatment** is indicated for patients with chronic anal fissure for the aim of symptomatic therapy, and if surgery is refused, in accordance with the recommendations for the treatment of acute anal fissure (Grade of recommendation - B; Level of evidence - 2).
- Patients should not get conservative therapy **for more than 8 weeks** (Grade of recommendation - B; Level of evidence - 2).

- Patients with chronic anal fissures should have **surgery**. The surgery for persistent anal fissure includes **fissure excision and several ways of internal sphincter relaxing** (Grade of recommendation – B; Level of evidence - 2).
- In patients with chronic anal fissures, sphincter spasms, and a high risk of anal incontinence after surgery (elderly patients, multiple and complicated childbirths in the past, clinical signs of perineal descent), **fissure excision combined with non-operative internal sphincter relaxation with botulinum toxin type A is recommended** (Grade of recommendation - B; Level of evidence - 2).
- If fissure excision is ineffective in combination with drug relaxation of the internal sphincter in patients with chronic anal fissure with sphincter spasming, it is indicated to combine it with **lateral internal sphincterotomy** (Grade of recommendation - A; Level of evidence - 1).
- Sphincterotomy should be **excluded** in patients with a high risk of persistent anal incontinence in the postoperative period (elderly patients, multiple and complicated childbirth in the history, clinical signs of the pelvic floor descent) (Grade of recommendation - A; Level of evidence - 1).
- **Lateral internal sphincterotomy** is the 'gold standard' of anal fissure treatment. The rate of fissure healing after sphincterotomy is from 88% to 100%, with the rate of anal incontinence — from 8% to 30%, with follow-up to 6 years (Grade of recommendation - A; Level of evidence 1).
- Oral or injectable **antibacterial drugs** acting on the intestinal flora and in soft tissues are advised for patients after surgery for anal fissure in the presence of significant wounds and immune status abnormalities (Grade of recommendation - C; Level of evidence - 5).
- It is recommended that all patients who have had anal fissure surgery perform daily **dressings** in the postoperative phase till wound healing by **cleansing wounds with antiseptic solutions** and applying ointment with anti-inflammatory and wound healing effects (Grade of recommendation – C; Level of evidence - 5).
- In the postoperative period until wound healing, all patients who have had surgery for anal fissure are advised to follow a **fiber-rich diet, taking dietary fiber to make a regular soft stool** (Grade of recommendation - C; Level of evidence - 5).
- To prevent recurrence and complications, all patients who have undergone surgery for anal fissure should be under the **observation** of a coloproctologist or a surgeon in their place of residence after discharge from the hospital, for

the duration of wound healing (Grade of recommendation – C; Level of evidence - 5).

- After surgery, several principles of **rehabilitation** should be followed:
  - ✓ Comprehensive assessment of the patient's initial condition and formulation of the rehabilitation program
  - ✓ Drawing up a plan of diagnostics and management necessary for rehabilitation;
  - ✓ Multidisciplinary approach for rehabilitation;
  - ✓ Monitoring the effectiveness of the management during the rehabilitation and at the end of the rehabilitation (Grade of recommendation - C; Level of evidence - 5)
- All patients who experience the **initial signs** of anal fissure are advised to consult a coloproctologist to establish preventive measures (normalization of the activity of the gastrointestinal tract, the elimination of constipation, compliance with the hygienic regime) aimed at preventing the disease's development and progression (Grade of recommendation – C; Level of evidence - 5)
- Following the completion of treatment and wound healing, all patients who have undergone anal fissure surgery should be followed up with a coloproctologist **once every 6 months** for the first year to improve disease control and prevent recurrence (Grade of recommendation – C; Level of evidence - 5)

Table 6. Criteria for Assessing the Quality of Medical Care

№	Quality Criteria	Level of evidence	Grade of recommendation
1	The patient's complaints and history were collected	2	A
2	A clinical examination was performed	2	A
	Patients with anal fissure, in the absence of clear clinical signs of the internal sphincter spasming according to clinical examination, underwent asphincterometry and/or profilometry.	4	C
3	For patients with anal fissure, in the absence of signs of the internal sphincter spasming, according to clinical and instrumental examination, and suspicion of erosive and ulcerative lesions of the anal canal of specific etiology, as well as the development of complications, it is recommended to perform by endoanal ultrasound and/or colonoscopy.	5	C
4	Conservative treatment of acute anal fissure was performed (taking into account the specific clinical situation).	2	B
5	Surgery for the chronic anal fissure was performed (taking into account the specific clinical situation, the ineffectiveness of conservative therapy, the presence of the internal sphincter spasming, fibrosis in the anal canal).	2	A
9	Absence of anal incontinence because of surgery.	1	A
10	Relief of pain after surgery for medical reasons.	2	A

Retrieved from Agapov MA, Aliev FS, Achkasov SI, et al. Анальная трещина. Колопроктология. 2021;20(4):10-21. doi:10.33878/2073-7556-2021-20-4-10-21.

1.3.2 The Spanish Association of Coloproctology and the Coloproctology Division of the Spanish Association of Surgeons Treatment Algorithm for Anal Fissure (2018)

The Spanish Association of Coloproctology and the Coloproctology Division of the Spanish Association of Surgeons published in 2018 a consensus document to aid with the decision making for non-surgical therapy and surgical treatment of anal fissure[12].

Hygiene and Dietary Treatment; Conservative Measures

The conservative treatment of AF is contemplated as an **initial therapeutic step**, both in the acute and chronic phases of this process.

1. A diet rich in **fiber** is recommended in the acute phase of AF, providing 25–30 g/day.
2. Maintained fiber intake is recommended to prevent recurrences of AF.
3. Fiber supplements (non-laxative) are recommended as a conservative treatment of AF.
4. **Sitz baths** with warm water (36–40 8C) for 10 min are recommended.
5. Sitz baths are recommended twice a day and after each bowel movement.
6. Adding other substances to the bath has not been demonstrated to be beneficial, so this recommendation is left to the criteria of the specialist.

Medical Treatment

Medical or pharmacological treatment should be aimed at achieving transitory relaxation of the internal anal sphincter.

1. Medical treatment of acute fissures is safe, has few side effects and should be the first-line treatment (Grade of recommendation 1).
2. **CCBs** have a similar effect on chronic AF as topical nitrates, butfewer side effects, and can be used as a first-line treatment (Grade of recommendation 1A).
3. **Botulinum toxin** has similar results for healing as other topical therapies as a first-line treatment in chronic AF and slightly better in terms of healing rates as a second-line option after topical treatment (Grade of recommendation 1C).
4. LIS is associated with clearly superior chronic AF healing rates compared to medical treatment.

Surgical Treatment

While surgical treatment is the **most effective long-term treatment** for chronic AF, it is the **second-line** treatment option after medical management. It may be indicated as a first-line option in young patients with severe untreatable acute proctalgia who accept the risk of fecal incontinence. LIS continues to be the surgical technique of choice. (Level of evidence 1A; grade of recommendation A)

1. Anal dilatation

The unacceptable risk of incontinence and inferiority as a technique compared to LIS have made it **obsolete** and no longer used.

2. Lateral internal sphincterotomy (LIS)

Healing rates vary from 92% to 100%, while early and late incontinence rates are 3.3% to 16%. Careful patient selection, absence of preoperative continence problems and meticulous surgical technique are necessary to achieve good results.

3. Advancement-flap anoplasty

The indications for this technique are the risk of incontinence (age, multiple childbirths, obstetric trauma, anorectal surgery) and the persistence of symptoms after conservative therapies or sphincterotomy. Studies did not find significant differences in the cure rates (98% advancement-flap anoplasty versus 100% LIS), with a lower risk of incontinence (0%–3.3%) and a lower rate of complications (dehiscence 5.9%) compared to LIS.

4. Fissurectomy

It can be considered a second-line therapy for chronic AF that is not cured with the use of topical therapy, or even as a first-line therapy for patients who have signs of chronic disease.

5. Fissurotomy

This technique allows for the cicatrization of the path, release of the perianal skin, as well as the widening of the anal canal, making sphincterotomy unnecessary. Incontinence is eliminated with a cure rate of 98.2%.

Figures 1 and 2 represent the treatment algorithms for the management of acute and chronic AF.

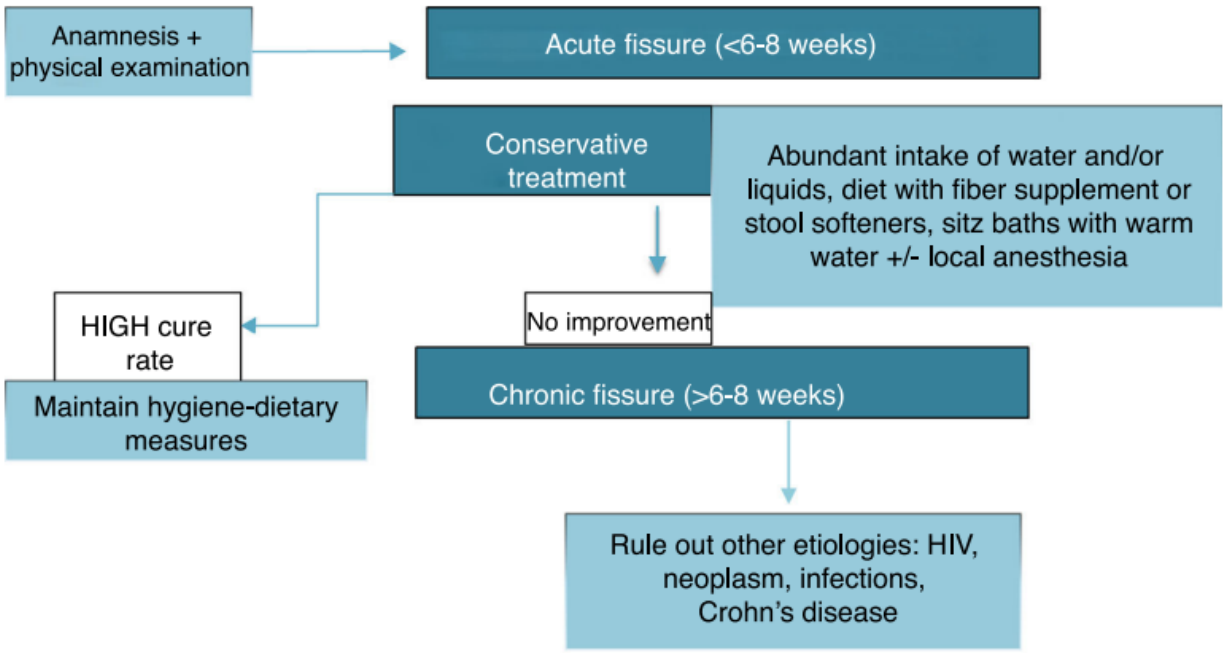

Figure 1. *Consensus Algorithm of the Spanish Association of Coloproctology and the Coloproctology Division of the AEC for the Management of Acute Anal Fissure. Retrieved from Arroyo A, Montes E, Calderón T, et al. Treatment Algorithm for Anal Fissure. Consensus Document of the Spanish Association of Coloproctology and the Coloproctology Division of the Spanish Association of Surgeons. Cirugía Española (English Edition). 2018;96(5):260-267. doi:10.1016/j.cireng.2018.05.008.*

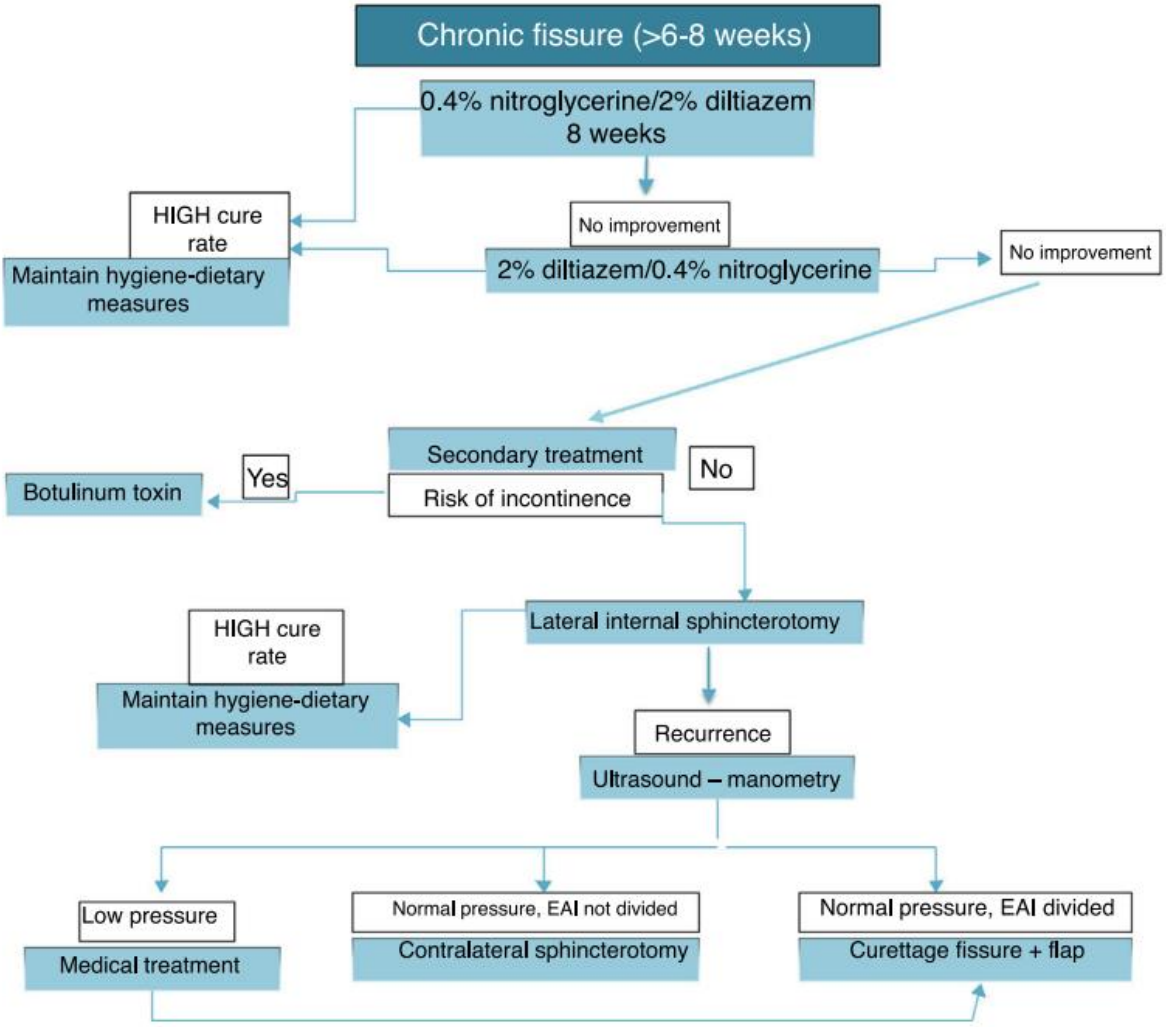

Figure 2. *Consensus Algorithm of the Spanish Association of Coloproctology and the Coloproctology Division of the AEC for the Management of Chronic Anal Fissure. Retrieved from Arroyo A, Montes E, Calderón T, et al. Treatment Algorithm for Anal Fissure. Consensus Document of the Spanish Association of Coloproctology and the Coloproctology Division of the Spanish Association of Surgeons. Cirugía Española (English Edition). 2018;96(5):260-267. doi:10.1016/j.cireng.2018.05.008.*

1.4 International Guidelines

1.4.1 World Society of Emergency Surgery (WSES)–American Association for the Surgery of Trauma (AAST) Guidelines for Anorectal Emergencies (2021)

This guideline summarizes the WSES and the AAST recommendations for the management of anorectal emergencies[13]:

- To rule out other reasons in patients with atypical acute anal fissure, collecting a **detailed medical history** and performing a full physical examination and laboratory tests depending on the suspected concomitant illness is recommended (Weak recommendation based on low-quality evidence, 2C).
- In patients with unusual acute anal fissure, **investigations** (endoscopy, CT scan, MRI, or endoanal ultrasound) should be performed only if there is a suspicion of inflammatory bowel disease, anal or colorectal malignancy, or occult perianal sepsis (Weak recommendation based on low-quality evidence, 2C).
- In patients who have had previous surgery, **anorectal manometry** may be needed, although it is typically too uncomfortable to do in the emergency scenario (Weak recommendation based on low-quality evidence, 2C).
- Non-operative management is recommended as the first-line treatment in patients with **acute anal fissure** (Strong recommendation based on moderate quality evidence, 1B).
- **Dietary and lifestyle** adjustments are recommended for patients with acute anal fissure, including increased fiber and water intake (Strong recommendation based on moderate quality evidence, 1B).
- Stool softeners, sphincter muscle relaxers and pain control represent the **cornerstones of non-operative management of anal fissure** (Strong recommendation based on moderate quality evidence, 1B).
- **Stool softeners** (increased intake of oral fluids, high fiber diet or fiber supplements, and bulk forming laxatives) are recommended (Strong recommendation based on moderate quality evidence, 1B).
- **Sphincter muscle relaxers** (warm sitz baths, local application of calcium channel blockers like Diltiazem or Nifedipine, local application of Nitrates like Nitroglycerin and Botulinum injection that determines a temporal paralysis of the anal sphincter muscle for 2–3 months) can be used in both acute and chronic anal fissure (Strong recommendation based on moderate quality evidence, 1B).
- In individuals with acute anal fissure, the use of **manual dilatation** is not recommended due to high risk of incontinence (Strong recommendation based on moderate quality evidence, 1B).
- In patients with acute anal fissure, combining **topical anesthetics** (lidocaine) with **typical pain relievers** (paracetamol or ibuprofen) if pain control is inadequate is recommended (Weak recommendation based on low-quality evidence, 2C).

- In patients with acute anal fissure, using **topical antibiotics** (metronidazole cream) if there is a risk of poor medication compliance or poor genital cleanliness is recommended. (Weak recommendation based on very low-quality evidence, 2D).
- **Surgical treatment** in patients with acute anal fissures is not recommended (Weak recommendation based on moderate quality evidence, 2B).
- In patients with anal fissures, **surgical therapy** is recommended in the chronic phase if they are unresponsive after 8 weeks of non-operative treatment (Strong recommendation based on moderate quality evidence, 1B).

Section 2.0 Drug Therapy

2.1 Topical Anesthetics

2.1.1 Lidocaine

Information on Lidocaine are detailed in the table below[14]:

Table 7. Drug Therapy with Lidocaine

SCIENTIFIC NAME **Lidocaine**	
SFDA Classification[15]	Prescription
SFDA Approval	Yes
US FDA[16]	Yes
EMA[17]	Yes
MHRA[18]	Yes
PMDA[19]	No
Indication (ICD-10)	K60.2
Drug Class	Local Anesthetic
Drug Sub-class	Analgesic
ATC Code	D04AB01
DRUG INFORMATION	
Dosage Form	Cream/Gel/Ointment
Route of Administration	Topical Use
Dose (Adult) [DDD]*	Apply to affected area up to 6 times daily
Maximum Daily Dose Adults*	5 %
Adjustment	Renal impairment prior to treatment: - No dosage adjustment is recommended by the manufacturer for any degree of reduced kidney function. Hepatic impairment prior to treatment: - No dosage adjustments provided in the manufacturer's labeling.
Prescribing edits*	N/A
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): N/A	

G (Gender Edit): N/A	
MD (Physician Specialty Edit): N/A	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): N/A	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	- Most common: Erythema; Petechia - Most serious: Pruritus; Anaphylaxis
Drug Interactions*	Antiarrhythmic Agents (Class IB): *Risk C: Monitor therapy* Cimetidine: *Risk C: Monitor therapy* Dapsone (Topical) and Nitric Oxide: May enhance the adverse/toxic effect of Methemoglobinemia Associated Agents. *Risk C: Monitor therapy*
Special Population	Acutely ill patients Elderly and debilitated patients Pediatric
Pregnancy	Lidocaine and its metabolites cross the placenta and can be detected in the fetal circulation. The amount of lidocaine absorbed topically varies by dose administered, duration of exposure, and site of application.
Lactation	Lidocaine is considered compatible with breastfeeding. The manufacturer recommends caution be used when administering topical lidocaine to breastfeeding women
Contraindications	- Hypersensitivity to lidocaine or any component of the formulation - Hypersensitivity to another local anesthetic of the amide type - Traumatized mucosa - Bacterial infection at the site of application

	- Tuberculous or fungal lesions of skin vaccinia - Varicella and acute herpes simplex
Monitoring Requirements	N/A
Precautions	- Hypersensitivity: Use with caution in patients with known drug sensitivities - Local effects: Irritation, sensitivity and/or infection may occur at the site of application; discontinue use and institute appropriate therapy if local effects occur. - Methemoglobinemia: Has been reported with local anesthetics; clinically significant methemoglobinemia requires immediate treatment along with discontinuation of the anesthetic and other oxidizing agents. Onset may be immediate or delayed (hours) after anesthetic exposure
Black Box Warning	Life-threatening and fatal events in infants and young children: Postmarketing cases of seizures, cardiopulmonary arrest, and death in patients under the age of 3 years have been reported with use of lidocaine 2% viscous solution when it was not administered in strict adherence to the dosing and administration recommendations.
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of Anal Fissure treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Lidocaine.**

Table 8. Lidocaine HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Lidocaine	NICE	N/A
	CADTH[20]	Two systematic reviews (1 with a network meta-analysis) were identified regarding the clinical effectiveness of topical anesthetics for patients undergoing dermatological procedures. **No evidence was identified regarding the cost-effectiveness of topical anesthetics** for patients undergoing dermatological procedures. One evidence-based guideline was identified regarding the use of topical anesthetics for dermatological procedures.
	HAS[21]	Approval of reimbursement for local contact anesthesia and lubrication for cystoscopy, catheterization, instrumental investigation procedures and other endourethral procedures for adult and adolescent male and female patients only. Disapproval of reimbursement for other marketing authorization indications.
	IQWIG	N/A
	PBAC	N/A

CONCLUSION STATEMENT – LIDOCAINE

In patients with acute anal fissure, combining topical anesthetics (lidocaine) with typical pain relievers (paracetamol or ibuprofen) if pain control is inadequate is recommended. Nonoperative methods such as sitz baths and the use of laxatives such as psyllium fiber or other bulking agents, with or without the addition of topical anesthetics or topical steroids, relieved the symptoms of nearly half of all patients with an acute anal fissure. Limitations for the use of lidocaine include hypersensitivity to lidocaine or any component of the formulation, hypersensitivity to another local anesthetic of the amide type, and traumatized mucosa and bacterial infection at the site of application.

2.2 Bulk-Forming Laxatives

2.2.1 Psyllium

Information on Psyllium are detailed in the table below:

Table 9. Drug Therapy with Psyllium

SCIENTIFIC NAME **PSYLLIUM**	
SFDA Classification	OTC
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	No
PMDA	No
Indication (ICD-10)	K59
Drug Class	Fiber Supplement
Drug Sub-class	Bulk-Forming Laxatives
ATC Code	A06AC01
DRUG INFORMATION	
Dosage Form	Granules
Route of Administration	Oral Use
Dose (Adult) [DDD]*	2.5 to 30 g per day in divided doses
Maximum Daily Dose Adults*	30 g
Adjustment	Renal impairment prior to treatment: - No dosage adjustment is recommended by the manufacturer for any degree of reduced kidney function. Hepatic impairment prior to treatment: - No dosage adjustments provided in the manufacturer's labeling.
Prescribing edits*	N/A
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): N/A	

PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): N/A	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	- Most common: Abdominal cramps, constipation, diarrhea, esophageal obstruction, intestinal obstruction - Most serious: Bronchospasm
Drug Interactions*	No known significant interactions
Special Population	Older adult: Use with caution in the elderly; may have insufficient fluid intake which may predispose them to fecal impaction and bowel obstruction.
Pregnancy	Psyllium is not absorbed systemically. When administered with adequate fluids, use is considered safe for the treatment of occasional constipation during pregnancy
Lactation	No available data
Contraindications	- Hypersensitivity to psyllium or any component of the formulation - fecal impaction - GI obstruction
Monitoring Requirements	N/A
Precautions	- Hypersensitivity reactions: Hypersensitivity reactions have been reported with ingestion or inhalation of psyllium in susceptible individuals. - Coronary heart disease (CHD): To reduce the risk of CHD, the soluble fiber from psyllium should be used in conjunction with a diet low in saturated fat and cholesterol. - Gastrointestinal disease: Use with caution in patients with esophageal strictures, ulcers, stenosis, or

	intestinal adhesions or difficulty swallowing - Administration: Products must be taken with at least 8 ounces of fluid in order to prevent choking. - Dosage form specific issues: Some may contain calcium, phenylalanine, potassium, sodium, or soy lecithin.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of Anal Fissure treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Psyllium.**

Table 10. Psyllium HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Psyllium	NICE	N/A
	CADTH	N/A
	HAS	N/A
	IQWIG	N/A
	PBAC	N/A

CONCLUSION STATEMENT – PSYLLIUM

Stool softeners such as bulk forming laxatives are recommended as a first line therapy for patients with acute anal fissure and are considered as a conservative treatment. Furthermore, psyllium laxatives are used after surgery in case of chronic anal fissure. No HTA analysis was conducted for psyllium by the concerned HTA bodies. Limitations for the use of oxylium include hypersensitivity to psyllium or any component of the formulation, and fecal impaction and gastrointestinal (GI) obstruction.

2.3 Neuromuscular Blocker Agents

2.3.1 Botulinum Toxin A

Information on Botulinum Toxin A are detailed in the table below:

Table 11. Drug Therapy with Botulinum Toxin A

SCIENTIFIC NAME **Botulinum Toxin A**	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	N/A
EMA	N/A
MHRA	Yes
PMDA	Yes; June 2015
Indication (ICD-10)	K64
Drug Class	Muscle Relaxants, Peripherally Acting Agents
Drug Sub-class	Neuromuscular Blocker Agent
ATC Code	M03AX01
DRUG INFORMATION	
Dosage Form	Powder for solution for injection
Route of Administration	Intramuscular use
Dose (Adult) [DDD]*	10 units of Botox (0.2 mL of 50 units per mL) each are injected into the internal anal sphincter on either side of the anal fissure with a 27-gauge needle
Maximum Daily Dose Adults*	0.4 mL
Adjustment	Renal impairment prior to treatment: - No dosage adjustment is recommended by the manufacturer for any degree of reduced kidney function. Hepatic impairment prior to treatment: - No dosage adjustments provided in the manufacturer's labeling.
Prescribing edits*	MD, ST
AGE (Age Edit): N/A	

CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): Only physicians specialized in gastroenterology and proctology should prescribe Botulinum Toxin A.	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): Botulinum toxin A injections should be tried in individuals who fail CCB or as an alternative to CCB. It can be added to topical nitrates in refractory cases.	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	- Most common: Bacteriuria; increased post-void residual urine volume; urinary tract infection; local soreness at injection site - Most serious: Upper respiratory tract infection
Drug Interactions*	- Aminoglycosides: *Risk C: Monitor therapy* - Anticholinergic Agents: *Risk C: Monitor therapy* - Muscle Relaxants (Centrally Acting): *Risk C: Monitor therapy* - Muscle Relaxants (Centrally Acting): the risk for increased muscle weakness may be enhanced. *Risk C: Monitor therapy*
Special Population	Older adult: Initiate therapy at lowest recommended dose.
Pregnancy	Botulinum toxin A has not been detected systemically in peripheral blood at recommended doses following intramuscular injection.
Lactation	It is not known if botulinum toxin A is present in breast milk.
Contraindications	Hypersensitivity to any botulinum toxin preparation or any component of the

	formulation; infection at the proposed injection site(s).
Monitoring Requirements	Detrusor overactivity associated with neurologic condition: Evaluate postvoid residual (PVR) urine volume within 2 weeks post-treatment and periodically thereafter up to 12 weeks in patients not catheterizing.
Precautions	- Anaphylaxis/hypersensitivity reactions: Serious and/or immediate hypersensitivity reactions (eg, anaphylaxis, serum sickness, urticaria, soft tissue edema, dyspnea) have occurred. - Antibody formation: Higher doses or more frequent administration may result in neutralizing antibody formation and loss of efficacy. - Cardiovascular events: Arrhythmia and myocardial infarction (some fatal) have been reported following administration. - Product interchangeability: Botulinum products (abobotulinumtoxinA, daxibotulinumtoxinA, incobotulinumtoxinA, onabotulinumtoxinA, prabotulinumtoxinA, rimabotulinumtoxinB) are not interchangeable; potency units are specific to each preparation and cannot be compared or converted to any other botulinum product.
Black Box Warning	Spread of toxin effect: Postmarketing reports indicate that the effects of all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects.

	These may include asthenia, generalized muscle weakness, diplopia, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence, and breathing difficulties.
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of Anal Fissure treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Botulinum Toxin A.**

Table 12. Botulinum Toxin A HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Botulinum Toxin A	NICE[22]	No cost-effectiveness studies were identified for the use of botulinum toxin type A to treat chronic anal fissure in a UK setting were identified. Evidence from 2 systematic reviews and 4 further randomized controlled trials (RCTs) suggests that botulinum toxin type A injection is less effective than surgery, no better or worse than topical glyceryl trinitrate (GTN; mostly 0.2% ointment) or isosorbide dinitrate, and no better than placebo or lidocaine at healing anal fissure. The Medicines and Healthcare products Regulatory Agency (MHRA) has warned healthcare professionals about the rare but serious risk of toxin spread when using all types of botulinum toxin.
	CADTH	N/A
	HAS	N/A
	IQWIG	N/A
	PBAC	N/A

CONCLUSION STATEMENT – BOTULINUM TOXIN A

Botulinum toxin A injections should be tried in individuals who fail CCB or as an alternative to CCB. It can be added to topical nitrates in refractory cases. According to NICE, botulinum toxin type A injection is less effective than surgery, no better or worse than topical nitrates and no better than placebo or lidocaine at healing anal fissure. Limitations for the use of Botulinum Toxin A include hypersensitivity to any botulinum toxin preparation or any component of the formulation; infection at the proposed injection site(s). The spread of toxin effect should be taken into consideration.

2.4 Topical Antibiotics

2.4.1 Metronidazole

Information on Metronidazole are detailed in the table below:

Table 13. Drug Therapy with Metronidazole

SCIENTIFIC NAME **Metronidazole**	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes, July 2005
EMA	No
MHRA	Yes
PMDA	No
Indication (ICD-10)	K60.2
Drug Class	Antibiotic
Drug Sub-class	Nitroimidazole
ATC Code	A01AB17
DRUG INFORMATION	
Dosage Form	Gel
Route of Administration	Topical Use
Dose (Adult) [DDD]*	Apply thin film to affected area once daily
Maximum Daily Dose Adults*	1 %
Adjustment	Renal impairment prior to treatment: - No dosage adjustment is recommended by the

	manufacturer for any degree of reduced kidney function. Hepatic impairment prior to treatment: - No dosage adjustments provided in the manufacturer's labeling.
Prescribing edits*	MD
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): Only physicians specialized in gastroenterology and proctology should prescribe topical metronidazole	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): N/A	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	- Most common: Headache; contact dermatitis; burning sensation of skin - Most serious: Hypertension
Drug Interactions*	Alcohol (Ethyl): Risk D: Consider therapy modification Tipranavir: Risk C: Monitor therapy
Special Population	N/A
Pregnancy	When used for the treatment of inflammatory lesions and erythema of rosacea, topical antibiotics, including metronidazole, are considered compatible with pregnancy
Lactation	When used for the treatment of inflammatory lesions and erythema of rosacea, topical antibiotics, including metronidazole, are considered compatible with breastfeeding
Contraindications	- Hypersensitivity to metronidazole, parabens, or other ingredients of the formulation or other nitroimidazole derivatives

	- use of alcohol or propylene glycol during therapy and for up to 24 hours after therapy discontinuation - use of disulfiram within the past 2 weeks
Monitoring Requirements	N/A
Precautions	- Carcinogenic: Possibly carcinogenic based on animal data. Unnecessary use should be avoided. - Eye irritation: May cause tearing of the eye; avoid contact with the eyes. In the event of accidental contact, wash out immediately.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of Anal Fissure treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable.

Table 14. Topical Metronidazole HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Metronidazole	NICE	N/A
	CADTH	N/A
	HAS	N/A
	IQWIG	N/A
	PBAC	N/A

CONCLUSION STATEMENT – METRONIDAZOLE

The HTA bodies did not issue any recommendation on the cost effectiveness of metronidazole.

In patients with acute anal fissure, using topical antibiotics (metronidazole cream) if there is a risk of poor medication compliance or poor genital cleanliness is recommended. Limitations for the use of Metronidazole include hypersensitivity to

metronidazole, parabens, or other ingredients of the formulation or other nitroimidazole derivatives, use of alcohol or propylene glycol during therapy and for up to 24 hours after therapy discontinuation, and the use of disulfiram within the past 2 weeks.

2.5 Calcium Channel Blockers (CCBs)

2.5.1 Diltiazem

Information on **oral** diltiazem is detailed in the table below:

Table 15. Drug Therapy with Oral Diltiazem

SCIENTIFIC NAME **Diltiazem**	
SFDA Classification	Prescription
SFDA Approval	No
US FDA	No
EMA	No
MHRA	No
PMDA	No
Indication (ICD-10)	K60.2
Drug Class	Calcium Channel Blocker
Drug Sub-class	Nondihydropyridine
ATC Code	C08DB01
DRUG INFORMATION	
Dosage Form	Tablets/Capsules
Route of Administration	Oral
Dose (Adult) [DDD]*	60 mg twice daily for 8 weeks
Maximum Daily Dose Adults*	120 mg
Adjustment	Renal impairment prior to treatment: - No dosage adjustment is recommended by the manufacturer for any degree of reduced kidney function. Hepatic impairment prior to treatment: - No dosage adjustments provided in the manufacturer's labeling.
Prescribing edits*	MD, ST

AGE (Age Edit): N/A	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): Only physicians specialized in gastroenterology and proctology should prescribe diltiazem for the treatment of anal fissure.	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): Oral diltiazem is a second-line option after the failure of topical therapies.	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	- Most common: Peripheral edema - Most serious: Bradycardia; complete atrioventricular block; hypotension
Drug Interactions*	- Ivabradine: Risk X: Avoid combination - Aprepitant/Fosaprepitant: Risk X: Avoid combination - Domperidone: Risk X: Avoid combination - Alprazolam: Risk D: Consider therapy modification - Budesonide: Risk X: Avoid combination (Topical); Risk D: Consider therapy modification (Systemic) - Colchicine: Risk D: Consider therapy modification - Strong CYP3A4 Inducers: Risk D: Consider therapy modification
Special Population	Older adult
Pregnancy	Adverse events have been observed in animal reproduction studies.
Lactation	- Diltiazem is present in breast milk - Due to the potential for serious adverse reactions in the breastfed infant, the manufacturer

	recommends a decision be made to discontinue breastfeeding or to discontinue the drug, considering the importance of treatment to the mother; however, other sources consider diltiazem compatible for use in patients who are breastfeeding
Contraindications	- Hypersensitivity to diltiazem or any component of the formulation - Sick sinus syndrome (except in patients with a functioning artificial pacemaker) - Second- or third-degree AV block (except in patients with a functioning artificial pacemaker) - Hypotension (systolic <90 mm Hg) - Acute MI and pulmonary congestion
Monitoring Requirements	- BP - Heart rate - Liver function
Precautions	- Hypotension/syncope: Symptomatic hypotension with or without syncope can rarely occur; blood pressure must be lowered at a rate appropriate for the patient's clinical condition. - Hepatic effects: Mild elevations of transaminases with and without concomitant elevation in alkaline phosphatase and bilirubin - Renal impairment: Use with caution in patients with renal impairment.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of Anal Fissure treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies

in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable.

Table 16. Oral Diltiazem HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Diltiazem	NICE	N/A
	CADTH	N/A
	HAS	N/A
	IQWIG	N/A
	PBAC	N/A

CONCLUSION STATEMENT – DILTIAZEM

Oral diltiazem is recommended as a second-line option for the management of anal fissures after the failure of topical therapies. There are no recommendations by HTA bodies regarding the use of oral diltiazem. However, diltiazem has been marketed for years with multiple generics available, leading to a relatively low cost of treatment.

2.5.2 Nifedipine

Information on **oral** nifedipine is detailed in the table below:

Table 17. Drug Therapy with Oral Nifedipine

SCIENTIFIC NAME Nifedipine	
SFDA Classification	Prescription
SFDA Approval	No
US FDA	No
EMA	No
MHRA	No
PMDA	No
Indication (ICD-10)	K60.2
Drug Class	Calcium Channel Blocker
Drug Sub-class	Dihydropyridine
ATC Code	C08CA05

DRUG INFORMATION	
Dosage Form	Tablets/capsules
Route of Administration	Oral
Dose (Adult) [DDD]*	20 mg twice daily, is typically given in an extended-release form for eight weeks
Maximum Daily Dose Adults*	40 mg
Adjustment	Renal impairment prior to treatment: - No dosage adjustment is recommended by the manufacturer for any degree of reduced kidney function. - Use of lower initial doses and more frequent monitoring is recommended in severe impairment (eg, CrCl <30 mL/minute) as these patients are more sensitive to nifedipine's BP lowering effects. Hepatic impairment prior to treatment: - No dosage adjustments provided in the manufacturer's labeling.
Prescribing edits*	MD, ST
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): Only physicians specialized in gastroenterology and proctology should prescribe nifedipine.	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): Oral nifedipine is a second-line option after the failure of topical therapies.	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	- Most common: Flushing; peripheral edema - Most serious: Acute myocardial infarction; cardiac failure

Drug Interactions*	- Dantrolene: May enhance the hyperkalemic effect of Calcium Channel Blockers. Dantrolene may enhance the negative inotropic effect of Calcium Channel Blockers. *Risk X: Avoid combination* - Strong CYP3A4 Inducers/Inhibitors: *Risk D: Consider Therapy Modification* - Grapefruit Juice: May increase the serum concentration of NIFEdipine. *Risk X: Avoid combination*
Special Population	Older adult
Pregnancy	- Nifedipine crosses the placenta - An increase in perinatal asphyxia, cesarean delivery, prematurity, and intrauterine growth restriction have been reported following maternal use
Lactation	- Nifedipine is present in breast milk.
Contraindications	- Hypersensitivity to nifedipine or any component of the formulation - Patients with ST-elevation myocardial infarction (STEMI)
Monitoring Requirements	- Heart rate - Blood pressure - Peripheral edema.
Precautions	- Hypotension/syncope: IR nifedipine should not be used for acute BP reduction. - Aortic stenosis: Use with extreme caution in patients with severe aortic stenosis; may reduce coronary perfusion resulting in myocardial ischemia. - Withdrawal: Abrupt withdrawal may cause rebound angina in patients with coronary artery disease.

Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of Anal Fissure treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable.

Table 18. Oral Nifedipine HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Nifedipine	NICE	N/A
	CADTH	N/A
	HAS	N/A
	IQWIG	N/A
	PBAC	N/A

CONCLUSION STATEMENT – NIFEDIPINE

Oral nifedipine is recommended as a second-line option for the management of anal fissures after the failure of topical therapies. There are no recommendations by HTA bodies regarding the use of oral nifedipine. However, nifedipine has been marketed for years with multiple generics available, leading to a relatively low cost of treatment.

2.6 Other Drugs

The following drugs are used for the treatment of anal fissure; however, they are **not SFDA registered**:

Topical Nifedipine

Topical nifedipine is used off-label for the management of anal fissures. Typically used as a 0.2 to 0.3% ointment or gel, nifedipine is applied after cleansing 2 to 4 times daily for 4 weeks[23].

Topical Diltiazem

Diltiazem 2% rectal gel is typically applied three times daily for 8 weeks. No significant side effects have been reported with the topical form[24].

Topical Nitroglycerin

FDA approved in June 2011, nitroglycerin is a vasodilator that can be used for the relief of symptoms associated with anal fissure. Typically used at a concentration of 0.2 to 0.4%, it is applied around the fissure(s) twice daily for 4 weeks; if symptoms persist, treatment can be continued for another 4 weeks for a total duration of 8 weeks[25].

Section 3.0 Key Recommendations Synthesis

Initial treatment

- For patients with a **typical anal fissure** (ie, a single posterior or anterior fissure without evidence of Crohn disease), we recommend initial therapy with a combination of **supportive measures** (fiber, stool softener, sitz bath, topical analgesic) and **one of the topical vasodilators** (nifedipine or nitroglycerin) for **one month**, rather than surgery (Grade 1B).
- For patients who have access to a **compounding pharmacy**, we suggest **nifedipine ointment** rather than nitroglycerin ointment as the topical vasodilator (Grade 2B). Nifedipine ointment has fewer side effects and potential drug interactions compared with nitroglycerin and may be more effective. For patients who do not have access to a compounding pharmacy, we use **0.4% nitroglycerin rectal ointment** (Rectiv), which is commercially available.

Interval evaluation

- After the initial treatment with supportive measures and one of the topical vasodilators for one month, patients are **reevaluated**, and those with persistent symptoms are prescribed **another month** of the same medical therapy. At the end of **two months**, patients who still have persistent symptoms attributable to their anal fissures are referred for endoscopy to rule out occult Crohn disease. Patients diagnosed with Crohn disease by endoscopy are referred to a gastroenterologist for further care. **If not diagnosed** with Crohn disease, the patient is referred to a colorectal surgeon for further treatment of the refractory anal fissure.

Subsequent management

- For typical anal fissure patients who **fail eight weeks** of initial medical treatment, we suggest **botulinum toxin type A injection** or a **lateral internal sphincterotomy**, rather than continued medical therapy (Grade 2C).
- Patients who are not willing or **not a candidate** to undergo invasive procedures are treated with the **alternate topical vasodilator** (nitroglycerin ointment if they were treated with nifedipine ointment, or nifedipine ointment if they were treated with nitroglycerin ointment) or one of the **second-line agents** (topical diltiazem, oral nifedipine, or oral diltiazem).
- Surgery is offered to patients who **fail medical therapy.**
- Patients who are **willing to undergo surgical treatment** are further triaged based upon their **risk of fecal incontinence**. Women who have had multiple vaginal deliveries and older patients may have a weak anal sphincter complex, which puts them at a high risk of developing fecal incontinence after surgical treatment of anal fissure.
- We suggest performing a **lateral internal sphincterotomy** in patients with a low risk of developing fecal incontinence (Grade 2C)
- We recommend performing a **tailored or partial sphincterotomy** (ie, fissure apex sphincterotomy) rather than a longer sphincterotomy (Grade 1B). The procedure can be performed in an open or closed fashion.
- For patients who are at a **high risk** of developing fecal incontinence (eg, multiparous women or older patients), surgical options include bot**ulinum toxin A injection, V-Y advancement flap, and subcutaneous fissurectomy**. These alternatives to lateral internal sphincterotomy do not require the internal sphincter muscle to be divided and thereby reduce the risk of fecal incontinence.

Anal fissures after sphincterotomy

- If a persistent or recurrent anal fissure develops after a lateral internal sphincterotomy was performed and causes the patient severe pain, **anal ultrasonography** is performed to determine the completeness of the prior sphincterotomy.
- Patients who have an **incomplete sphincterotomy** should undergo repeat sphincterotomy on the same or opposite side.
- Patients who have a **complete sphincterotomy** should undergo a fissurectomy followed by V-Y advancement flap closure.

Atypical anal fissures

- The finding of an **atypical anal fissure** (multiple, off midline, large, or irregular) should alert the surgeon to the possibility of a secondary manifestation of a systemic illness, such as Crohn disease, tuberculosis, HIV infection, adenocarcinoma, metastatic basal cell carcinoma, lymphoma, or leukemia. Aggressive and optimal medical management of the underlying medical disease should be performed prior to operative management of an atypical anal fissure.

Key recommendations

- **Nonoperative treatment** of acute anal fissures is safe and should typically be first-line treatment.
- **Topical nitrates** may be employed for treatment, but headache symptoms may limit their efficacy.
- **Calcium-channel blockers** (CCBs) are comparably efficacious for chronic anal fissures, have a better side-effect profile, and can be used as first-line treatment.
- **Botulinum toxin** is comparable to topical therapies as first-line treatment for chronic anal fissures and yields modestly improved healing rates as second-line treatment after failed topical therapy.
- **Lateral internal sphincterotomy** (LIS) may be offered to selected patients with chronic anal fissure who have not been treated pharmacologically. It is the treatment of choice for chronic anal fissures in selected patients without baseline fecal incontinence (FI).
- Either **open or closed techniques** may be used for LIS; results are similar. Compared with traditional LIS extending to the dentate line, LIS tailored to fissure length yields similar healing rates and lower FI rates.
- **Limited short-term outcome** data suggest that repeat LIS or botulinum injection for recurrent anal fissure yields good healing rates with a low risk of FI.
- **Anocutaneous flap** is a safe surgical alternative for chronic anal fissure, with healing rates comparable to those of LIS and a lower risk of FI. Addition of an anocutaneous flap to botulinum toxin injection or LIS may decrease postoperative pain and allow for primary wound healing.

Section 4.0 Conclusion

The recommendations provided in this report are intended to assist in the management of Anal Fissure.

These recommendations should be used to support and not supplant decisions in individual patient management.

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Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

I. Prescribing Edits (ensure consistent use of abbreviations, e.g., CU, ST)

Some covered drugs may have additional requirements, rules or limits on coverage. These requirements and limits may include:

Prescribing edits Tools	Description
AGE (Age):	Coverage may depend on patient age
CU (Concurrent Use):	Coverage may depend upon concurrent use of another drug
G (Gender):	Coverage may depend on patient gender
MD (Physician Specialty):	Coverage may depend on prescribingphysician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limits):	Coverage may be limited to specific quantities per prescription and/or timeperiod
ST (Step Therapy):	Coverage may depend on previous use of another drug
EU (Emergency Use only):	This drug status on Formulary is only for emergency use
PE (Protocol Edit):	Use of drug is dependent on protocol combination, doses and sequence oftherapy

Appendix B. Level of Evidence Description

ASCRS guideline Level of evidence and Grade of Recommendations

	Description	*Benefit vs risks and burdens*	*Methodologic quality of supporting evidence*	*Implications*
1A	Strong recommendation, high-quality evidence	Benefits clearly outweigh risks and burdens or vice versa	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation; can apply to most patients in most circumstances without reservation
1B	Strong recommendation, moderate-quality evidence	Benefits clearly outweigh risks and burdens or vice versa	RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise) or exceptionally strong evidence from observational studies	Strong recommendation; can apply to most patients in most circumstances without reservation
1C	Strong recommendation, low or very low-quality evidence	Benefits clearly outweigh risks and burdens or vice versa	Observational studies or case series	Strong recommendation but may change when higher-quality evidence becomes available
2A	Weak recommendation, high-quality evidence	Benefits closely balanced with risks and burdens	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation; best action may differ depending on circumstances or patients' or societal values
2B	Weak recommendation, moderate-quality evidence	Benefits closely balanced with risks and burdens	RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation; best action may differ depending on circumstances or patients' or societal values
2C	Weak recommendation, low or very low-quality evidence	Uncertainty in the estimates of benefits, risks, and burdens; benefits, risks, and burdens may be closely balanced	Observational studies or case series	Very weak recommendation; other alternatives may be equally reasonable

GRADE = Grades of Recommendation, Assessment, Development, and Evaluation; RCT = randomized controlled trial.
Adapted from Guyatt et al.[7] Used with permission.

Appendix C. PubMed Search Methodology Terms

The following is the result of the PubMed search conducted for Anal Fissure guideline search:

Query	Sort By	Filters	Search Details	Results
((((((Anal Fissure Fissure, Anal Anal Ulcer Anal Ulcers Ulcer, Anal Ulcers, Anal) OR (Anal Fissure [Title/Abstract])) OR (Fissure, Anal[Title/Abstract])) OR (Anal Ulcer[Title/Abstract])) OR (Anal Ulcers[Title/Abstract])) OR (Ulcer, Anal[Title/Abstract])) OR (Ulcers, Anal[Title/Abstract])	Best Match	Guideline, in the last 5 years	((("fissure in ano"[MeSH Terms] OR ("Fissure"[All Fields] AND "ano"[All Fields]) OR "fissure in ano"[All Fields] OR ("Anal"[All Fields] AND "Fissure"[All Fields]) OR "anal fissure"[All Fields]) AND ("fissure in ano"[MeSH Terms] OR ("Fissure"[All Fields] AND "ano"[All Fields]) OR "fissure in ano"[All Fields] OR ("Fissure"[All Fields] AND "Anal"[All Fields]) OR "fissure anal"[All Fields]) AND ("fissure in ano"[MeSH Terms] OR ("Fissure"[All Fields] AND "ano"[All Fields]) OR "fissure in ano"[All Fields] OR ("Anal"[All Fields] AND "Ulcer"[All Fields]) OR "anal ulcer"[All Fields]) AND ("fissure in ano"[MeSH Terms] OR ("Fissure"[All Fields] AND "ano"[All Fields]) OR "fissure in ano"[All Fields] OR ("Anal"[All Fields] AND "Ulcers"[All Fields]) OR "anal ulcers"[All Fields]) AND ("fissure in ano"[MeSH Terms] OR ("Fissure"[All Fields] AND "ano"[All Fields]) OR "fissure in ano"[All Fields] OR ("Ulcer"[All Fields] AND "Anal"[All Fields])) AND ("fissure in ano"[MeSH Terms] OR ("Fissure"[All	4

			Fields] AND "ano"[All Fields]) OR "fissure in ano"[All Fields] OR ("Ulcers"[All Fields] AND "Anal"[All Fields]) OR "ulcers anal"[All Fields])) OR "anal fissure"[Title/Abstract] OR "fissure anal"[Title/Abstract] OR "anal ulcer"[Title/Abstract] OR "anal ulcers"[Title/Abstract] OR (("Ulcer"[MeSH Terms] OR "Ulcer"[All Fields] OR "ulcerate"[All Fields] OR "ulcerated"[All Fields] OR "ulcerates"[All Fields] OR "ulcerating"[All Fields] OR "ulceration"[All Fields] OR "ulcerations"[All Fields] OR "ulcerative"[All Fields] OR "Ulcers"[All Fields] OR "ulcer s"[All Fields] OR "ulcerous"[All Fields]) AND "Anal"[Title/Abstract]) OR "ulcers anal"[Title/Abstract]) AND ((y_5[Filter]) AND (guideline[Filter]))	

Appendix D. Treatment Algorithm

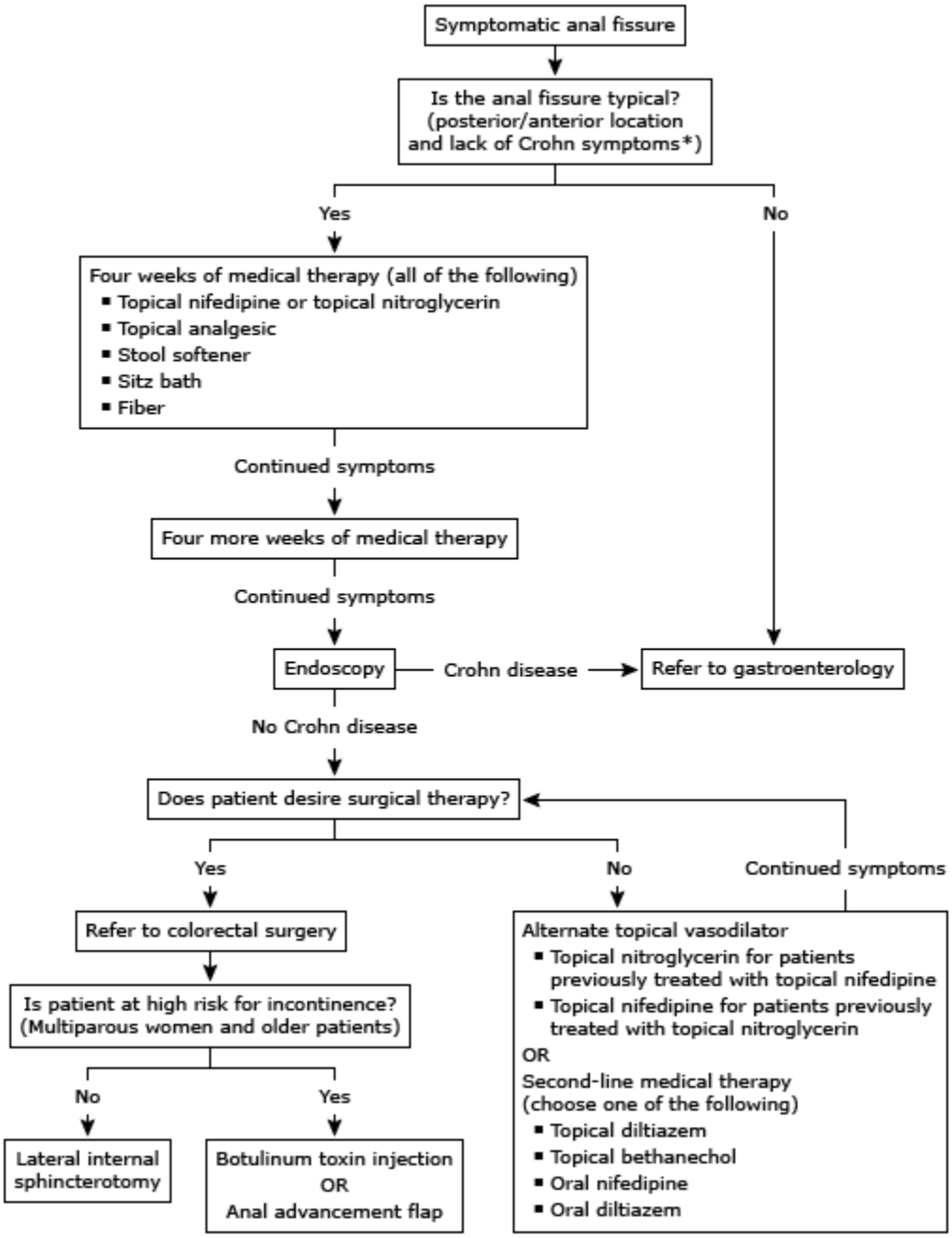

Figure 3. *Treatment Algorithm for the Management of Symptomatic Anal Fissure*