Belgian consensus guideline on the management of anal fissures

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Abstract

Introduction: **Acute and chronic anal fissures are common proctological problems that lead to relatively high morbidity and frequent contacts with health care professionals. Multiple treatment options, both topical and surgical, are available, therefore evidence-based guidance is preferred.**

Methods: **A Delphi consensus process was used to review the literature and create relevant statements on the treatment of anal fissures. These statements were discussed and modulated until sufficient agreement was reached. These guidelines were based on the published literature up to January 2023.**

Results: **Anal fissures occur equally in both sexes, mostly between the second and fourth decades of life. Diagnosis can be made based on cardinal symptoms and clinical examination. In case of insufficient relief with conservative treatment options, pharmacological sphincter relaxation is preferred. After 6-8 weeks of topical treatment, surgical options can be explored. Both lateral internal sphincterotomy as well as fissurectomy are well-established surgical techniques, both with specific benefits and risks.**

Conclusions: **The current guidelines for the management of anal fissures include recommendations for the clinical evaluation of anal fissures, and their conservative, topical and surgical management.**
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Keywords: anal fissures, hypertonia, pharmacological relaxation, sphincterotomy, fissurectomy.

Abbreviations

AIDS	acquired immunodeficiency syndrome
BT	botulinum toxin
CAF	chronic anal fissure
CCB	calcium channel blocker
DRE	digital rectal examination
GI	gastrointestinal
GTN	glyceryl trinitrate
HAART	highly active antiretroviral therapy
HIV	human immunodeficiency virus
IAS	internal anal sphincter
IBD	inflammatory bowel disease
ISDN	isosorbide dinitrate
ISMN	isosorbide mononitrate
LIS	lateral internal sphincterotomy
NO	nitric oxide
NSAID	nonsteroidal anti-inflammatory drugs
RCT	randomized controlled trial
RT	radiotherapy
STD	sexually transmittable disease

Introduction

An anal fissure is a tear of the tender anoderm of the anus, distally from the dentate line, and therefore painful. The fissure can be primary or secondary to other conditions. The primary fissure may be acute or chronic upon diagnosis. There are multiple conservative and surgical treatment options to manage anal fissures, but the treatment should be selected according to the individual patient, the duration of the complaints and the aspect of the fissure at diagnosis.

The purpose of this manuscript is to provide an evidence-based consensus review on the practical management of primary anal fissures. Secondary anal fissures are dealt with in a separate manuscript (1). For reasons of clarity, the word 'primary' will be omitted in the majority of the manuscript.

Methods

The Belgian Working Group on Proctology initiated a Delphi process, to develop consensus statements for the management of anal fissures in clinical practice. The Delphi approach, which combines the principles of evidence-based medicine, supported by systematic literature reviews and a voting process, aims at determining consensus for complex problems in medicine for which evidence from controlled trials is lacking (2).

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The principal steps in the process were similar to the steps described in the *Belgian consensus guideline on the management of hemorrhoidal disease* (3), namely: 1) selection of a Working Group of 5 proctologists (both surgeons and gastroenterologists) with expertise in management of anal fissures; 2) selection of a national Consensus Group consisting of experts in proctology (11 gastroenterologists and 6 surgeons; 13 experts from academic hospitals, 4 experts from non-academic hospitals); 3) drafting of statements allowing to evaluate the current knowledge on management of anal fissures; 4) systematic literature reviews to identify evidence to support each statement; 5) two rounds of repeated voting of the statements and voting discussion until a stable level of consensus was reached; and 6) grading of the strength using accepted criteria.

The 5 Working Group members drafted a list of topics which were distributed among the Consensus Group members for critical literature review. A number of relevant statements was deduced by the Working Group and distributed among the Consensus group members for voting and review. After a first voting round by all members, a consensus meeting was organized where all statements were extensively discussed and reconciled where necessary and possible. Next, the 5-member Working Group drafted a revised list of statements which was again distributed for voting. For each voting round, each statement was presented with the evidence summary, and then the entire panel indicated the degree of agreement for the statement using a 6-point Likert scale (Table 1). When 80% of the Consensus Group agreed (A+ or A) with a statement, this was defined as consensus and included in the formal guideline document. All votes were mutually anonymous. The strength of evidence for each statement was scored using the GRADE system (Table 2) (4). All statements that reached consensus are listed in Table 3.

Table 1. — **6-Point Likert scale to indicate agreement**

A+	strongly agree
A	mostly agree
A-	somewhat agree
D-	somewhat disagree
D	mostly disagree
D+	strongly disagree

Table 2. — **GRADE system used to score the strength of evidence**

High (A)	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate (B)	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low (C)	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low (D)	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Definitions

Acute fissure = anal pain + hypertonia less than 6-8 weeks duration.
Chronic fissure = anal pain + hypertonia longer than 6-8 weeks duration (independent of signs of chronicity e.g. white base and/or fibrotic fibres, undermined edges, sentinel marisca or papilla).

Acute anal fissures appear as superficial, well-demarcated 'papercut' wounds in the anal canal, with a fresh, clean base and without surrounding tissue reaction. Chronic anal fissures (duration > 6 weeks) are frequently wider and deeper, often with raised edges. Sphincter muscle fibres may be visible at the base of the fissure. At the distal margin, a skin tag or sentinel pile may be visible; at the internal margin (proximal to the dentate line), a hypertrophic anal papilla may be observed. In the majority of studies a difference between 'acute' and 'chronic' is not clear. Therefore, in this manuscript the term 'anal fissure' is used when it's not specified in the referred literature. Furthermore, in most interventional studies the endpoint is often symptomatic relief. Complete healing rates often lack in the results.

Epidemiology

STATEMENT 1: Anal fissure occurs equally in both sexes and mostly between the second and fourth decades of life. *Agreement 100%. Grade A.*

Anal fissure is a tear in the anoderm of the anal canal. It was first recognized as a disease in 1934 (5). As all proctologic conditions, the incidence of anal fissure is underreported and underestimated, and epidemiologic data are scarce.

Anal fissure is the second most common reason for proctologic consultation after hemorrhoidal disease and represents ± 10% of proctologic diagnoses (6-8). With an estimated overall annual incidence of 0.11% (1.1 cases per 1000 person-years), and a cumulative lifetime incidence of 7.8 to 11.1%, it occurs equally in both sexes, mostly between the second and fourth decades of life, the higher incidence being among females 12-24 years and males 55-64 years (9,10).

a) Risk factors

STATEMENT 2: Constipation (especially hard stools) is the most important risk factor for primary anal fissure. *Agreement 100%. Grade C*

Table 3. — **STATEMENT**

	AGREEMENT	GRADE
1. Anal fissure occurs equally in both sexes and mostly between the second and fourth decades of life.	100%	A
2. Constipation (especially hard stools) is the most important risk factor for primary anal fissure.	100%	C
3. The main pathophysiological process of typical anal fissures is local ischemia secondary to reactive internal anal sphincter hypertonia.	100%	A
4.1. Anal pain during and after defecation (with or without blood loss) is the cardinal symptom of acute anal fissure.	100%	A
4.2. Primary anal fissures are situated in the posterior midline, and to a lesser extent in the anterior midline.	100%	A
5.1. Diagnosis of an acute fissure can already be made based on cardinal symptoms and visualisation of a fissure.	100%	B
5.2. After visualisation of an acute fissure, digital rectal examination (DRE) and anoscopy can be postponed in the acute setting but needs to be performed during follow-up to exclude underlying disorders.	94%	B
5.3. If DRE/anoscopy are still not possible during follow-up, examination under general anaesthesia can be considered.	94%	C
6.1. First-line approach of acute anal fissures should include optimizing stool consistency and bowel habit regulation (high-fibre diet, increasing fluid intake, laxatives) and non-opiate analgesia.	100%	B
6.2. In case of hard stools, maintenance of high-fibre diet is recommended to prevent recurrence of acute anal fissures.	94%	C
6.3. In case of complications (abscess, fistula), first-line surgical treatment is mandatory.	100%	A
7.1. In case of anal sphincter hypertonia, topical pharmacological sphincter relaxation is recommended.	100%	A
7.2. Topical 2% diltiazem is preferred over nitrates in the treatment of acute anal fissures.	100%	B
7.3. Sclerosing agents and steroid containing creams have no proven effect in the treatment of acute anal fissures and should be avoided.	94%	B
8.1. In case of insufficient clinical improvement after 6-8 weeks topical pharmacological sphincter relaxation, injection of botulinum toxin can be used in case of persistent anal hypertonia.	100%	A
8.2. Injection of botulinum toxin in the internal anal sphincter or intersphincteric groove, divided in 1-4 injections, is recommended.	94%	B
9. In case of insufficient clinical improvement despite adequate topical treatment (with or without botulinum toxin), causes of atypical fissures should be explored.	94%	B
10. Recurrent acute anal fissures can be re-treated with topical pharmacological sphincter relaxation and/or botulinum toxin before referring to surgery.	100%	B
11. Surgical treatment should be considered for symptomatic chronic fissures after at least 6-8 weeks topical treatment and/or injection of botulinum toxin. Surgery for asymptomatic anal fissures should be discouraged.	94%	A
12.1. Anal fissure surgery can be performed in ambulatory setting under local, regional or general anaesthesia (depending on the patient's and surgeon's preference).	100%	A
12.2. There is no need for routine venous thromboembolism prophylaxis, bowel preparation or prophylactic pre-operative antibiotic treatment.	100%	B
13. Lateral internal sphincterotomy (open or closed based on the surgeon's preference) is a well-established treatment option in case of anal hypertonia. The IAS should be incised along the length of the fissure.	94%	A
14. Fissurectomy ± anocutaneous flap ± botulinum toxin is a well-established treatment option in case of anal hypertonia but should always be accompanied by resection of anal papilla and sentinel marisca.	94%	A
15.1. After anal surgery multimodality pain control (local infiltration with long acting anaesthetics, paracetamol and NSAID orally) is recommended.	100%	C
15.2. Warm sitz baths and fibre supplements can be considered as additional treatment after anal surgery.	88%	C
16.1. To prevent anal fissure during or immediately after pregnancy, prevention and treatment of constipation is recommended during second and third trimester.	100%	C
16.2. During pregnancy and lactation anal fissures are preferentially treated with conservative measures.	100%	C
16.3. During pregnancy and lactation topical treatment or injection of botulinum toxin should not be used as effects on the foetus or new-born cannot be excluded	88%	C
17.1. Pharmacological sphincter relaxation, injection of botulinum toxin or surgery focused on reducing sphincter hypertonia is not indicated in low pressure fissures.	100%	A
17.2. Fissurectomy (± anocutaneous flap) is indicated for the treatment of low pressure fissures.	100%	B
18.1. Patients with anal fissure and Crohn's disease should be offered the same conservative and topical treatment options as well as injection of botulinum toxin as patients without Crohn's disease.	88%	B
18.2. Surgery for symptomatic anal fissure/ulceration in patients with Crohn's disease should be avoided in case of active endoluminal disease.	94%	B
19. Patients with immunodepression should be offered the same conservative and topical treatment options as well as injection of botulinum toxin as patients with adequate immunity.	88%	B

Chronic constipation is frequently pointed out as the predisposing factor for anal fissure. However, it is not so unequivocal in the literature, as constipation is found in 14 to 64% of patients suffering from anal fissure, and diarrhoea is a predisposing factor in 4 to 7% patients (6, 9-13).

Studies about the role of diet revealed that low intake of dietary fibres increases the risk of anal fissure (11), and consumption of spicy food worsens symptoms (14). Neither tea, coffee, and alcohol consumption were associated risk factors. In contrast, frequent consumption of raw fruits, vegetables, and whole-grain bread significantly decreases the risk for anal fissure (11).

Other risk factors are described among various studies: hypothyroidism, obesity (10), sexual abuse, traumatic anal sex (15), bariatric surgery (16), and functional evacuation disorders (17). However, whether dyschezia is a cause or a consequence of anal fissure (fear of pain associated with bowel movements) remains unclear and has to be evaluated.

More anecdotal is the suspected role of saddle vibration in professional mountain bikers, causing anal microtrauma (18).

b) Pathophysiology

STATEMENT 3: The main pathophysiological process of typical anal fissures is local ischemia secondary to reactive internal anal sphincter hypertonia. *Agreement 100%. Grade A.*

Irrespective of the cause, the laceration of the sensitive anoderm distal of the dentate line leads to the typical sharp pain during and after defecation and gives rise to a reactive spasm of the internal anal sphincter. This hypertonia leads to a reduction of the perfusion of the anoderm and therefore local ischemia, especially on the dorsal midline due to a precarious blood circulation. This relative ischemia impairs healing of the fissure and supports the evolution to fibrosis and chronicity(12,19,20).

In general the majority of fissures appear dorsally, while there is a female predominance in the less frequent ventral fissures. The dorsal midline is the weaker point of the anoderm where a tear can occur, and is specifically vulnerable for ischemia as fewer arterioles are present as well as lower blood flow, worsened by anal sphincter spasm (21-24).

c) Clinical characteristics

STATEMENT 4
4.1. Anal pain during and after defecation (with or without blood loss) is the cardinal symptom of acute anal fissure. *Agreement 100%. Grade A.*
4.2. Primary anal fissures are situated in the posterior midline, and to a lesser extent in the anterior midline. *Agreement 100%. Grade A*.

The main complaint leading these patients to consult the proctologist is the intense sharp/burning pain that is triggered by defecation and that can last several minutes to hours after defecation (5,25). This symptom is present in 90.9% of patients with anal fissure. Bleeding is the second cardinal symptom in anal fissure and is seen in 71.4% of patients (13,26). This is typically bright red and not abundant blood. In chronic anal fissure, a sentinel pile may be felt by the patient which can also be painful. Symptoms of a fissure may wax and wane.

More for research purposes, a scoring system was developed assessing severity of anal fissure, including duration of pain, need to take painkillers, bleeding and effects on quality of life (27).

The stool pattern should be questioned thoroughly to identify the underlying risk factor and treat accordingly.

Alarm symptoms should be questioned to assess the need for further evaluation (fever, weight loss, familial history of colon cancer).

Diagnosis

STATEMENT 5:
5.1. Diagnosis of an acute fissure can already be made based on cardinal symptoms and visualisation of a fissure. *Agreement 100%. Grade B.*
5.2. After visualisation of an acute fissure digital rectal examination (DRE) and anoscopy can be postponed in the acute setting but needs to be performed during follow-up to exclude underlying disorders. *Agreement 94%. Grade B.*
5.3. If DRE/anoscopy are still not possible during follow-up, examination under general anaesthesia can be considered. *Agreement 94%. Grade C.*

Approximately, 73-90% of anal fissures are located in the midline posteriorly (7,13,24-26,28,29). About 9-16% are located in the anterior midline location, these are seen mostly in women and are often related to vaginal delivery, complicated episiotomy, rectocele, recto-anal intussusception, and with external anal sphincter dysfunction or injury (13,25,26,30,31). Concomitant anterior and posterior midline fissures are found in about 3%. About 1% of fissures are atypical in appearance. This can be characterized by non-painful lesions, non-midline or multiple fissures, and should warrant further evaluation, as these are often secondary to an underlying condition (malignancy, IBD, sexually transmittable diseases, granulomatous disorders)(1,25).

Anal fissure diagnosis is straightforward and based on typical symptoms and a profound proctological examination (29, 32). Inspection during gentle separation of the buttocks will often reveal the lesion, especially during straining. Sometimes anal sphincter spasm may reduce visibility. A digital rectal exam (DRE) may reveal sphincter hypertonia but may be too painful in the acute

phase. If the anamnestic and visual diagnosis is clear enough, this part of the exam can be delayed (but should never be omitted) until the fissure is (partially) healed or less painful to exclude other anorectal pathology. The same reasoning can be made for the use of anoscopy. If DRE and anoscopy are still not possible during follow-up after initiation of treatment, a proctological examination under general anaesthesia should be performed because of the – albeit low – risk of malignancy (33).

For diagnostic purposes there is no need for gastrointestinal endoscopy, anal manometry or endoscopic ultrasound (EUS). In case of blood loss, change in defaecation and/or a family history of colorectal cancer additional colonoscopy can be warranted (26).

Conservative treatment

STATEMENT 6:
6.1. First-line approach of acute anal fissures should include optimizing stool consistency and bowel habit regulation (high-fibre diet, increasing fluid intake, laxatives) and non-opiate analgesia. ***Agreement 100%. Grade B.***
6.2. In case of hard stools, maintenance of high-fibre diet is recommended to prevent recurrence of acute anal fissures. ***Agreement 94%. Grade C.***
6.3. In case of complications (abscess, fistula), first-line surgical treatment is mandatory. ***Agreement 100%. Grade A.***

First-line treatment of anal fissures traditionally aimed at eliminating constipation and softening of the stools to institute and maintain atraumatic defaecation. These goals can be accomplished with fibre therapy or laxatives (e.g. macrogol) to keep the stools soft (34) and formed to prevent trauma of anal canal lining during defaecation. Constipation and hard bowel movements however are not universally present in patients with an anal fissure. In a study including 439 females and 437 males with anal fissures, infrequent hard bowel movements occurred in only 13.8 % of the patients (13).

In clinical studies evaluating a variety of additional treatment options for anal fissure patients were encouraged to increase their dietary fibre and fluid intake, with or without commercially available fibre supplements such as psyllium, pectin, wheat dextrin or oat products.

In a large study including 876 patients with fissure-in-ano 45% healed with bulk laxatives or fibre supplementation (13). In another randomized study including 103 patients with a first episode of acute fissure, the group treated with sitz bath and bran had significantly more healed fissures than the group treated with lignocaine ointment (87% vs. 60%) (35). In a retrospective study conducted by Shub *et al*. including 397 patients with anal fissure, 44% were cured with first-line measures within four to eight weeks (36).

Controlled clinical trials evaluating the pure effect of a standardized high-fibre diet or supplements of specific bulk laxatives on fissure healing and pain relief are not available. In a study by Gupta, including 52 patients with acute anal fissures, sitz-bath treatment in addition to psyllium husk was not associated with a significant effect on healing and pain relief as compared to psyllium alone (37). One of the beneficial effects of a sitz bath with lukewarm water after defecation could be anal sphincter relaxation. A review including four RCTs studying the use of sitz bath in patients with anorectal disorders however demonstrated a lack of data to support the beneficial effect of this time consuming recommendation. Sitz baths had no impact on accelerating fissure healing (38).

In studies assessing topical treatments for anal fissure, patients are most likely to receive also dietary counselling and/or bulk laxatives. However, in many trials testing pharmacologic sphincter relaxation information on additional fibre therapy is lacking. In a series of nine GTN trials only in four of them information on dietary counselling and soft laxative intake was communicated (39-47).

Long-time maintenance treatment with fibre supplements appears effective in preventing recurrence of acute anal fissure. In a double-blind placebo-controlled trial including 90 patients, 5 g of unprocessed bran three times a day for one year was more effective than placebo in preventing recurrence (16% vs. 68%) (48).

Suppurative pathologies associated with chronic anal fissures, such as fissure abscess, post-fissure fistula, and post-fissure aseptic abscess (sinus) are common but not well documented. The true incidence of septic complications in chronic anal fissures is debated since it ranges widely between 3.3% and 51% of cases in the literature. In 71% of the patients, the onset of the infection occurred during long-standing, conservative treatment of a chronic fissure (median 15 months, range 10-23) (49-51).

The surgical strategy aims to eliminate both the sepsis and the fissure: e.g. wide drainage of the abscess and excision of the whole fissure, or performing a fistulectomy with curettage of the fissure. The success rate of the surgical treatment of complicated anal fissures reaches a high rate of success, as reported in the literature where almost 100% of patients were cured at long-term follow-up (28,52-55).

Topical treatment

STATEMENT 7:
7.1. In case of anal sphincter hypertonia, topical pharmacological sphincter relaxation is recommended. ***Agreement 100%. Grade A.***
7.2 Topical 2% diltiazem is preferred over nitrates. ***Agreement 100%. Grade B.***
7.3. Sclerosing agents and steroid containing creams have no proven effect in the treatment of acute anal fissures and should be avoided. ***Agreement 94%. Grade B.***

The treatment of acute anal fissures has traditionally included a high-fibre diet, increasing fluid-intake, laxatives and analgesia (37,48). Approximately 90% of acute fissures heal spontaneously, without any intervention and without any assessment by a specialist (56). However, a faster recovery may be expected when topical treatment is added and the likelihood of progression to a chronic fissure decreased (35,41,57-66).

Although medical therapy is less effective than surgery, especially for chronic anal fissures, it should be offered first because of its wide availability, better tolerance, and lack of severe complications. Minor faecal incontinence (defined as inadvertent escape of flatus or partial soiling of undergarments with liquid stool) is more likely with LIS than medical therapy. This difference is significant, but the absolute risk alteration seems rather small 3/1.000 using conservative measures vs. 14/1.000 with LIS (95% CI 6-31) (67).

Topical pharmacological sphincter relaxation or "*chemical sphincterotomy*" reversibly reduces internal anal sphincter tone, resulting in an increased anodermal blood flow and thus enhanced blood supply to the anal fissure (20,22,68).

NO donors

Nitric oxide (NO) is an important inhibitory neurotransmitter, mediating internal anal sphincter relaxation. Three different topical NO donors have been tested in the treatment of anal fissures: glyceryl trinitrate or nitroglycerin (GTN), isosorbide dinitrate (ISDN) and isosorbide mononitrate (ISMN). GTN 0.2% has been studied most, applied directly to the anus two to three times a day for six to eight weeks.

Taking into account the placebo-effect, GTN was found to be significantly better than placebo in healing anal fissures (RR 1.96 and 95% CI 1.35-2.84) (63,66,67). However, follow-up studies up to 1 year reported recurrence rates up to 67% after initial healing by GTN. Studies with longer follow-up are needed to distinguish complete healing and persistence of a disease that waxes and wanes (67).

Scholefield *et al*. compared placebo against 3 active treatment arms; 0.1%, 0.2%, and 0.4% GTN ointment as a treatment of chronic anal fissures and found superior healing rates for 0.1% and 0.4% GTN (24% in placebo group vs. 50% in the 0.1% GTN group and 57% in the 0.4% GTN -group; resp. p= 0.05 and p=0.03) (69).

The major drawback of the topical use of NO donors is headache, occurring in 16 to 32% of the patients, leading to interruption of the treatment (28,67,69,70).

Two small studies investigated alternative application methods. Torrabadella *et al*. found a lower incidence of headache with controlled intra-anal dosing of topical 0.3% GTN using specialized dose-delivery devices and anal cannulas compared to conventional digital perianal application (1 of 10 patients vs. 10 of 12 patients; p=0.0027) (71). Similarly, the study of Emami *et al*. demonstrated a similar healing rate and a lower rate of headache for 0.2% GTN suppository in the healing of chronic anal fissure to what was reported in trials using topical GTN (72).

Calcium channel blockers (CCB)

Topical CCB, typically diltiazem and nifedipine, generate an inhibition of the calcium ion entry into the vascular smooth muscle leading to vascular dilatation, increased tissue perfusion and reduced anal resting pressure (20,68).

The results of the meta-analysis of Jin *et al*. observed a non-significant advantage comparing diltiazem vs. placebo but this analysis was limited to a small number of studies (66). Both topical and peroral treatment with CCB was studied for chronic anal fissures. Considering a higher incidence of systemic side effects associated with peroral treatment, topical delivery of CCB was preferred (73,74). Headache was less frequent with the use of topical CCB namely 16% with topical CCB and 37.5%-39% with peroral CCB (25,67,74).

Topical nifedipine 0.3% and 0.5% is less extensively investigated but meta-analysis of three studies showed no superiority to placebo in healing anal fissure (66, 75-77).

The study of Jin *et al*. analysed eleven RCTs comparing the effectiveness of diltiazem and GTN topical treatment for the management of anal fissure. Although marginally, diltiazem was shown to be better than GTN at healing anal fissures (RR 1.16 95% CI 1.01-1.33) with a lower risk of headache (66, 78). Nelson *et al*. drew similar conclusions in 2017 (67).

Compared to CCB, GTN is associated with a higher incidence of recurrence (resp. 9% vs. 19%, RR 0.51) and headache (resp. 9% vs. 62%, RR 0.15) which causes poor compliance (78, 79). Moreover, GTN ointment is more expensive than diltiazem preparations in Belgium.

Other pharmacological agents

No superiority was found for topical *captopril*, an angiotensin-converting enzyme inhibitor, over topical diltiazem in the RCT from Ala *et al*. in the treatment of chronic anal fissure (80).

In a small pilot study of Hang *et al*., 2% and 4% topical *diazepam* provided significant pain reduction and bleeding relief in chronic anal fissures but an objective measurement of anal fissure healing in a randomized, double-blind study was lacking (81).

Local application of *L-arginine*, an amino acid and intrinsic precursor of NO, was tested in a small pilot study with 15 patients with a chronic anal fissure (82). The fissure healing rate was 62% without typical NO-induced headache as side effect after an extended treatment period of 18 weeks. However, a clinical trial on 60 patients with a chronic anal fissure compared internal sphincterotomy and topical L-arginine gel and found healing in resp. 57% vs. 27% (61).

Minoxidil, a pyrimidine derivate, is a vasodilator and smooth muscle relaxant, acting by opening potassium channels. Topical 0.5% minoxidil was not superior in healing fissures compared to lignocaine alone or a combination of both agents (83) nor to topical diltiazem (84). Furthermore, Alvandipour *et al*. noted pruritus as bothersome side effect with minoxidil in 27% of the cases (84). The RCT of Emile *et al*. compared topical 5% minoxidil gel to topical 0.2% GTN cream in the treatment of chronic anal fissure. Treatment with this higher dosage of minoxidil achieved more (77% vs. 47%, p=0.03) and quicker healing (4.1 $\pm$ 1.9 vs. 5.3 $\pm$ 2.7 weeks, p=0.048) of chronic anal fissures and fewer adverse effects than topical 0.2% GTN cream (7% vs. 41%, p=0.002) but surprisingly higher post-treatment pain scores (4 $\pm$ 1.2 vs. 4.9 $\pm$ 1.25; p=0.005) (85).

The manometric study of Torrabella *et al*. showed that topical administration of *sildenafil*, a phosphodiesterase-5 inhibitor, significantly reduced anal sphincter pressure in patients with chronic anal fissure (86). Subsequently, Moghimi *et al*. found respectively 100 and 86% effectiveness in the short term and long term management of chronic anal fissures with topical treatment by sildenafil compared to placebo (87). No other clinical trials are available but this agent may be worth further investigation.

Grekova *et al*. concluded in 2015 that culturing a fissure and selective decontamination with *1% metronidazole* was a promising approach in the treatment of chronic anal fissures. Almost half of the patients had anaerobic bacteria in swabs and were randomized to the treatment group (23 patients) or control group (24 patients). Topical metronidazole resulted in more rapid resolution of pain and clinical signs of inflammation in the anoderm than the control group (88). Karapolat included local antibiotics in the treatment of acute anal fissure, comparing 5% lidocaine pomade and 5% lidocaine pomade with metronidazole cream 1%. An increased healing rate was observed: 56% vs. 86% (p=0.004) (89). The most recent study of Mert randomized patients into a topical diltiazem 2% group and a diltiazem 2% and metronidazole 1% group. Adding topical metronidazole to conventional treatment reduced the duration and severity of pain, shortened healing time and increased the healing rate (90). More robust data are needed to understand the efficacy of metronidazole in both acute and chronic fissures.

In conclusion, there is currently insufficient evidence to recommend the use of captopril, diazepam, L-arginine, mixonidil or sildenafil in the treatment of anal fissures. Topical 1% metronidazole can be considered as additional treatment for anal fissures.

(Auto)dilation

Regular passive dilatation of the anus used to have a place in the conservative first-line treatment of acute and chronic anal fissures by reducing anal sphincter pressure. In this procedure, the anal canal is dilated in a (semi-) standardized way. The different techniques described include manual, dilators type St Marks, cryothermal dilators (1.8 to 3 cm) (91,92), Parks spreader (up to 4.8 cm), Hegar marker (up to 4 cm) and balloon (up to 4 cm or 1.4 bar). Because there is no control over the damage to the sphincter, the semi-controlled (manual) dilatation is discouraged (93).

A prospective controlled trial including 40 patients with acute anal fissure comparing the efficacy of passive dilatation with dilators and nitro derivatives, showed complete resolution of the fissure after 4 weeks in 90% of the patient treated with dilators and 45% in those treated with topical NO donors. The relapse rate was also lower in the group that used dilators (59). Another randomized prospective trial including 50 patients with acute anal fissure compared the use of dilators or a finger for regular anal dilatation. Patients in both groups showed a highly significant reduction in anal pain after defecation. After the treatment, 60% of the group using dilators and 80% treated with anal self-massage showed healing of their fissures (94). In contrast, the randomized clinical trial conducted previously by Gough and Lewis including 82 patients with a posterior fissure-in-ano comparing topical 2% lignocaine gel alone to the local anaesthetic in combination with regular use of anal dilators, could not demonstrate an added value for regular anal dilations (43.6% healing versus 41.9% after 4 weeks) (95).

For controlled pneumatic dilatation, there is no conclusive evidence that this technique results in more incontinence than LIS. On the contrary, the limited literature shows significantly less incontinence after 2 years (0% vs. 16% in LIS). The success rate of the dilatation is significantly lower (82 vs. 92%) (96). The risk of other complications such as bleeding, hematoma and discomfort was also similar to the risk after LIS.

Despite the scientific evidence (auto)dilation is currently no longer recommended due to the risk of uncontrolled damage, risk of complications and efficient alternative treatment options.

PTNS

PTNS (Percutaneous Tibial Nerve Stimulation) is a well-known treatment for complaints of faecal incontinence. It also improves rectal blood flow and stimulates mucosal healing after trauma (97,98). The limited literature on this topic shows that 72% of the chronic fissures treated with PTNS are cured after 2 months. In addition, there was a significant improvement in the Wexner incontinence score (99-101). This technique may be considered as an additional conservative therapy in case of chronic fissure in a patient who does not want or cannot be operated on.

Sclerotherapy

In an era before pharmacologic sphincter relaxation, sclerotherapy for anal fissures was the standard for

the treatment of both acute and chronic anal fissures (102,103). For decades it was first-line treatment in proctological practices, especially in France and Belgium (104). More recently Dessily *et al*. reported high healing rates in patients with anal fissure treated with an injection of a sclerosing agent in a retrospective study (105). According to the first publications, sclerotherapy compared with other local treatments resulted in a better outcome and less need of surgery. The procedure resulted in immediate relief without accelerating healing and in a very low complication rate (102,103). Sclerotherapy was recommended when other conservative methods failed and considered a good alternative for classical recommended treatments including topical nitric oxide donors, botulinum toxin injection and lateral internal sphincterotomy (103,105).

The sclerosing agent injected under the fissure is aimed at creating a scar at the site of the fissure. Phenol, menthol in peanut oil or quinine urea were used as sclerosing agent and injected under the fissure after local anaesthesia (103-105). The procedure has been used for acute and chronic fissures both uncomplicated and complicated, greatly reducing the duration of anal pain. Dessily *et al*. reported healing rates of 91.4% and 78.4% in 58 patients with acute fissure and in 51 patients with chronic fissure respectively (105). Complications treated medically occurred in 2.7% of the patients after one or two injections. Recurrence rate for acute fissure was 13.8% and for chronic fissure 17.6%. Of the patients with chronic fissures who failed to heal 50.4% required surgery (103). Since these are uncontrolled trials and the earlier communications of complications, e.g. local abscess, sclerosing injections are not recommended.

The effect of local anaesthesia and steroid containing pomades is not proven as there are no placebo-controlled studies. Moreover, steroid-containing preparations can cause skin atrophy, sensitization and allergic reactions.

Botulinum toxin

STATEMENT 8:
8.1. In case of insufficient clinical improvement after 6-8 weeks topical pharmacological sphincter relaxation, injection of botulinum toxin can be used in case of persistent anal hypertonia. ***Agreement 100. Grade A.***
8.2. Injection of botulinum toxin in the internal anal sphincter or intersphincteric groove, divided in 1-4 injections, is recommended. ***Agreement 94%. Grade B.***

Botulinum toxin (BT) is a neurotoxin produced by the bacterium *Clostridium botulinum* which can release several different exotoxins, the most potent of which is type A (65,106,107). The use of botulinum toxin type A for the treatment of anal fissures was first described by Jost *et al*. in 1993 (108).

Botulinum toxin type A blocks cholinergic transmission resulting in flaccid paralysis and autonomic nerve dysfunction (109,110). By blocking the inhibitory extrinsic cholinergic innervation to the IAS, botulinum toxin relaxes the hypertonic sphincter and facilitates healing (110,111). BT also has an effect on the striated muscle of the external anal fissure. Paralysis occurs within a few hours and the transmission of neuromuscular impulses resumes after the growth of new axon terminals (112,113). Weakening of the muscle is observed clinically for about three months. Effects on pain begin to appear 1 week after injection (114,115). BT produces a constant, sustained reduction in maximum resting pressure rather than a short-lived, transient reduction, and so over a two-month period the internal anal sphincter will remain longer in a normotensive state than with a topical therapy like GTN (116).

Healing rates vary widely from 27% to 100% (28, 70, 114,117-122), at least partially based on the definitions used for the assessment of healing (from 'absence of pain' to 'proven re-epithelialization'). BT injection is less expensive and easier to perform than surgical treatment, but more expensive than topical nitrates or CCB. A big benefit with BT is that compliance problems related to daily application of topical treatment are eliminated. Currently, BT is not reimbursed in Belgium for this indication.

The most common studied formulations of BT are either Botox® (100U) or Dysport® (500U). Patients are positioned on their left side, in the lithotomy, knee-elbow or jack-knife position and a 25-27 Gauge needle is used for injection. The procedure can be performed in an outpatient clinic without local anaesthesia or sedation, after local anaesthesia of the affected area, under sedation or under general anaesthesia.

There is no consensus on the optimal dose of Botulinum toxin to use. Dosage of the injection can vary from 10U to 100U. In most studies Dysport® or Botox® are used. It is important to note that when botulinum toxin-haemagglutinin complex (Alluzience®, Azzalure®, Dysport®) is used instead of botulinum toxin (Bocouture®, Botox®, Vistabel®, Xeomeen®), a conversion factor of 3:1 needs to be applied (123).

Many reports suggest an increased effectiveness with larger doses and with more injection sites (120, 121,124-126). This is confirmed in a more recent study by Ravindran *et al*. where the recurrence rate post-BT injection was significantly lower in the high-dose group (80-100U vs. 20-40U). There was no long-term incontinence in either groups (127). However, in a meta-analysis by Lin *et al*., it was shown that fissure healing with lower doses of BT (10-20U) was as effective as with high doses (30-50U). By increasing the dosage of BT the healing rate at 3 months decreased and incontinence and recurrence rates increased (128). In the meta-analysis by Bobkiewicz *et al*. also no BT dose dependent efficiency for chronic anal fissures (CAF) was shown. Moreover, postoperative incontinence rate as well as complication

rate were not related to the BT dosage. There was also no difference in healing rate observed in regard to the injection site and the number of injections per sessions (129).

In the literature many injection sites are suggested: the external anal sphincter, the internal anal sphincter or the intersphincteric groove in the direction of the internal anal sphincter. Unilateral and bilateral injections are used, either into the anterior or posterior midline, on each side of the anterior midline, lateral to the fissure or at 3 and 9 o'clock of the IAS or EAS. In the majority of studies injection in the internal anal sphincter is used because hypertonia of the IAS is assumed to play an essential role in the pathophysiology of anal fissures. In a few studies injection into the EAS is preferred because it is easier to find and less painful to inject. Paresis of the IAS will occur through diffusion (114,126,128-131). Injection-related pain is similar in bilateral and unilateral injections. Unilateral injection appears to be as effective as bilateral injections in healing and improving fissure pain at 1 year without any deterioration in continence (132). Up till now, there is no consensus on the optimum injection site or number of injections.

A study by Menteş *et al*. compared BT injection (20-30U) and LIS. Overall healing rates were similar in both groups at 6 months, with 10 of 61 patients requiring a second BT injection at two months. However, the response rate was higher at 1 and 2 months in the sphincterotomy group. The response to BT was not as durable as surgery at 12 months falling at a success rate of 75.4% whereas it remained stable in the LIS group (94%) (133).

In general, low frequencies of adverse events were reported and most of them were topical. Almost all of the side effects were only temporary and didn't need any treatment (118,134,135). Compared to topical nitrates, BT caused more transient incontinence but less headache and other side effects (65). Compared to diltiazem, BT caused less perianal itching (118). Transient episodes of incontinence to flatus or liquids/faeces were 14.4% after BT treatment (70). In almost all studies no permanent incontinence was reported. Another possible side effect was the prolapse of internal haemorrhoids. It remains to be determined whether this was caused by the influence of BT on the smooth muscle that attaches the mucosa and anal cushions to the muscle wall of the anus (134). Other rare side effects are perianal hematoma, perianal pain, limited subcutaneous infection at the site of puncture, perianal abscess and perianal dermatitis/intertrigo/itch. Perianal bleeding is possible but was absent in the systematic review by Boland *et al*. (70). Although it is extremely rare, Fournier gangrene has been reported after botulinum toxin injection for treatment of anal fissure in a 77-year-old male suffering from diabetes mellitus (136,137).

In case of hypersensitivity to the substance, pregnancy or neurological disease including myasthenia gravis, Lambert Eaton syndrome and amyotrophic lateral sclerosis the use of botulinum toxin is contraindicated (130,137,138). Co-administration with aminoglycosides is contraindicated because of the possibility of enhancement of the action of the toxin (137,138). Other interfering medications include baclofen, dantrolene and diazepam (123).

Follow-up

STATEMENT 9: In case of insufficient clinical improvement despite adequate topical treatment (with or without botulinum toxin), causes of atypical fissures should be explored. ***Agreement 94%. Grade B.***

Although it was initially thought that anal fissures were associated with anal cancer (139), more recent studies suggest that the presence of benign inflammatory lesions such as anal fissures does not increase the risk of anal cancer (140). However, early cancers can present as non-healing fissures (33,141). Therefore, the healing of a fissure should be established by the treating physician if complaints persist after 8-12 weeks of treatment. If no healing is observed, a biopsy should be taken to rule out malignancy, especially in case of an at-risk condition e.g. HIV, Crohn's disease (139,142,143). If the refractory anal fissure/ulceration is painful an excision is to be considered in order to have a therapeutic advantage and to have histology (144).

Atypical fissures are characterized by any of the following features: fissures in lateral/non-midline positions, multiple simultaneous fissures, nonlinear/excavated/indurated ulcer in the anal canal, associated with discharge of pus or bloody fluid, or fissures associated with ulcerated and indurated skin tag. They particularly should arouse our attention, and malignancy, underlying systemic disease or infection should be ruled out (33,141). An overview of secondary anal fissures can be found in the recent review by Ruymbeke *et al.* (1). Sexually transmittable disease (STD) screening (Chlamydia, gonorrhoea, syphilis, monkey pox) and endoscopic evaluation to rule out endoluminal inflammation/Crohn's disease should also be considered.

Recurrence

STATEMENT 10: Recurrent acute anal fissures can be re-treated with topical pharmacological sphincter relaxation and/or botulinum toxin before referring to surgery. ***Agreement 100%. Grade B.***

A recurrent acute anal fissure can be a complex problem. Before starting treatment again, a complete evaluation of the symptoms and the aspect of the fissure, along with the patient's history and treatment preferences, is recommended. NO donors and CCB have been extensively investigated as topical treatment options for anal fissure. They appear to be effective, but

most studies have been marked by inadequately follow-up, thus missing late recurrences, which are common (67).

As for topical therapy, the recurrence rate after BT is rather high. There are significant differences regarding the follow-up periods ranging from 2 to 5 years (70, 145). After 3 years recurrence rate is even as high as 41.7% (70). In a study by Abd Elhady *et al*. patients were followed for 5 years. Recurrence rate was 52.5% in the group of botulinum toxin (145). This is not the case with LIS as overall recurrence rate was as low as 6.9% in the review by Boland *et al*. (70).

Retreatment with BT after failure of a first injection or early recurrence is very effective with healing rates up to 100% after 6 months (122,146,147). Long-term recurrence rate after BT injection however is high. Combined BT and fissurectomy can be an effective and durable option for these patients.

Surgical treatment

STATEMENT 11: Surgical treatment should be considered for symptomatic chronic fissures after at least 6-8 weeks topical treatment and/ or injection of botulinum toxin. Surgery for asymptomatic anal fissures should be discouraged. ***Agreement 94%. Grade A.***

In case of evolution to chronic fissure, treatment still includes topical treatment options but also surgical options. However, topical treatment may be applied only with a chance of cure that is marginally but significantly better than placebo (148).

Recently systematic reviews and meta-analysis of randomized clinical trials included over 12.000 patients with chronic anal fissures either treated with surgery or topical therapies (67,70). Healing percentage at 8 weeks was highest after surgery (95.1%), followed by BT (66.7%), nitrates (63.6%) and diltiazem (52.3%) (67,70).

STATEMENT 12

12.1. Anal fissure surgery can be performed in ambulatory setting under local, regional or general anaesthesia (depending on the patient's and surgeon's preference). ***Agreement 100%. Grade A.***

12.2. There is no need for routine venous thrombo-embolism prophylaxis, bowel preparation or prophylactic pre-operative antibiotic treatment. ***Agreement 100%. Grade B.***

In the seventies and early eighties all anorectal procedures were performed with several days of hospital stay. Currently it is widely accepted that more than 90% of the anorectal procedures can be performed in an ambulatory setting (149-151). High patient satisfaction and low readmission rates are reported. Preoperative assessment and education of the patient is necessary.

The clinical guidelines for ambulatory anorectal surgery also recommend the possibility of local anaesthesia with or without sedation for anorectal surgery mainly based on safety and cost-effectiveness (151-154).

The literature considering spinal anaesthesia is limited with small numbers and heterogeneous techniques. Spinal anaesthesia avoids airway manipulation and the adverse effects of drugs used in general anaesthesia and provides better postoperative pain control with less opioid need. Since the introduction of fast-track general anaesthesia with avoidance of benzodiazepine and deep anaesthesia, opioid sparing and minimal neuromuscular blockage, the advantage of spinal anaesthesia remains questionable. Further limitations of spinal anaesthesia are the prolonged onset, delayed offset, unreliability and urinary retention (155).

Perioperative fluid restriction to less than 1 litre has been shown to decrease incidence of urinary retention following ambulatory anorectal surgery (156,157).

The saddle block anaesthetic technique that addresses the lowest sacral spinal segments allows a preservation of the lower extremity motor function and faster recovery. It can be an effective method of analgesia to avoid general anaesthesia with a low rate of adverse events (158). Saddle block anaesthesia seems to be more effective than lumbar epidural or caudal block for depressing anal sphincter tone (159).

Venous thromboembolism (VTE) is a preventable cause of postoperative morbidity and mortality. As part of the general preoperative investigations a thrombosis (e.g. Caprini score) – and bleeding risk assessment is recommended (160), together with the procedure related-related risk factor. VTE and need for thrombosis prophylaxis was generally said to be low in ambulatory (minor type of) surgery (range from 0,06-1,18%) (161,162). Nevertheless Samama *et al*. concluded in a more recent prospective national cohort study that better assessment of VTE in the ambulatory setting is necessary (163). The European guidelines recommend that for low-risk procedures (anal fissure surgery) with additional risk factors general measures of thromboprophylaxis are indicated (early ambulation and optimal hydration) and assessing pharmacological prophylaxis with LMWH should be considered (164).

Intravenous prophylactic antibiotic treatment is still routinely used in anorectal surgery. A few large studies concluded that in patients undergoing haemorrhoidectomy there was no evidence for a reduction in surgical site infection or wound healing by antibiotic administration (165). Also oral antibiotics are widely prescribed post-operatively (166). Its role for postoperative analgesia is unclear. Most studies fail to show benefit (167,168).

Lateral internal sphincterotomy (LIS)

STATEMENT 13
Lateral internal sphincterotomy (open or closed based on the surgeon's preference) is a well-established treatment option in case of anal hypertonia. The IAS should be incised along the length of the fissure. *Agreement 94%. Grade A*.

In literature, this procedure is considered the gold standard for the treatment of chronic fissures (66). The goal is to incise the internal anal sphincter to achieve a reduction in hypertonia. Classically, the incision is created on the lateral side because of the risk of scarring and the formation of a "key-hole" malformation in case the incision is created at the level of the fissure. Both open and closed procedures are possible (25).

In the open procedure, an incision is made over the intersphincteric groove. The internal anal sphincter (IAS) is then visualized and can be incised under sight. The wound can be closed, but usually it is left open.

In the closed procedure, a small incision is made laterally from the intersphincteric groove and subsequently the scissors are tunnelled subcutaneously to the groove. On the basis of palpation, the scissors are brought into the groove to split the IAS and the external anal sphincter (EAS). The submucosa is then released from the IAS, also based on palpation and sight. As soon as the IAS is released, it can be cut along the length of the fissure. If necessary, a haemostatic gause can be placed in the radial incision and a haemostatic sponge placed intra-anally to reduce the risk of blood loss or hematomas. For this, intersphincteric and submucosal infiltration can also be done with an adrenaline-containing solution.

The cure rate after LIS is around 90% (70,169,170). The main complication of LIS is soiling or flatus incontinence. The incidence within 3 months after surgery varies between 15 and 20%, but after 12 months this is greatly reduced to 4 to 5% (169,170). A meta-analysis with follow-up for more than 2 years shows that incontinence for flatus can persist in 9%, soiling in 6%, and incontinence for liquid and solid bowel movements in 1% of patients (171).

Based on the literature, it is not possible to identify clear risk groups for incontinence after LIS. However, the risk of soiling and (severe) incontinence seems to be increased in women after vaginal delivery. Since the sphincter complex in women is less developed anteriorly, it is advised to only carry out the LIS in these cases in centres with proctological experience. Multiparous women as well as elderly patients, patients with existing sphincter defects or previous surgery, postpartum anal fissure, diarrhoea, irritable bowel syndrome or diabetes are not good candidates for LIS and therefore can benefit from chemical denervation with BT that is only temporary.

The risk of faecal incontinence is lower if the IAS is incised along the length of the fissure rather than up to the dentate line (172). In women with high resting pressure on manometry and no complaints of incontinence, the risk of faecal incontinence appears to be lower if the IAS is incised over less than 25% of the length (173). This finding was confirmed in a more recent study in which 20 % of the IAS was incised using an open LIS technique (174). Healing at 12 months is 100%, with a CCF-S (Cleveland Clinic Fecal Incontinence Score) of 0. Follow-up of the patients in this study was limited to 12 months so that no statements can be made about long-term incontinence.

The incidence of short-term complications such as bleeding, urinary retention and thrombosed haemorrhoids was less than 5%.

The LIS can also be performed bilaterally, repeating the same procedure on the contralateral side. A randomised comparison showed a lower probability of therapy failure (2.7% vs. 16.4%) with a similar risk of subsequent incontinence (175). The result is promising, but the studies are still limited.

Fissurectomy ± botulinum toxin

STATEMENT 14: Fissurectomy ± anocutaneous flap ± botulinum toxin is a well-established treatment option in case of anal hypertonia but should always be accompanied by resection of anal papilla and sentinel marisca. *Agreement 94%. Grade A.*

A simple fissurectomy means the resection – by scalpel or diathermy – of the fissure and its edges, the accompanying overlying sentinel pile and the hypertrophic papilla (also called fibro-epithelial polyp). The wound is left open so secondary wound healing can occur. Fissurectomy is an easy and quick procedure best performed under general anaesthesia with the patient in lithotomy position. Although less comfortable for the patient, local anaesthesia could also be considered. The procedure is generally proposed in normo- or hypotensive chronic anal fissures, or in patients that are at risk for anal incontinence (elderly women, previous anal surgery, etc…) (25).

The technique of simple fissurectomy is very popular in France. In this country it is sometimes associated with a rectal mucosal advancement flap (the so-called anoplasty). In other countries an anocutaneous advancement flap is the most frequently implemented technique.

A French multicentre prospective trial showed that 264 CAF patients showed good symptom relief and adequate wound healing at a median of 7.5 weeks (range 2-36 weeks) after surgery (176). At 1 year there were no relapses and *de novo* clinically significant anal incontinence was present in only 7% of patients (176). No

difference in outcome or healing was observed between the groups with or without associated anoplasty, however the study was not powered nor conceived to make strong claims in this regard.

In a single-centre prospective trial from Paris that included 50 patients who underwent a simple fissurectomy for CAF, the success rate (defined as a combination of wound healing and relief of pain) was 94% (177). Mean time for healing was 10.3 weeks (range 5.7-36.4 weeks). There were no changes in the pre- and postoperative incontinence scores.

A Dutch study reported a low recurrence rate and minimal effect on incontinence 5 years after simple fissurectomy (178). Fifty-three patients were followed for a median of 8 years (range 5.5-12.2 years). Of this group, 5 patients (11.6%) relapsed within this time frame. Anal incontinence scores did not vary significantly during follow-up, and were not different from these of a matched control group.

The above studies did not differentiate according to the presence or absence of associated anal sphincter hypertonia. The combination of fissurectomy and BT can avoid the need of LIS in a high percentage of patients. In a study by Lindsey *et al.* more than 90% healed with this approach (179). In more recent studies the healing rates were 67 to 83% and the fissure recurrence rates 0 to 17%. There were only minor incontinence rates of 3 to 7% (179-182).

The largest retrospective series in this regard was performed in Leuven-Belgium. In this study a retrospective review of 293 patient files was performed (24). A significant difference in cure rates could be observed between the group that underwent simple fissurectomy and the group in whom botulinum toxin injection was associated, with respective cure rates of 81.1% and 90.1% ($p<0.05$). The decision to inject botulinum toxin was made by the operator, and driven by the presence of anal hypertonia.

In a recent retrospective study by Andicoechea *et al*. fissure healing was initially achieved in 49 of 52 patients (94.2%) and LIS was required in the remaining 3 patients (5.8%). After initial healing, 18 patients (34.7%) developed 23 recurrences at a mean time of 27 months (5-83 months). Of these patients, healing with conservative sphincter measures was obtained in 11 cases (GTN in 8 and repeat fissurectomy and BT in 3); 2 patients are currently under treatment with GTN and 5 underwent LIS (183).

Particularly in women, it can be useful to avoid LIS due to the increased risk of incontinence. In a study by Baraza, fissurectomy and botulinum toxin injection for the treatment of chronic anal fissure in this specific group (females) seemed to be effective in the medium-term but there was a high rate of late recurrence. Only a minority of patients, however, proceeded to more invasive surgical intervention, which may make it a useful option in patients suspect for having sphincter defects in whom LIS should be avoided (184).

Although randomized trials between the different surgical procedures are lacking, a simple fissurectomy appears to be an appropriate treatment for CAF. The main disadvantage is a long wound healing time (up to 10 weeks or more), although this is not painful for the patient. The anal sphincter integrity is preserved with this technique and the previously suggested "keyhole deformity" giving rise to anal incontinence, has not been confirmed in recent trials. Some data suggest that associating a botulinum-toxin injection might be useful in this situation, most likely through better wound healing. The absence or presence of sphincter hypertonia, however, does not seem to influence the results of the procedure.

Additional anocutaneous flap

Various surgical techniques can be used (V-Y plasty, rhomboid flap, diamond flap, house flap) with similar results in terms of postoperative complications and healing rate. A recent meta-analysis on anoplasty for anal stenosis revealed that house flap is the best option (119).

In comparison to LIS, fissurectomy + anocutaneous flap ensures similar healing rates and a decreased risk of faecal incontinence. The association of anocutaneous flap with botulinum toxin/LIS in high pressure fissure is associated with less postoperative pain and faster healing.

D'Orazio *et al*. recently concluded that fissurectomy with anoplasty with V-Y cutaneous flap in combination with pharmacological sphincter relaxation (BT or nifedipine and lidocaine) is an effective approach in patients with hypertonic IAS (185,186). Fissurectomy combined with isosorbide dinitrate cream is also described as an effective treatment for chronic fissure not responding to conservative treatment (187).

STATEMENT 15

15.1. After anal surgery multimodality pain control (local infiltration with long acting anaesthetics, paracetamol and NSAID orally) is recommended. *Agreement 100%. Grade C.*

15.2. Warm sitz baths and fibre supplements can be considered as additional treatment after anal surgery. *Agreement 88%. Grade C.*

Good analgesia contributes to smooth discharge, early recovery and good quality of life and reduction of readmission (188).

Nonsteroidal anti-inflammatory drugs in a single intravenous dose perioperative reduce postoperative pain and decrease postoperative oral analgesics (189). In the postoperative phase the combination of paracetamol and NSAID is accepted to be effective (190). Opioids are often prescribed after anorectal surgery but should be reserved for breakthrough pain and its use limited to avoid constipation and addiction. A multimodality pain regimen is important to avoid excessive opioid prescriptions and not contribute to opioid epidemic,

without compromising satisfactory pain control in ambulatory anorectal procedures (191,192).

The role of gabapentin in the postoperative management of anorectal surgery is unclear. The concept of pre-emptive analgesia seems promising but is still understudied (193).

Warm sitz baths improve the local hygiene, decrease the pain and decrease the hypertonicity of the sphincter muscle (194). Sitz baths are proven to be effective after sphincterotomy (195).

Topical anaesthetics are commonly used for home pain relief. It has been studied in Ferguson haemorrhoidectomy but not in anal fissure surgery (196). Other topical agents (sucralfate, glyceryl trinitrate) have not been evaluated in anal fissure surgery. No studies are available about the use of topical antibiotics post anal fissure surgery.

Postoperative prevention of constipation and straining to avoid pain and compromising flap healing is advised. There is little evidence that one regimen is superior to another.

Special conditions

Pregnancy and lactation

STATEMENT 16
16.1 To prevent anal fissure during or immediately after pregnancy, prevention and treatment of constipation is recommended during second and third trimester. ***Agreement 100%. Grade C.***
16.2 During pregnancy and lactation anal fissures are preferentially treated with conservative measures. Agreement 100%. Grade C.
16.3 During pregnancy and lactation topical treatment or injection of botulinum toxin should not be used as effects on the foetus or new-born cannot be excluded. Agreement 88%. Grade C.

Anal complaints during pregnancy and after childbirth are not rare and often attributed to haemorrhoids, but when defaecation-related anal pain is present, one should suspect an anal fissure. From three prospective trials we know this occurs in 3 to 11% of women during pregnancy and/or the postpartum period (197-199). Location is mostly anteriorly (30). A French prospective study reported a frequency of 1.2% of anal fissure during the third trimester of pregnancy, and 15.2% within the 2 months after delivery (199). A Belgian prospective trial suspected anal fissure in 5% during the third trimester of pregnancy and in 9% up to 3 months postpartum (198). The most important and independent risk factor for developing an anal fissure during/after pregnancy is constipation (198,199). Risk factors such as dyschezia, a personal history of anal problems, traumatic delivery, long delivery time and high birth weight of the new-born were variably withheld as risk factors (197-199).

Low-pressure fissures

STATEMENT 17
17.1. Pharmacological sphincter relaxation, injection of botulinum toxin or surgery focused on reducing sphincter hypertonia is not indicated in low-pressure fissures. ***Agreement 100%. Grade A.***
17.2. Fissurectomy ± anocutaneous flap is indicated for the treatment of low-pressure fissures. ***Agreement 100%. Grade B.***

Limited data about low-pressure anal fissure exist. Patients with anterior anal fissures have been shown to have significantly lower anal pressure, suggesting a different pathophysiology (68). Paradoxical contractions in response to treatment with botulinum toxin were reported, supporting this idea (200).

Primary low-pressure fissures occur mostly in postpartum patients (201). In the acute setting, these fissures should be treated conservatively. Evidence for treatment of chronic low-pressure fissures is scarce. Procedures that alter sphincter mechanism should be avoided (201). In the only prospective study available reporting on the surgical treatment for this subset of patients (202), a fissurectomy with anal advancement flap was performed in 16 patients. At 12 months follow up, no recurrence was reported and continence disturbance was reported in 2 patients.

Patients with low-pressure fissure anal fissures are at risk for incontinence with measures directed at reducing anal hypertonia. Procedures altering sphincter mechanism should be avoided. Fissurectomy and anal advancement flap seems the treatment of choice (53, 203).

Crohn's disease

STATEMENT 18
18.1 Patients with anal fissure and Crohn's disease should be offered the same conservative and topical treatment options as well as injection of botulinum toxin as patients without Crohn's disease. ***Agreement 88%. Grade B.***
18.2 Surgery for symptomatic anal fissure/ulceration in patients with Crohn's disease should be avoided in case of active endoluminal disease. ***Agreement 94%. Grade B.***

Anal lesions occur relatively frequent in patients with Crohn's disease (up to 50% with at least 10 years Crohn's disease) (204), and are even more prevalent compared to the general population (205). As mentioned earlier the full extent of (peri-)anal lesions related to Crohn's disease is discussed elsewhere. In general, a multidisciplinary approach is advised including collaboration of gastroenterologists, surgeons and radiologists with the goal of symptom improvement and prevention

of complications such as sphincter damage or anal canal stenosis (1).

As the underlying pathophysiology of IAS spasm and relative ischaemia is identical in patients with Crohn's disease compared to the general population, identical conservative and topical treatment options (incl. botulinum toxin) can be offered (206).

Patients with immunodepression

STATEMENT 19: Patients with immunodepression should be offered the same conservative and topical treatment options as well as injection of botulinum toxin as patients with adequate immunity. *Agreement 88%. Grade B.*

Patients receiving chemotherapy for an haematological disorder or malignancy may present with infectious or non-infectious anorectal complications. A retrospective cohort of 92 patients with anorectal complications reported that in one third the anal pain is linked to an anal fissure or anal ulceration (207). A smaller, but prospective trial, reported 27 patients in which half of them presented with an anal fissure/ulceration (208). In both publications the majority of anal fissures were located at the midlines and presented as classical anal fissures. The others were defined as "peri-anal ulcerations". Constipation, due to chemotherapy, was found to be the most important risk factor for developing an anal fissure (208). In both case series conservative management lead to resolution and healing of the fissure (local and systemic analgesia, stool softening).

Most chemotherapeutic agents interfere with local wound healing causing large, painful non-healing fissural ulcers. In a retrospective longitudinal observational study in 26 patients with anal fissure and chemotherapy, injection of botulinum toxin in the anal sphincters was observed to be a safe and effective analgesic option in patients with anal fissure while actively receiving chemotherapy (209).

When a patient with HIV/AIDS presents with an anal fissure/ulceration an infectious cause should be ruled out in the first place (1,25). In the era before HAART (highly active anti-retroviral treatment) so-called idiopathic anal ulcers were not rarely observed: up to 10% (210). However, in this study there was only a weak association with the CD4 count. This has in fact been confirmed by a trial comparing 117 AIDS patients from 1994-1995 (no HAART) with 109 AIDS patients from 2001-2002 (HAART) (211). In both groups the presentation of anorectal pathology was similar: 9% anal fissures and 33% anal ulcerations in the first group and 4% anal fissures and 33% anal ulcerations in the latter group. The authors conclude that anorectal pathology was not altered by the introduction of HAART. Our personal opinion and experience is completely the opposite. If we see nowadays anal ulcerations in this patient group, these have an infectious cause, a malignant origin or a classical anal fissure. We haven't seen idiopathic anal ulcers anymore since the introduction of HAART in our patient cohort (personal experience).

Conclusions

The current guidelines were generated using a Delphi consensus process and include recommendations on the clinical evaluation and management of anal fissures. It remains crucial to discuss all possible treatment options and their advantages and disadvantages with the patient, and balance them with patients' expectations.

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