

# Statement of the expert group on the current practice and prospects for the treatment of complex perirectal fistulas in the course of Crohn's disease

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A – Study Design  
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## ABSTRACT:

Perirectal fistulas in the course of Crohn's disease (CD) constitute an important problem in this group of patients. They are observed in a vast majority of patients with involvement through colorectal inflammation. Perirectal fistulas in CD present a great diagnostic and therapeutic challenge due to the intensified clinical symptoms and worse prognosis than in the case of crypt originating fistulas. The condition for implementation of effective treatment of perirectal fistulas in the course of CD is correct diagnosis, defining the anatomy of fistulas, presence of potential stenoses and inflammation in the gastrointestinal tract. Treatment of these fistulas is difficult and requires close cooperation between the colorectal surgeon and the gastroenterologist. The combination of surgical and pharmacological treatment has higher efficacy compared to surgical treatment or pharmacotherapy alone. In conservative treatment, aminosalicylates and steroids are of minor importance, while chemotherapeutics, antibiotics and thiopurines find application in daily clinical practice. TNF- $\alpha$  neutralizing antibodies such as infliximab (IFX), adalimumab (ADA) or certolizumab (CER) prove to be the most effective. Surgical treatment may be provided as ad hoc; in this case drainage procedures are recommended, usually with leaving a loose seton. Planned procedures consist in the excision of fistulas (simple fistulas) or performing more complex procedures, such as advancement flaps or ligation of the intersphincteric fistula tract. Surgical measures can be complemented by the use of video technology (video-assisted anal fistula treatment VAAFT) or vacuum therapy. In extreme cases, it may be necessary to create the stoma. Treatment of perirectal fistulas includes adhesives or so-called plugs. High hopes may be associated with the introduction of stem cells into clinical practice, which is the administration of non-hematopoietic multipotent cells to the fistulas to induce the phenomenon of immunomodulation and tissue healing.

## KEYWORDS:

Crohn's disease - perianal fistula - surgical treatment of fistulas - biological treatment - stem cells

*The paper constitutes a description of the current methods in the treatment of complex perirectal fistulas in patients with Crohn's disease prepared by a multidisciplinary team of experts who deal with their treatment on a daily basis.*

## INTRODUCTION

Despite the development of diagnostics and introduction of new pharmacological and surgical therapies, Crohn's disease (ChLC) is recognized as an inflammatory bowel disease and is still a major challenge in gastroenterological and surgical practice. It usually takes a chronic course, progressing with periods of exacerbations and remissions, with hospitalization required in many cases, with the need for intensive pharmacotherapy and surgical procedures. A particular problem are perianal lesions in the course of ChLC, especially fistulas, which occur in about half of patients [1].

They are observed in 12% of patients with isolated localization in the ileum, 15% with involvement of the small intestine and large intestine, 41% in the large intestine except the rectum and 92% in the colon with involvement of the rectum [1]. Peripheral fistulas in ChLC are a major diagnostic and therapeutic challenge due to the increased clinical symptoms and worse prognosis than in the

case of crypt originating fistulas. This results from a different etiology and pathophysiology [2]. Crypt originating fistulas arise as a result of infection of the anal glands located in the rectal sinuses. Fistulas in ChLC arise as a result of damage to the intestinal epithelial barrier caused by a chronic inflammatory process. Migration to fibroblasts to the lamina propria at the site of epithelial damage is inhibited and the intestinal epithelium is transformed, initially into transient cells, followed by myofibroblasts, under the influence of cytokines and other inflammatory mediators. In addition, there are changes in the extracellular matrix [2]. Fistulas in ChLC are often branched with segmental stenoses and additional internal and external openings. This often leads to stagnation of purulent content and recurrent inflammation. Approximately 70% of patients with fistulas require surgical treatment and long-term follow-up. Diagnostics and treatment of perirectal fistulas in the course of this disease are complicated, and optimal management requires a multidisciplinary approach of gastroenterologists and surgeons [3].

Due to the complex clinical picture, the currently used diagnostics and treatment methods often lead to unsatisfactory results [4]. There is no unambiguous consensus regarding the classification of perirectal fistulas in this group of patients. Of course, Parks' anatomical classification of fistulas is valid.

In Parks' classical division, the type of fistula is dependent from its course in relation to the external sphincter; four types are distinguished:

- intersphincteric fistula - B
- transsphincteric fistula - C
- suprasphincteric fistula - D
- extrasphincteric fistula - E [5].

From a practical point of view, everyday practice accepts the division into simple fistulas and complex fistulas as the simplest and the most immediate therapeutic measures [4].

According to the definition of the American Society of Colon and Rectal Surgeons (ASCRS), simple fistulas are either low intersphincteric fistulas or low transsphincteric, involving less than 30% of the external sphincter, with a single internal opening, without purulent reservoirs. The other fistulas are complex fistulas running above the anal pecten, with more than one external opening, which may be accompanied by abscesses, anal stenosis or other disease of the nearby organs, such as the vagina or bladder [6].

## DIAGNOSTICS

The condition for implementation of adequate and the most effective treatment of perirectal fistulas in the course of ChLC is correct diagnosis, which will allow to determine the following details, most important from a practical point of view:

1. What is the anatomy of the fistula/fistulas, including the location of the external and internal openings, evaluation of the course of the tract/tracts and the possible presence of fluid collections/purulent reservoirs?
2. Is there a narrowing in the gastrointestinal tract?
3. Is there any active inflammation in the digestive tract?

Obtaining answers to these questions is possible thanks to a detailed physical examination, imaging and endoscopy [7]. Physical examination should consist in a detailed assessment of the perineum area including per rectum examination. Because this assessment may be painful for the patient, it is recommended to perform evaluation under anesthesia - EUA. Among radiological studies, magnetic resonance imaging of the lesser pelvis (MR) and/or transrectal ultrasonography (TRUS), which are complementary methods, should be the methods of choice, whereas the choice of the type of diagnostic imaging should depend on the experience and capabilities of the center [7,8]. Ultrasound of the buttock may also prove to be valuable complementary examination. In each case, endoscopic assessment for the presence of narrowing as well as active inflammation is also necessary. This is due to the fact that, from a pathophysiological point of view, the presence of deep ulcerations in the intestine, as well as disorders in the passage

of intestinal contents secondary to stenosis, constitute the main causative factor for the formation of perianal fistulas in ChLC. First of all, the lack of treatment of these etiological factors may be the cause of ineffectiveness of further therapy. In addition, for any narrowing of the digestive tract, it is necessary to exclude its oncological background by collecting biopsy specimens for histological examination. This is due to the fact that the long-term course of the complicated form of ChLC is associated with an increased risk of developing cancer. There are also more and more descriptions of cases of malignant neoplasms in the fistula tract itself - in this case, radiological evaluation with an attempt to collect tissue material for cytological or histopathological examination remains the method of choice [7-9].

## TREATMENT – GENERAL COMMENTS

Selection of the proper treatment technique depends on many factors. On the one hand, it depends on the clinical condition, anatomy of the fistula and the course of the natural disorder, on the other hand, on the experience of the center and the available methods. Comparing the results of treatment of complicated perianal fistulas in the course of ChLC is difficult, which is associated with high heterogeneity in this group of patients. It may result from a number of technical differences in the scope of performed surgical procedures, as well as from the lack of unambiguous criteria for the final results of therapy and variously defined terms of "success" or "effectiveness" of treatment. The key condition for therapeutic success is the close cooperation of a colorectal surgeon or general surgeon with experience in the treatment of colorectal diseases with a gastroenterologist. So far, studies have unambiguously shown that the combination of operating methods with optimal pharmacological treatment, the implementation of multidisciplinary management give a better chance of improving the patient's clinical condition than surgical treatment or pharmacotherapy alone without parallel procedural management [7-10].

### Non-surgical/conservative treatment

In the case of most perirectal fistulas, it is necessary to combine surgical and conservative treatments [7-9]. This mainly results from the fact that one of the conditions for the effectiveness of surgical intervention is lack of active inflammation in the gastrointestinal wall. Besides, the presence of perianal complications is a rarely isolated manifestation of ChLC and is usually only one of the components of this complex disease, which should be treated in a systemic and comprehensive manner. The possibilities of pharmacological therapy are unfortunately relatively limited. In the case of a patient with perianal fistulas, the therapeutic strategy should be individualized. The introduction of biological treatment at the beginning of the 21st century constituted substantial progress in the conservative treatment of ChLC with perianal fistulas. Hence, making some simplification, the medicines used in this indication can be divided into non-biological and biological.

### Non-biological drugs

It has not been proven that aminosalicylates (e.g., mesalazine) or steroids are useful in the treatment of fistula ChLC. Moreover, this second group of drugs may predispose to the development of septic complications [11]. However, everyday clinical practice

involves the use of chemotherapeutics, antibiotics and thiopurines. The most commonly used among chemotherapeutics and antibiotics include fluoroquinolones (mainly ciprofloxacin) and metronidazole. Nevertheless, scientific data confirming their real effectiveness are not very extensive [7-9, 12]. It is known that they reduce the leakage from fistulas, especially in the case of a significant bacterial infection and may be useful as a therapy to prepare interventions in patients with perinatal abscesses. However, their effectiveness is often limited to the duration of their use. An important problem is also the side effects, which exclude the possibility of conducting chronic treatment. An alternative antibiotic with a broad spectrum of activity and good tissue penetration is amoxicillin with clavulanic acid [7-9]. The next antibiotic with a particularly favorable spectrum of action and pharmacokinetic profile is dalbavancin [13]. In selected cases, the microbiological examination of the fistula and evaluation of antibiotic susceptibility, targeted therapy can also be implemented. However, taking into account the large variability and complexity of the bacterial flora of perirectal fistulas, this procedure does not guarantee therapeutic success. In conclusion, antibiotic therapy constitutes an important complementary element of treatment of complicated, complex perianal fistulas in ChLC and should not be the only form of their treatment.

The basic group of drugs used in maintaining the remission of ChLC are preparations from the group of thiopurines, possibly methotrexate (MTX) [7-9]. These are drugs of good clinical efficacy which show important healing action of the gastrointestinal mucosa prognostic wise. Their disadvantage involves the long time needed to achieve full therapeutic efficacy (usually 8-12 weeks since commencement of therapy), as well as possible side effects that sometimes prevent continuation of treatment [7-9]. We do not currently have any good, prospective, multi-center studies on the efficacy of the above-mentioned drugs in the healing of perirectal fistulas. One meta-analysis has shown that the percentage of clinical response in perianal fistulas in the course of ChLC treated with thiopurines or methotrexate was significantly greater than with the effect of a placebo (54% vs. 21%). Nevertheless, these data should be interpreted with caution, due to the heterogeneous manner of defining perianal healing in various analyzed studies [14]. Taking into account that we have other, more effective possibilities as far as pharmacotherapy is concerned, the use of thiopurine or MTX in monotherapy should be limited to patients with mild severity of symptoms in the course of fistula ChLC [7-911]. These drugs, on the other hand, constitute a very important supplement to biological therapy, dedicated to symptomatic patients with complex perirectal fistulas [11].

### Biological drugs

#### Anti-TNF alpha antibodies

The largest part of evidence for efficacy in conservative treatment of perianal fistulas in ChLC relates to antibodies that neutralize tumor necrosis alpha (TNF). This group includes medicines such as infliximab (IFX), adalimumab (ADA) or certolizumab (CER) [15]. So far, two prospective clinical trials assessing the effectiveness of IFX in the treatment of perirectal fistulas in the course of ChLC have been carried out [16,17]. Both studies demonstrated a significant advantage of IFX over placebo in the healing of fistulas, although it is worth noting that the primary and secondary endpo-

ints of the studies did not imply performing a control assessment in MR imaging. In fact, the percentages of truly healed perirectal fistulas were most likely smaller, as confirmed by later analyzes of smaller groups of patients [18]. In relation to therapy with the use of ADA or CER, we have subanalyses of clinical trials which demonstrate good clinical utility in healing of perianal fistulas in ChLC, also in anti-TNF-alpha antibodies [19, 20]. Despite of the lack of head to toe assessments, comparing the effectiveness of individual drugs in this group, the current ECCO (European Crohn's and Colitis Organization) and ACG (American College of Gastroenterology) recommendations point to IFX as the biological drug of first choice [7,8]. This mainly results from the captured largest number of good quality scientific data, in favor of IFX. The favorable pharmacokinetic profile, or IFX also seems to be important; it is administered intravenously (in contrast to ADA and CER) and demonstrates the fastest therapeutic effect. In addition, results of the SONIC study (Study of Biologic and Immunomodulator Native Patients in Crohn's Disease) have shown that combo therapy (IFX + thiopurine) is significantly more effective than monotherapy using IFX or thiopurine [21]. Although the study itself did not only concern the ChLC fistula, patients with perirectal fistulas commonly accept the principle of combined treatment if there is such a possibility.

Another topic worth discussing in relation to anti-TNF alpha therapy is the optimization of treatment through pharmacokinetic monitoring. Rigid dosing regimens were initially used in the majority of studies on the suitability of this group of pharmaceuticals. It is now clear that the effectiveness of anti-TNF alpha drugs largely depends on their actual concentration in the patient's blood [22]. Hence, measurements of IFX concentration (or relatively ADA) with the possible evaluation of the presence of the so-called neutralizing anti-drug antibodies which may cause secondary loss of efficacy, are increasingly used to individualize therapy. Recent years of research indicate, that in the case of fistula ChLC, higher trough level concentrations (these are concentrations recorded just prior to the next dose of anti-TNF-alpha) are associated with significantly higher effectiveness of treatment [11]. One of the best methodologically conducted analyzes showed that these values should exceed 10 µg/ml, in contrast to the luminal form of ChLC (no complications in the form of perianal narrowing or lesions, type B1 according to the Montreal Classification), where concentrations > 3 µg/ml [11,23,24] are considered appropriate. This information carries important practical implications as it indicates that to obtain a healing effect in the fistula, a higher dosage of IFX, exceeding 5 mg/kg body weight, is required. However, further prospective studies in this area are recommended

In order for the patient to benefit from the combination of surgical treatment and anti-TNF alpha therapy, both therapeutic methods should be implemented in the right order. During the first stage, it is necessary to master the septic state, drain all purulent reservoirs to enable the use of biological drugs in the next stage, at the same time without abandoning further phases of the procedure [7-911].

Due to the good results of research on the use of anti-TNF alpha drugs in treatment of perianal fistulas in ChLC, there are also attempts to apply these antibodies locally in the form of injection within the diseased tissues [25]. So far, the results of these studies are unfortunately not encouraging, and the lack of standardization of the drug's local application remains a major problem [11].

The usefulness of other biological drugs in the treatment of fistulas in ChLC is currently the subject of further research.

## Surgical treatment

### Excision of fistula

Excision of the fistula is basically limited to cases of simple fistulas, without any co-existing inflammation, when there are no signs of abscess in the course of the fistula. In patients with long-term treatment of intestinal or perianal ChLC, fistula resection should be performed during remission, or, if biological treatment is used, between successive cycles [7].

Excision of the fistula can also be proposed in selected cases of complex fistulas after their proper preparation. However, a large percentage of potential failures should be taken into account as well as a significant risk of functional disorders, mainly in the form of mild or moderate incontinence, which occurs in about 40% of patients undergoing such procedures [26, 27].

Fistula excision procedures in the group of patients with ChLC should be performed after an extremely careful assessment of the anatomical situation and technical capabilities, due to the lower efficiency of surgical treatment, a greater extent of inflammatory lesions and often weakened sphincter function [28]. According to French recommendations in cases where perirectal fistulas are complex, excision of fistulas is not recommended due to the very high risk of fecal incontinence mentioned above [29].

### Fistula repair procedures

The use of endorectal advancement flaps is generally characterized by fairly good results (success rates up to 60-70%), but is associated with a significantly higher percentage of complications compared to setons [30, 31]. Their use in patients with Crohn's disease is possible, although the chance for cure are much lower in this group, the risk of recurrence reaches 50% and more, whereas as far as treatment of relapses is concerned, it is often necessary to exteriorize the stoma or even definitive end stoma [32].

Surgery with ligation of intersphincteric fistula tract (LIFT) consists in dissection and ligation of the fistula tract in the sphincter, with the excision of its external part and development of the internal opening, with various technical modifications of this method being used.

In selected cases, its use may take place in patients with ChLC, however, there are no unambiguous results of studies regarding its effectiveness, especially in the assessment of the percentage of complications or long-term results [33-36].

The above-mentioned procedures, although acceptable in the group of patients with ChLC, should be used only in selected cases, after individual assessment of the patient, only in specialized centers. The patient must be fully aware of potential adverse events and complications. Often, patients for this type of surgery require preparation by applying an earlier fistula drainage. It is important that the surgeon closely cooperates with the gastroenterologist in terms of use of conservative, especially biological treatment.

### Drainage procedures

In accordance with the guidelines for optimizing management of perirectal fistulas in the course of ChLC as the preferred technique in the treatment of complex fistulas, it is recommended to implant setons as the so-called "bridging" treatment (for further stages of surgical treatment) or, more and more often, as part of a comprehensive treatment (in combination with biological treatment or administration of, e.g., stem cells) without surgical excision or fistula ligation [37].

The presence of an abscess in the course of the fistula or in its vicinity requires earlier preparation of the fistula with drainage (loose seton). In the case of simple fistulas with comorbid clinical symptoms, it is recommended to prepare the patient for further stages of treatment by using Metronidazole, antibiotic therapy (most commonly ciprofloxacin) and performing a drainage procedure (loose seton) [7].

How long the drain can be maintained with a loose seton is not clearly defined and depends on the clinical condition, the patient's acceptance and further therapeutic plan. Depending on the center's technical capabilities and experience, the procedure for complex fistulas should each time include precise imaging diagnostics with MRI or transrectal ultrasound [7].

Drainage techniques used in this group of patients allow for quick limitation of inflammation, reduction of abscesses, and also lead to rapid resolution of clinical symptoms and limitation of disease progression. It should be emphasized that especially in patients with ChLC, the so-called cutting seton (placed under tension) should not be used. Only activities using the so-called loose seton, whose task is to prevent premature closure of the external opening and efficient discharge of purulent content, are recommended [3,7].

Often, a loose drainage seton is placed in the fistula tract/tracts already during initial assessment as the first step to clean the fistula tract and prevent formation of subsequent abscesses [38, 39]. Many materials, such as surgical threads (non-absorbable, appropriate thickness), can be used as a seton. The use of monofilament thread, or the so-called strand, especially of large thickness, can give the patient an unpleasant stinging sensation and cause discomfort. In turn, the use of a soft thread, the so-called braid, leads to its rapid contamination and the seton's coverage with bacterial biofilm. Hence, a good solution is to introduce soft silicone materials such as very thin drains. Elastic vessel loops, which are easy to insert, have adequate thickness and are well tolerated by patients, seem to be particularly useful. Such loops can be tied, the ends can also be sewn together with a thin, non-absorbable thread [40]. There are also readymade silicone sets with a simple end connection system but their disadvantage is a relatively high price.

The loose seton technique is often used as a short-term (several weeks-months) bridging therapy for more complex repair techniques. It is also an acceptable long-term therapy for complex anal fistulas. For patients with multiple unsuccessful repairs or intractable complex fistulas or for those patients who simply do not want to undergo further surgical intervention, a well-constructed drainage kit can be kept in the fistula for years, reducing symptoms associated with the fistula and preventing recurrent infections.

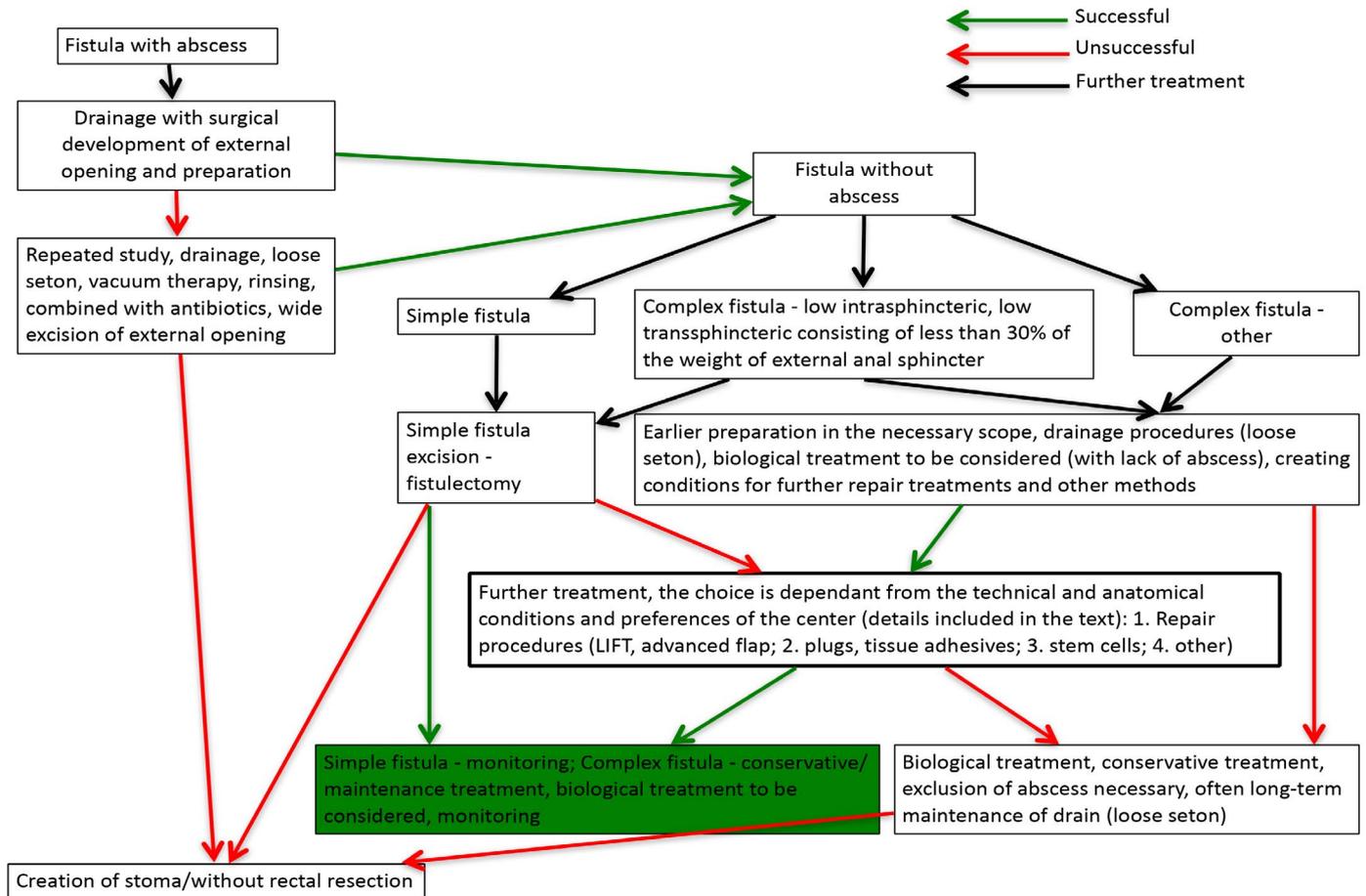


Fig.1. Diagram of possible therapeutic variants including surgical treatment of perirectal fistulas in patients with Crohn's disease.

Drainage procedures with purification of abscess and prevention of its relapses are extremely valuable in the group of patients receiving biological treatment. With regards to the sphincter apparatus, they allow fast, minimally invasive and safe elimination of abscess and continuation of biological treatment. This effect can be completed by administering a single dose of a long-acting antibiotic, which allows to shorten the time of hospitalization and gives a good clinical effect [41].

Figure 1 presents the possible therapeutic variants including surgical treatment of perirectal fistulas in patients with Crohn's disease shown schematically.

### Vacuum therapy in treatment of fistulas

As far as the perianal area is concerned, the form of hypotensive therapy, popular in the treatment of other wounds and healing disorders, is used relatively rarely, which may be due to the difficulty with sealing a classic vacuum dressing. However, it can constitute a valuable supplement to drainage methods, especially in the case of large, high (pelvic) abscesses, in which purification is not achieved after the seton has been set up. Vacuum therapy allows continuous and effective wound drainage and reduction of inflammation [42]. Negative pressure in the cut external hole and fistula tract provides good conditions for closure of the canal and granulation tissue development, especially at wide incisions of external openings [43].

A valuable modification of this method, allowing its easy application and sealing is called Endovac - a system in which a sponge or other element causing even pressure distribution, e.g., a net dress-

ing is placed at the end of the drain connected to a vacuum device. The drain is inserted directly into the fistula tract and sealed with, for example, an ostomy paste.

### VAAFT, or video-assisted anal fistula treatment

An advantage of the video-assisted anal fistula treatment is the thorough cleaning of its tract from necrotic tissue and infected granulation tissue under visual control, with the possibility of identifying additional tracts and closing the internal opening using a dedicated stapling device. The row of staples is reinforced with a synthetic glue that is inserted through the external opening. This method is limited by its high costs and the still not well-defined tactics of patient selection and its effectiveness [44]. In few studies conducted in patients with ChLC, promising results were found when combining VAAFT with advancement flap, with a success rate greater than 80% [45]

There are also publications indicating the high efficiency of this technique in the management of symptomatic fistulas with signs of infection, where a rapid resolution of symptoms was achieved. However, in this study VAAFT performed the role of supporting drainage techniques, the recleaning of the fistula tract was followed by insertion of a seton [46].

### Endoscopic dilatation of stenosis

In treatment of perirectal fistulas, comprehensive assessment of factors that may contribute to problems with their treatment or

increase the risk of recurrence is important. One of the most important elements in the treatment of complex perirectal fistulas is the assessment of the distal segment of the rectum and anal tract in order to exclude their strictures. The presence of strictures makes it difficult to empty the rectum, increases pressure within the rectum and may intensify symptoms of the fistula as well as impede its closure. Endoscopic dilatation in patients with ChLC is an accepted and even currently recommended procedure for localization of disease in the final section of the ileum, where quite good results and long periods free from surgical intervention are obtained in more than 50% of patients [47,48].

There are existing reports that dilatation of anal tract strictures can be effective and performed using simple dilators, for example bougie. This procedure is relatively safe, improves the clinical condition of patients with ChLC and can be safely repeated [49].

### *Exteriorization of stoma*

Despite the increasingly better results of treatment of perirectal fistulas in the course of ChLC, it may still be necessary to exteriorize the stoma in some patients at a certain stage of treatment. The most frequent recommendations include:

- recurrent active fistulas with high inflammatory/purulent lesions, not susceptible to treatment, including surgical treatment;
- a significant degree of functional deficiency of sphincter apparatus caused either directly by fistulas and inflammation or earlier procedures;
- co-existing vaginal and bladder fistulas;
- recurrent purulent states in the pelvis and abdominal cavity in patients for whom biological treatment is indicated
- neoplastic lesions or high-grade dysplasia.

In the above situations, the exteriorization of a temporal or final stoma should be considered. In a situation where it is possible to cure inflammatory lesions and infections in fistulas and perianal tissues, a loop (temporary) stoma may be a good solution improving the patient's comfort, but above all, increasing the chances of healing. Of course, in some situations such as the diagnosis of neoplastic lesions, only resection with exteriorization of the final stoma is necessary. The extent of resection depends on the nature of the disease, primarily the degree of cancer, location of inflammatory lesions and their extent [50]. However, it should be emphasized that removal of the rectum with the exteriorization of final stoma does not guarantee resolution and elimination of perineal inflammatory lesions. This group of patients display significant healing disorders, recurrent abscesses of the pelvis and soft perineal tissues; no syncretion is observed. Women may display purulent fistulas from the pelvic to the vagina, which can be very difficult to treat. All this results in the necessity to undertake great precaution when deciding on the scope of the resection procedure.

## **Alternative treatment**

### *Plugs (stoppers) for fistulas (fistula plug)*

The technique involves cleaning the fistula tract and inserting a bioprosthetic plug into the tract. Initial results were very promi-

sing; however, subsequent studies did not confirm the effectiveness of this method. Most studies with longer follow-up showed efficacy below 50% or even 24% [51-54].

In the summary of 12 studies on the use of plugs, it was found that this procedure is safe, fraught with low risk of complications, including urinary incontinence and the results justify its use. Difficulties in the unambiguous interpretation of research are caused by small numbers and heterogeneous groups of patients, as well as various types of fistulas qualified for treatment and different methods of preparation, including, for example, earlier cleaning of the fistula immediately before surgery, long-term maintenance of loose drainage [55].

There are also data that speak against plug reinsertion after failure of the first attempt. The chance for cure is in this case very small, with an additional risk of increased inflammation or formation of subsequent abscesses [56].

### *Adhesives and fillers*

Treatment of anal fistulas via injection of fibrin glue was initially used due to the simplicity of this technique. The method consists in filling the fistula with glue after previous cleaning of the fistula tract and/or closure of the internal fistula opening [57]. In a review lasting over a year, full healing of the fistula was observed only in 14% of patients [58].

The use of fibrin glue and other sealing agents did not live up to the expectations, but ASCRS recommendations still mention them as an acceptable treatment method. For patients with ChLC, this effectiveness seems to be even lower. In the case of relapses, the failure of prior application of glue may hinder further treatment, both drainage and surgical.

### *Stem-cell therapy*

Because of the lack of one, fully effective method of treatment of complex perirectal fistulas, research on new alternative therapies is still under way. One such method, already quite well-documented via research, is stem-cell therapy [59,60]. The method of treatment consists in the application of non-hematopoietic multipotent cells (the so-called mesenchymal stem cells - MSCs) in the fistula to induce the phenomenon of immunomodulation and tissue healing [59-61]. MSCs can be isolated from adipose tissue, bone marrow or other tissues. The largest number of experiments regarding the treatment of ChLC fistula are related to the use of adipose-derived stem cells, or ASCs.

These cells are easily grown in breeds, which is important from a practical point of view. Their mechanism of action is complex. After application, ASCs migrate to sites of ongoing inflammatory reaction, promoting regeneration of tissues and demonstrating immunomodulatory properties in the graft versus host reaction (GvH) [59-62]. The therapeutic effect results from the anti-inflammatory effect of ASCs, inter alia by inhibiting the activity of dendritic cells or CD4+ memory cells, as well as by changing the concentrations of many cytokines. As a result, the inflammatory process is reduced, vascularity is improved, fibrosis is limited and local healing is stimulated [63-66]. A very important element of therapy with the use of ASCs is proper preparation of the fistula

tract, removal of necrotic tissues and fibrin, earlier drainage of purulent reservoirs. In the case of chronic, partially epidermized fistulas, it is important to remove the superficial scar layer of the epidermis so that the fistula tract is formed by granulated and uninfected tissue.

In 2016 Lancet published the results of a multicenter, randomized, double-blind phase III study in which the effectiveness of individual, focal ASCs allogeneic injections (line Cx601) were compared to placebo in adult patients with complex fistulas in the course of ChLC [67]. The study involved 212 patients observed over a 24-week period.

Clinical and radiological assessment of magnetic resonance imaging showed a statistically significant advantage of the use of ASCs in the healing of complex fistulas. Subsequent analyzes also confirmed the effectiveness and safety of therapy using ASCs in the annual follow-up [68]. In 2018 ASCs were registered in the EU by the European Medicines Agency (EMA) under the name darvadstrocel for use in treatment of complex perianal fistulas in adult patients with inactive/mild ChLC in the case of insufficient response to at least one line of conventional or biological therapy [69].

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## CONCLUSION

Conservative treatment should complement surgical treatment of perianal ChLC fistulas. After initial surgical management of the septic state and possible treatment of GI strictures, it is recommended to use anti-TNF alpha antibodies (with indication of IFX) optimally in combination with a thiopurine derivative. It is necessary to monitor the effectiveness and safety of conservative procedures (clinical, laboratory, imaging and endoscopic assessment - the scope of research depending on the needs) with its possible optimization/individualization in the absence of healing of inflammatory lesions in the gastrointestinal wall. The decision regarding continuation of surgical treatment and the choice of method depends on the individual clinical situation and experience of the treatment center. There are many surgical techniques that have been used for many years in the treatment of fistula ChLC. Recently there have been new therapeutic options emerging for patients after ineffective conventional treatment (including vacuum therapy, use of stem cells), whose implementation increases the chance of healing fistulas and reducing the risk of anal sphincters. The key condition necessary to achieve therapeutic success is constant cooperation of the surgical and gastroenterological teams.

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