Clinical guidelines for the management of gastrointestinal fistula – developed by experts of the Polish Surgical Society*

Wytyczne leczenia przetok przewodu pokarmowego. Stanowisko Grupy Ekspertów Towarzystwa Chirurgów Polskich

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A – Study Design
B – Data Collection
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ABSTRACT:

Introduction: Gastrointestinal fistula is one of the most difficult problems in gastrointestinal surgery. It is associated with high morbidity and mortality, numerous complications, prolonged hospitalization, and high cost of treatment.

Aim: This project aimed to develop recommendations for the treatment of gastrointestinal fistulas, based on evidence-based medicine and best clinical practice to reduce treatment-related mortality and morbidity.

Material and methods: The preparation of these recommendations is based on a review of the literature from the PubMed, Medline, and Cochrane Library databases from 1.01.2010 to 31.12.2020, with particular emphasis on systematic reviews and clinical recommendations of recognized scientific societies. Recommendations in the form of a directive were formulated and assessed using the Delphi method.

Results and conclusions: Nine recommendations were presented along with a discussion and comments of experts. Treatment should be managed by a multidisciplinary team (surgeon, anesthetist, clinical nutritionist/dietician, nurse, pharmacist, endoscopist).

KEYWORDS: gastrointestinal fistula, negative pressure therapy, parenteral nutrition, treatment

STRESZCZENIE:

Wstęp: Nieszczelność przewodu pokarmowego należy do najtrudniejszych problemów w chirurgii przewodu pokarmowego. Związana jest ona z: wysoką chorobowością i licznymi powikłaniami, dużym ryzykiem zgonu, przedłużoną hospitalizacją oraz zwielokrotnieniem kosztów leczenia.

Cel: Zadaniem zespołu było opracowanie zaleceń dotyczących leczenia przetok przewodu pokarmowego zgodnie z aktualną wiedzą medyczną w celu ograniczenia śmiertelności oraz chorobowości związanej z leczeniem.

Materiały i metody: Opracowanie niniejszych zaleceń oparto na przeglądzie dostępnego piśmiennictwa z baz PubMed, Medline i Cochrane Library z okresu od 1.01.2010 do 31.12.2020, ze szczególnym uwzględnieniem przeglądów systematycznych oraz zaleceń klinicznych uznanych towarzystw naukowych. Zalecenia sformułowano w formie dyrektywnej i poddano je ocenie metodą *Delphi*.

Wyniki i wnioski: Przedstawiono 9 zaleceń wraz z omówieniem oraz uwagami ekspertów. Leczenie powinno być prowadzone w oparciu o zespół wielodyscyplinarny (chirurg, anestezjolog, specjalista żywienia klinicznego/dietetyk, pielęgniarka, farmaceuta, endoskopista).

SŁOWA KLUCZOWE: leczenie, przetoka przewodu pokarmowego, terapia podciśnieniowa, żywienie pozajelitowe

ABBREVIATIONS

BMI – Body Mass Index
CT – computed tomography
EAF – Enteroatmospheric Fistula
ECF – Enterocutaneous Fistula
EIF – Exomphalos with Intestinal Fistulation
EN – Parenteral Nutrition
kcal – kilocalorie
kg mc – kilogram body weight
LAF – laparotomy accompanying fistula
PN – parenteral nutrition
RTU – ready-to-use parenteral nutrition prepared by combining three pre–prepared mixtures in water: amino acids with electrolytes, glucose and fat emulsion
SSIL DE FISTula – Stabilization, Sepsis control, correcting Imbalance and Losses, Drainage and Diagnosis, Evaluation and plan, Feeding and route of nutrition, further Investigation, Spontaneous closure or Theatre approach
US – ultrasound

EXPERTS

AD – Adam Dziki
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MK – Marek Kunecki
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WT – Wiesław Tarnowski

INTRODUCTION

Gastrointestinal fistula is one of the most challenging problems in gastrointestinal surgery. This condition is associated with: high morbidity and mortality, numerous complications, prolonged hospitalization and high treatment costs [1, 2]. Treatment of gastrointestinal fistula should be conducted by a multidisciplinary health team (surgeon, anesthesiologist, clinical nutritionist/dietician, nurse, pharmacist, endoscopy specialist).

Enterocutaneous fistulae (ECF) are the most commonly observed type of fistulae. ECF is defined as an abnormal connection between the gastrointestinal tract and the skin. Although it may develop spontaneously in patients with neoplastic diseases, with a history of radiation exposure or in those suffering from inflammatory conditions, such as inflammatory bowel disease, ECF is more often diagnosed as a complication of gastrointestinal surgery [1, 3]. However, this definition is not sufficient. Since modern surgical procedures are associated with numerous complications involving various types of gastrointestinal fistulae, it is necessary to extend the nomenclature and implement a prognosis-based classification which could be used to determine clinical management. Progress in medicine entails changes in treatment of many disease entities, including gastrointestinal fistulae. Introducing open abdominal surgery and damage control into the canon of surgical strategies, together with the achievements of effective intensive care have all contributed to the improved survival of patients with particularly difficult and anatomically complex fistulae. Progress observed in both diagnostic and treatment approaches allows us to provide successful therapies for patients who, until recently, were dying due to a severe course of gastrointestinal fistula [4].

The more comprehensive definition emphasizes that gastrointestinal fistula is a non-physiological connection between two epithelial structures. However, this explanation still remains incomplete, as it fails to include e.g. enteroatmospheric fistula. In these guidelines we focus on the treatment of postoperative fistulae and use the term "gastrointestinal fistula" to describe any connection between the lumen of the gastrointestinal tract or secretory organs (pancreatic and bile ducts) with another epithelial or body surface. The major criteria for classification of fistulae relate to their: etiology, anatomical location, morphology and secretory activity. When it comes to the location, fistulae may be divided into (1) internal (e.g., gastrointestinal, enterovesical, enterovaginal) and (2) external, which connect the intestinal lumen to the body surface. Contrary to internal fistulae, the diagnosis of which may be challenging at first, identifying external fistulae is usually simple. The primary goals of treatment involve fighting metabolic imbalances and septic complications, as well as promoting healing of the fistula. Other important elements of therapy include full control of symptoms (skin protection, reduction and control of secretion) and improvement of patients' quality of life (ensuring active rehabilitation in order to allow patient's unrestricted movement, as well as providing psychological support).

METHODS

In order to develop these guidelines, the authors have carried out a thorough analysis of current literature regarding the management of gastrointestinal fistulae. The summary of recommendations is based on an in-depth review of studies published over the past ten years. The main goal of our work was to extract current knowledge and introduce latest treatment approaches which have not been

Tab. I. Gastrointestinal fistula treatment recommendations.

RECOMMENDATION	SCORE	COMMENTS	RECOMMENDATION STRENGTH
Recommendation 1.			
It is advised to implement clinical-prognostic classification of gastrointestinal fistulae which indicates optimal therapeutic management.	2.8	GW	strong
Recommendation 2.			
It is recommended to treat fistulae in accordance with the SSIL DE FISTula principle.	2.9	no comments	strong
Recommendation 3.			
Management of fistulae is aided by the use of minimally invasive techniques in order to control the fistula output and septic collections. Indications for laparotomy are limited only to situations when sepsis cannot be effectively managed with minimally invasive techniques.	2.5	GW, TB, MK	strong
Recommendation 4.			
Parenteral and/or enteral nutrition administered distally from the fistula should be commenced immediately, i.e. after stabilization of the circulatory system and correction of water-electrolyte and acid-base imbalances.	2.9	TB	strong
Recommendation 5.			
It is recommended to deliver nutrition in one bag (*All in One system*), infused 24 hours a day, and mixture adjusted to patient's individual needs and metabolic limits.	2.7	TB, MK	strong
Recommendation 6.			
Negative pressure therapy is the treatment of choice in grade 2 (EIF) and 3 (EAF) fistulae. Endoscopic techniques for discharge of intestinal contents proximally from the fistula (grade 3 to 1 conversion) are also effective.	2.8	GW	strong
Recommendation 7.			
In case of treatment failure after 6 weeks of therapy and absence of prognostic signs suggesting fistula healing in metabolically stable patients, it is recommended to continue outpatient treatment with home parenteral nutrition or enteral nutrition administered distally to the fistula.	2.6	GW, TB	strong
Recommendation 8.			
Surgical treatment is indicated only if it is technically possible to reestablish continuity of the gastrointestinal tract and the body's metabolic condition allows for effective healing.	2.9	TB	strong
Recommendation 9.			
Surgical treatment should be carefully planned and preceded by a detailed anatomical evaluation. It is recommended to conduct reconstructive surgical procedures in reference centers.	3.0	no comments	strong

implemented yet [5–9]. Development of these guidelines was based on literature review from PubMed, Medline and Cochrane Library databases between 1 January 2010 and 31 December 2020, with special regard to systematic reviews and clinical recommendations published by acclaimed scientific associations [10]. According to this key, 71 publications were qualified and analyzed in our research. Recommendations of acclaimed scientific associations for clinical nutrition, particularly those published by ESPEN and ASPEN, were taken into account and adjusted to the Polish healthcare system.

These guidelines are of general nature and require individual analysis and adjustment to specific clinical situations.

The process of developing these guidelines was planned and carried out in the following stages:

1. developing research process and document plan, identifying and inviting experts (Jacek Sobocki, Wiesław Tarnowski, Adam Dziki, Michał Stanisławski),
2. literature review and formulation of preliminary recommendations with comments (Jacek Sobocki, Wiesław Tarnowski, Michał Stanisławski),
3. creating a draft (Jacek Sobocki, Wiesław Tarnowski, Michał Stanisławski, Zuzanna Zaczek),
4. draft proofreading and preparing a version for further evaluation (Jacek Sobocki, Michał Stanisławski, Zuzanna Zaczek, Wiesław Tarnowski),
5. evaluation and submission of corrections with the use of the Delphi method (Jacek Sobocki, Marek Jackowski, Adam Dziki, Wiesław Tarnowski, Marek Kunecki, Tomasz Banasiewicz, Maciej Słodkowski, Mariusz Frączek, Piotr Richter, Andrzej Matyja, Grzegorz Wallner),
6. formulation of a corrected version (all authors),
7. re-evaluation and submission of corrections (all authors),
8. should another corrections be submitted – repeat steps 6 and 7 (all authors),
9. formulation of the final version (all authors).

RESEARCH PROCESS

The recommendations were formulated in a directive form and evaluated with the use of the Delphi method. The draft document, comprising 9 recommendations with comments, was reviewed by

Tab. II. Clinical-therapeutic classification of gastrointestinal fistulae.

GRADE	CHARACTERISTIC	EXAMPLES FROM CLINICAL PRACTICE
Type I – enterocutaneous fistula, ECF	Connects the intestinal lumen with the skin surface.	Fistula through an abdominal drain.
Type II – enteroincisional fistula, EIF	Connects the intestinal lumen with a surgical wound.	· Fistula resulting from placing a suture through the intestinal wall during abdominal closure. · Fistula resulting from hernia mesh migration to the intestinal lumen.
Type III – enteroatmospheric fistula, EAF	Connects the intestinal lumen with a granulating wound surface in patients with abdominal wall defect.	Due to partial abdominal wall defect, exposed intestine drains enteral contents directly on the extensive wound surface. This type of fistula most often occurs after open abdominen tehcnique or multiple laparotomies performed in a short period of time. This condition usually accompanies frozen abdomen.
Type IV – laparostomy accompanying fistula, LAF	Intestinal leak not limited by granulation in a patient with abdominal wall defect. Enteral contents drain to the peritoneal cavity and outside the body.	Eventration in obese patients, in whom peritoneal closure was impossible due to abdominal wall defect, with accompanying gastrointestinal fistula (shortening of the mesentery makes impossible stoma construction). Since the intestines have not attached into the abdominal wall yet, intestinal contents is spreading in the peritoneal cavity instead of being limited to the granulation tissue.

a wider group consisting of eleven experts (1st Iteration), whose evaluation was based on the following scale of approval:

- 3 – strong acceptance,
- 2 – acceptance with some objections,
- 1 – acceptance with serious objections,
- 0 – rejection.

Numerous corrections and arrangements were introduced at the stage of creating the document, therefore avoiding repeated iterations in subsequent stages. The document was then reviewed by the entire team (2nd Iteration). It was decided that recommendations with mean acceptance score > 2 would be considered as strong, recommendations with mean acceptance score ≤ 2 and ≥ 1 would be defined as weak and recommendations with mean acceptance score <1 would be rejected. All recommendations presented in this publication received an average score of > 2. All experts' comments were introduced into the text. Since the strongest level of recommendations was achieved and no more corrections were submitted, the Delphi process was successfully completed. Eleven experts – members of the Association of Polish Surgeons – participated in the process of formulating and evaluating recommendations with the use of the Delphi method.

RECOMMENDATIONS

Summary of recommendations, along with average scores, a list of experts who raised objections and strength of recommendations, are presented in Tab. I.

Recommendation 1.

It is advised to implement the clinical-prognostic classification of gastrointestinal fistulae which indicates optimal therapeutic management.

External fistulae most often develop as postoperative complications (80% of fistulae) with high incidence, reaching 1–2.4 % of all abdominal surgeries.

The 2019 ESPEN guidelines on clinical nutrition present a classification system supported by a summary of extensive clinical experience. It is based on anatomical characteristics and determines adequate therapeutic management (Tab. II., Fig. 1.) [11].

The severity of a patient's condition, the level of treatment complexity, duration of therapy and mortality rate increase from type 1 to 4, respectively. The aim of the treatment is to convert clinical stages of fistula in the opposite direction, i.e. from type 4 to 3, from 3 to 2 and from 2 to 1.

The majority of types 1 and 2 fistulae resolve with conservative treatment administered for up to 4–6 weeks. Moreover, in fistulae classified as type 1 and 2 the volume of discharge is of significant prognostic value:

- low-output fistula < 200 mL/daily,
- moderate-output fistula 200–500 mL/daily
- high-output fistula > 500 mL/daily.

The course of low-output fistulae does not involve any serious water or electrolyte imbalances and these lesions usually resolve with conservative treatment. On the other hand, high-output fistulae are associated with a high risk of metabolic instability (disturbances in the water-electrolyte balance and acid-base balance which may lead to renal failure) and require intensive systemic treatment along with wound care and sepsis control. Fistulae which form in the upper gastrointestinal tract are usually characterized by high-output (duodenal fistula, jejunostomy) in opposite to other segments of the gastrointestinal tract. Enteral nutrition is contraindicated in high output fistulae, as they promote loss of water, electrolytes, protein and energy (due to metabolic limits, parenteral nutrition cannot compensate for these losses), as well as increase the risk of metabolic and organ disfunction (e.g. liver damage) [12–14].

Type 3 and 4 fistulae always require delayed surgical reconstruction. The greatest challenge is posed by a type 4 fistula – although it is similar to grade 3, it is more complex due to uncontrolled spread of intestinal contents into peritoneal cavity. Type 3 and 4 fistulae entail high mortality rates (up to 60% in non-specialized healthcare

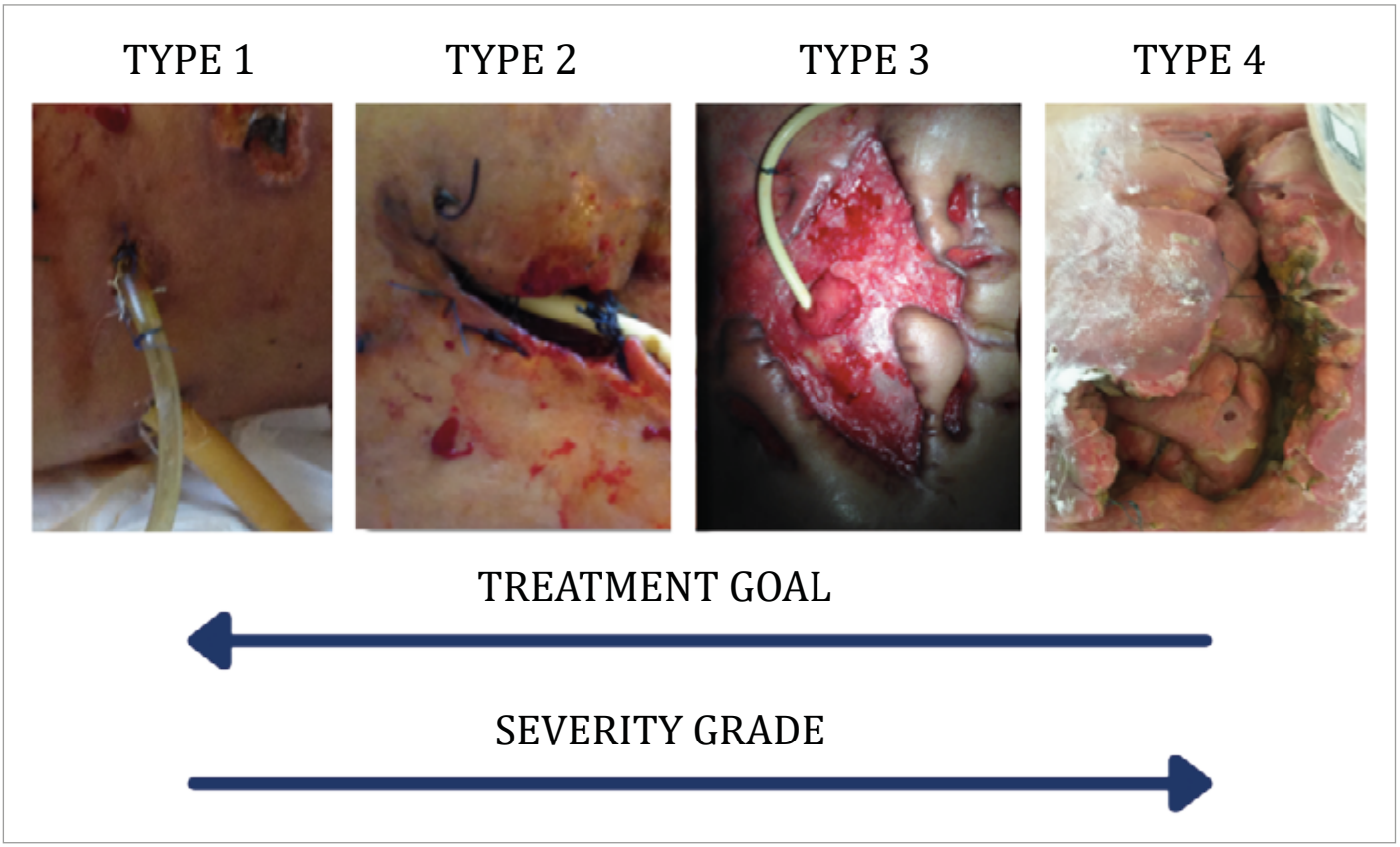

Fig. 1. Clinical-prognostic classification of gastrointestinal fistulae.

institutions and less than 20% in specialized centers). Treatment in centers specialized in the management of gastrointestinal fistulae reduce risk of mortality, as well as life-long disability (such as the short bowel syndrome resulting from multiple laparotomies and bowel resections). These fistulae are associated with severe systemic complications and require multidisciplinary care, several weeks of hospitalization and final surgical intervention postponed for several months since skin defects are healed, which usually takes 9–12 months of HPN [3].

Expert's comment

- (GW:) there are nearly 60 different classifications of fistulae, a dozen of which refer to the esophagus, stomach and duodenum, several to pancreatic-biliary fistulae and a several dozen to intestinal fistulae. Systematic use of a particular classification is always justified.

Recommendation 2.

It is recommended to treat fistulae in accordance with the SSIL DE FISTula principle.

In 1964, Chapman published main goals and time frames for treatment of fistulae, which were acronymized as SSNAP (Stabilization, Sepsis and Skin care, Nutrition, Anatomy assessment, surgical Procedure) later on. This management includes: stabilization of the patient (cardiovascular system, water-electrolyte and acid-base balances), infection control (fistula drainage, antibiotic therapy), skin protection (against erosions caused by fistula secretions) [3, 15, 16], effective nutrition [17] and, in case a fistula does not heal spontaneously, assessment of the anatomical structure of a fistula (location, pattern) and implementation of surgical treatment after adequate preparation (see recommendations 8. and 9.).

Upon the development of knowledge and progress in the field of minimally invasive procedures, this acronym evolved into SSIL DE FISTula (Stabilization, Sepsis control, correcting Imbalance and Losses, Drainage and Diagnosis, Evaluation and plan, Feeding and type of nutrition, further Investigation, Spontaneous closure or Theater approach). This approach emphasizes the effectiveness of conservative treatment which is characterized by a lower mortality rate and a lower risk of disability associated with extensive bowel resection conducted in difficult anatomical conditions.

Although clinical management is carried out in sequences, within specific time frames (Tab. III.), particular stages may overlap and require differentiation between specific fistula types. A patient diagnosed with a fistula usually presents acid-base and water-electrolyte imbalances. Patients who develop a fistula during hospitalization remain under continuous medical supervision, as any imbalances should be identified and treated early. More serious disorders are observed in patients who develop a fistula after discharge from hospital. Correction of water-electrolyte and acid-base imbalances should be achieved within 24 hours and not exceed 48 hours. Simultaneously, it is necessary to start immediately treatment for progressing sepsis. First-line management includes computed tomography (CT)-guided or ultrasound-guided percutaneous abscess drainage, as long as it can be performed safely and effectively. The use of endoscopic methods to treat gastrointestinal wall defect from the side of its lumen (stent placement, Ovesco clip, negative pressure endotherapy) and performing gastrointestinal decompression (catheter placement or decompression stoma construction proximally to the fistula) should also be considered.

Tab. III. Fistula treatment stages.

TREATMENT STAGE		TIME FROM DIAGNOSIS	TREATMENT GOAL
1.	Diagnosis and stabilization	**24** hours	Correction of water-electrolyte and acid-base imbalances, stabilization of the circulatory system. Cultures from blood and fistula contents, empirical antibiotic therapy, pharmacotherapy (somatostatin). Abdominal CT scan – assessment of the effectiveness of drainage and presence of septic lesions. Drainage of fistulae and abscesses. Skin protection.
2.	Nutrition	**48–72** hours	Parenteral nutrition introduced progressively day by day.
3.	Anatomical evaluation of fistula	**after 7–10** days	Assessment of fistula location, extent and tract. If necessary, switch to targeted antibiotic therapy.
4.	Decision regarding further management	**after 4–6** weeks	Assessment of the effects of conservative treatment on fistula healing chances, decision to postpone the surgery and continue treatment with parenteral or home enteral nutrition, establishing surgical treatment date.
5.	Definitive surgical treatment	**2–12** months *if patient's condition allows for uncomplicated postoperative course*	Fistula excision, reconstruction of digestive tract continuity.

Protecting the skin reduces the risk of fistula progression, improves healing rate, facilitates wound care and reduces patient complains (stoma pouch placement, hydrocolloid-based protective skin paste or zinc paste). The disturbances caused by a fistula depend on the type and length of the excluded gastrointestinal segment, as well as on the presence or absence of inflammation in the fistula tract. Fistulae located in the upper portion of the gastrointestinal tract usually produce more secretions which are rich in electrolytes and protein – therefore leading to more dynamic metabolic disturbances and extended damage to the skin. Clinical presentation of these fistulae is more dynamic.

Patients suffering from a fistula usually present with water retention which, in combination with fluid loss through the fistula, results in renal dysfunction and the development of water-electrolyte and acid-base disorders (most often hypokalemia and acidosis). Progressing hypovolemia and hyponatremia, as well as the activation of neurohormonal mechanisms limiting diuresis, quickly lead to uremia and aggravation of metabolic disorders. Necessary interventions include: intensive fluid therapy (35 mL/kg bw <70 years of age or 30 mL/kg bw >70 years of age + deficit of water + current loss), stimulation of diuresis and sometimes providing temporary support with catecholamine i.v. Despite adequate control of the sepsis and optimal treatment with fluids and amines, a small percentage of patients may require administration of albumin in order to maintain vascular volume. Electrolytes should be administered in accordance with the results of frequent laboratory tests. In case of high-output fistulae, fluid balance should be assessed every 6–8 hours. Fluid losses through fistulae of the upper gastrointestinal tract are replenished with an equivalent volume of 0.9% NaCl with 10 mEq of KCl per liter. Duodenal or pancreatic fistulae require additional bicarbonate replacement. Secretion of ions in subsequent portions of the gastrointestinal tract is presented in Tab. IV. It is important to keep in mind that fistula fluid loss results from the imbalance between secretion and absorption in the proximal segments of the gastrointestinal tract. Inadequate treatment may cause excessive secretion of more than 5000 mL per day in patients allowed for oral nutrition. Such losses cannot be compensated by any type of nutrition and inevitably lead to death. It is therefore necessary to completely discontinue the administration of any food or fluids through the gastrointestinal tract in high output fistula patients.

After correcting water-electrolyte and acid-base imbalances, controlling sepsis and excluding other possible contraindications, it is recommended to immediately initiate nutrition [18–20]. This should be performed within the 48 hours and the composition and volume of the nutrition mixture should be adjusted individually, based on the metabolic condition of each patient. Although macronutrients (protein, carbohydrates, fats) should initially be started progressively in low doses (risk of refeeding syndrome), water, electrolytes, micronutrients and vitamins must fully cover the demand [21–24].

Feeding techniques

Maintaining or improving a patient's nutritional status is an important prognostic factor for both morbidity and mortality [25–27]. As soon as the fistula is diagnosed, enteral nutrition and hydration should be stopped until the anatomical and functional diagnostic procedures are completed. Total parenteral nutrition is initiated at this time but most patients require it to be continued throughout the entire treatment period. Attempts to introduce enteral nutrition are made at later stages, provided that: (1) the fistula is well drained (CT shows no leakage outside the fistula tract and clear intestinal contents without pus are drained), (2) enteral nutrition is effective and (3) it does not increase fistula output. Enteral nutrition is effective for as long as it is possible to maintain enteral access and provide adequate nutrient supply for many weeks [28]. Enteral nutrition can successfully replace intravenous supply of macronutrients only in a small number of patients, but some patients will require parenteral administration of electrolyte solutions. If the fistula is not healed after 4 weeks of parenteral nutrition, nourishing the patient through a feeding tube inserted in the fistula tract may be attempted. After 4 weeks the fistula tract usually becomes strong, tight, straight and shortened. This procedure is justified if the small bowel segment distal to the fistula is functional and its length exceeds 150 cm.

If there is no chance for a fistula to heal, artificial nutrition shall be continued until final surgical treatment is performed. In the long term, adequate enteral feeding is safer and more effective, especially when conducted in an outpatient setting. However, parenteral nutrition is the treatment of choice in patients with gastrointestinal failure or in case of inability to gain safe and stable enteral access

Tab. IV. Ion concentration in enteral secretions (according to 4).

	VOLUME mL/24 h	Na^+ mmol/L	K^+ mmol/L	Cl^- mmol/L	HCO_{3^-} mmol/L
Salivary glands	1500	10	26	15	50
Stomach	1500	100	10	100	0
Duodenum	2000	130	5	90	10
Small intestine	3000	140	5	100	30
Pancreas	800	140	5	75	115
Bile	800	150	5	100	35
Colon	Non-significant amounts				

[29, 30]. Parenteral nutrition should be administered via central veins, with the use of a dedicated vascular access (CVC, PICC, port). Parenteral nutrition may be administered through the peripheral veins only for a short period of time in a hospital setting, in exceptional circumstances when central venous access is lost. Peripheral parenteral nutrition causes peripheral vein damage and suffering for the patient, while failing to meet the metabolic needs.

Supplementary key procedures

Regular physical therapy is an important element of treatment which should accompany nutrition therapy. Patient mobilization: stimulates anabolism, prevents protein loss, increases metabolic limits and reduces the risk of secondary infections.

Intestinal fistula is a potentially fatal complication which puts a patient in a difficult life situation, aggravated by discomfort associated with physical suffering and prolonged hospital stay. It is therefore recommended to dedicate more time to explain the situation to patients suffering from fistula and present to them a detailed treatment plan with prognosis. Furthermore, patients require assistance from a clinical psychologist. Administration of somatostatin and its analogues in pancreatic or biliary fistula cases has been proven to improve healing [31–38]. Somatostatin can also be used in high output gastrointestinal fistulae, as it temporarily reduces the volume of fistula secretions; however, it does not affect healing. It may also be helpful in treatment of skin erosions around the fistula caused by digestive enzymes. However, somatostatin and its analogues reduce fistula output, only somatostatin improve the spontaneous closure rate [6, 35, 39].

Recommendation 3.

Management of fistulae is aided by the use of minimally invasive techniques in order to control the fistula output and septic collections. Indications for laparotomy are limited only to situations when sepsis cannot be effectively managed with minimally invasive techniques.

In principle, treatment of fistulae is based on non-surgical methods. However, the main goal of introducing surgical procedures involves creating adequate conditions for the effecive healing of a fistula by means of conservative treatment [4]. Surgical treatment is indicated in the following cases:

1. emergency procedures:

- septic collection due to ineffective fistula drainage,
- diffuse peritonitis,
- patient condition deteriorates and there is little chance for spontaneous fistula healing (major anastomotic leak).

2. elective procedures:

- final repair in patients who are in optimal condition for surgery and who did not benefit from conservative treatment.

Immediate sepsis control is critical for a patient's life. Empirical broad-spectrum antibiotic therapy must be administered immediately. A CT scan on the day of a fistula diagnosis allows to assess the septic collections and verify the presence of other pathologies requiring urgent action. Minimally invasive techniques are the approach of choice (CT-guided or ultrasound-guided percutaneous abscess drainage, endoscopic drainage with the use of e.g. EndoVac, minilaparotomy etc.), since they ensure adequate control over septic collections without extending the wound (extensive laparotomy in difficult anatomical conditions, e.g. frozen abdomen). Limiting the injury while also maintaining effective drainage results in lower mortality rates. Moreover, the reduction of surgical trauma is directly proportional to the fistula healing time and inversely proportional to the risk of fistula progression (e.g. type I to II or II to III). Laparotomy is recommended if the fistula and septic lesions cannot be successfully managed with minimally invasive techniques.

Experts' comments

- (MK:) other live-saving indications for surgery may occur, e.g., haemorrhage;
- (GW:) there are too many prognostic factors, as well as clinical, laboratory and etiological parameters which should be taken into account in order for this recommendation to not be regarded as controversial. The type of treatment should be adjusted individually based on a patient's final assessment and adequate qualification for different options of either conservative or surgical treatment (endoscopic or surgical) = tailored therapy/tailored surgery;

- (AD:) patients with fistulae usually present with a history of surgeries, therefore making it impossible to implement minimally invasive techniques;
- (TB:) the initial stages of fistula treatment are usually conservative. Additional indication for laparotomy includes severe fluid loss through a fistula, which cannot be effectively treated with enteral or parenteral nutrition;
- (JS:) In most cases, limitation of excessive secretion from a fistula can be achieved by discontinuation of enteral feeding, as a result of pharmacological intervention (loperamidum, somatostatin, PPI) or by treating gastrointestinal tract infections. Urgent surgical treatment of high output fistulae bears a great risk of complications and it is rarely a necessary management.

Recommendation 4.

Parenteral and/or enteral nutrition administered distally from the fistula should be commenced immediately, i.e. after stabilization of the circulatory system and correction of water-electrolyte and acid-base imbalances.

Improvements in the treatment of intestinal fistula and the reduction in mortality from over 60% to less than 4% have been possible owing to the advances in parenteral nutrition. Early administration of adequate nutrition ensures optimal conditions for a fistula to heal [40–43]. Delayed nutrition makes treatment results significantly worse. Since fat is a concentrated source of energy in the body, it is metabolized only in small amounts during the disease, while the demand for protein and glucose increases significantly. Massive proteolysis (autophagy) causes rapid muscle loss (which impedes rehabilitation) and deterioration in the functioning of many organs. Finally, these mechanisms lead to increasing insulin resistance which in turn propels the vicious cycle of metabolic disorders.

It is recommended to discontinue delivery of any food and water through the gastrointestinal tract in the first days after diagnosis. Enteral nutrition may be considered if the fistula is stabilized, i.e. after confirming that the fistula tract is stable (no leakage of contents outside the controlled fistula tract, no risk of obstruction, enteral nutrition will not slow down the healing process).

In case of inadequate tissue perfusion (shock) and water-electrolyte or acid-base imbalances, the metabolism of macronutrients becomes ineffective, leading to severe metabolic complications. Nutrition should be introduced as soon as the above-mentioned disturbances are corrected. It is also important to note that, in such situations, nutrition must be introduced gradually, in order to avoid exceeding metabolic limits [44].

Expert's comment

- (TB:) depending on a patient's individual acceptance and metabolic condition, as well as on the character of fistula output (volume and contents), individually adjusted oral nutrition may be considered if the lower gastrointestinal tract is functional. Ensuring regular bowel movements (even in the absence of nutrition) is also a crucial element of treatment, as it allows to avoid faecal retention.

Recommendation 5.

It is recommended to deliver nutrition in one bag (All in One system), infused 24 hours a day, and mixture adjusted to patient's individual needs and metabolic limits.

Parenteral nutrition enables patients with gastrointestinal fistula to survive for several weeks, therefore providing time for fistula healing. Only administration of adequate amount of nutrition yields the expected therapeutic results. Nutrition should be administered with the use of All in One system, i.e. all ingredients mixed in a single bag. Multiple-bottle systems, i.e. separate infusions of macronutrients (e.g. RTU), vitamins, electrolytes or trace elements are unacceptable and not recommended, as this type of nutrition critically alters pharmacokinetics and increases the risk of metabolic complications. The composition of nutritional mixtures should be adjusted to individual needs and compliant with metabolic limits. Although composing mixtures individually for each patient offers greater margin of safety, individual preparation of nutritional solutions for the majority of patients may be based on RTU bags supplemented with electrolytes, vitamins and trace elements. Continuous infusion of parenteral nutrition for 24 hours a day is reccomended, since the body does not take any night breaks during its struggle to fight sepsis. Every interruption in parenteral nutrition lasting more than 60 minutes activates proteolysis and deteriorates therapeutic outcomes.

Metabolic limits must be defined in all metabolically unstable patients. In clinical practice, nutrition begins with administration of lower doses on the first day (0.6 g protein/kg bw, 10 kcal/kg bw) which are gradually increased to full doses (1.5 g protein/kg bw, 25 kcal/kg bw) under watchful monitoring of clinical signs and laboratory test (glycemia, triglycerides, urea, patient's general condition). Further increases of macronutrient doses are justified only when a patient regains physical fitness outside of bed.

A universal equation for calculating nutritional demand has not been developed yet, as nutritional demands vary among individual patients and alter dynamically, along with disease stages and treatment course. Exceeding metabolic limits interferes with immunological processes and increases the risk of complications. Metabolic limit is defined as the maximum amount of a nutrient which can be metabolized in a time unit (e.g. 300 g of glucose per day). It seems that an effective way to optimize nutrition and reduce the risk of exceeding the metabolic and volume limits at this stage of treatment is to set infusion pump on 24 hours.

There are two stages of nutritional therapy in patients suffering from a fistula:

1. Early stage (sepsis, low metabolic limits) – nutrition aims to reduce losses (especially proteolysis) caused by fistula secretions and progressing sepsis;
2. Stabilization stage (sepsis is successfully controlled) – the nutritional mixture should cover all nutritional needs, as well as replace losses caused by a fistula. The aim is to achieve anabolism which enables healing of a fistula.

Apart from water and electrolytes, losses through a fistula also involve protein, energy, bicarbonates, bile salts, vitamins and trace elements [45]. Protein loss amounts to approximately 2 g N (12.5 g protein)

for every liter of fistula secretions. Protein loss is aggravated by sepsis and immobilization. Therefore the major goal of treatment is to reduce losses (limiting fistula secretions, providing physical rehabilitation, introducing effective treatment of sepsis), whilst infinitely increasing nutritional supply is associated with the risk of metabolic and organ complications.

Although the evaluation of the impact of various feeding methods on the final therapeutic results in GI fistulae is difficult due to the lack of randomized clinical trials comparing different nutritional interventions, the route of administration appears to be of secondary importance as long as nutritional demands are satisfied. The risk of liver dysfunction in patients suffering from a fistula is associated with sepsis, impaired enterohepatic circulation of bile salts or surpassing individual metabolic limits (inaccurate composition of nutritional mixture). However, this risk may be reduced by fistuloclysis technique, which is defined as infusion fistula contents into the distal part of the intestine. This procedure is complex and difficult to apply [46–48]. Some patients with upper gastrointestinal fistulae may receive nutrition to the intestinal segment located distally from the fistula, which allows to reduce the intensity of intravenous administration of nutrients or even completely discontinue the procedure in a small number of patients.

It is important to prevent complications of parenteral nutrition. As proved in a study carried out in Polish surgical wards, the most common mistakes in fistula management include: delayed nutrition, administration of incomplete nutritional mixture, incorrect dosage (overfeeding), short transfusion time, lack of regular lab tests, central catheter infection, peripheral parenteral nutrition for more than 5 days [49].

Experts' comments

- (MK:) not all patients require nutrition 24 hours a day;
- (JS:) reducing the time of parenteral nutrition to less than 24 hours a day in patients with high demand for protein leads to exacerbation of proteolysis, therefore significantly worsening treatment outcomes;
- (TB:) intravenous administration of RTU-based mixtures may be considered in patients receiving partial enteral nutrition.

Recommendation 6.

Negative pressure therapy is the treatment of choice in grade 2 (EIF) and 3 (EAF) fistulae. Endoscopic techniques for discharge of intestinal contents proximally from the fistula (grade 3 to 1 conversion) are also effective.

Numerous techniques based on negative pressure have been described in the treatment of fistulae: foam secured with occlusive dressing, negative pressure with the use of an ostomy bag drain, endoscopic negative pressure techniques (e.g. EndoVac), negative pressure applied by siphon technique through an abdominal drain, nipple technique etc. [50, 51]. Negative pressure allows for shortening the time of enteral contents' contact with the wound, therefore protecting it against infection or injury by enzymes and accelerating wound contraction. Negative pressure also causes hyperemia which stimulates granulation and healing [21, 52–55]. Negative pressure therapy is the recommended treatment for grade 2 and 3 fistulae. Endoscopic techniques for draining gastrointestinal secretions proximally to the fistula (grade 3 to 1 conversion) are also effective. VAC therapy implementation allows for healing of fistulae which previously required surgical interventions, even when applied in the second or third month of treatment. The process of fistula healing is aided by: mobilizing the patient, altering gut microbiota, providing psychological support (improving a patient's well-being, strengthening a patient's belief about treatment effectiveness and success, close cooperation and patient's active participation in the therapeutic process) and inducing anabolism by means of clinical nutrition [56].

Expert's comment

- (GW:) There are lacking meta-analyses which would unequivocally prove the effectiveness of negative pressure therapy.

Recommendation 7.

In case of conservative treatment failure after 6 weeks of therapy and absence of any prognostic signs suggesting fistula healing in metabolically stable patients, it is recommended to continue outpatient treatment with home parenteral nutrition or enteral nutrition administered distally to the fistula.

As early as in 1970, Dudrick et al. published the outcomes of parenteral nutrition treatment in 78 patients with gastrointestinal fistulae – implementation of conservative treatment led to spontaneous fistula closure in 70% of patients with a mortality rate of 6% [57]. Another three retrospective studies compared patients treated conservatively with parenteral nutrition. Each of these trials recorded a significant increase in the percentage of spontaneous fistula closures, from 27% to 56%, from 34% to 81% and from 35% to 65%, respectively, as well as a significant reduction in the mortality of patients who were treated with nonsurgical approach [23, 58–62]. Results of conservative treatment of fistulae published in literature vary considerably, ranging from 19% to 92% of successful outcomes. Out of all cases of healed fistulae, 90% closed in the first month after sepsis had resolved, while another 10% closed in the second month. It is uncommon for a fistula to heal after 8 weeks. If conservative treatment has not been successful in healing of a fistula, it is recommended to prolong feeding and prehabilitation involving home parenteral and/or enteral nutrition, in order to achieve optimal local and metabolic conditions for reparative abdominal surgery [63–72].

Expert's comment

- (TB:) after stabilizing a patient's metabolic condition, educating him or her on proper fistula wound care and ensuring adequate parenteral nutrition or enteral nutrition combined with parenteral nutrition, outpatient treatment may be commenced earlier than after 6 weeks. Some fistulae may achieve metabolic compensation at home and will therefore heal much later.

Recommendation 8.

Surgical treatment is indicated only if it is technically possible to reestablish continuity of the gastrointestinal tract and the body's metabolic condition allows for effective healing.

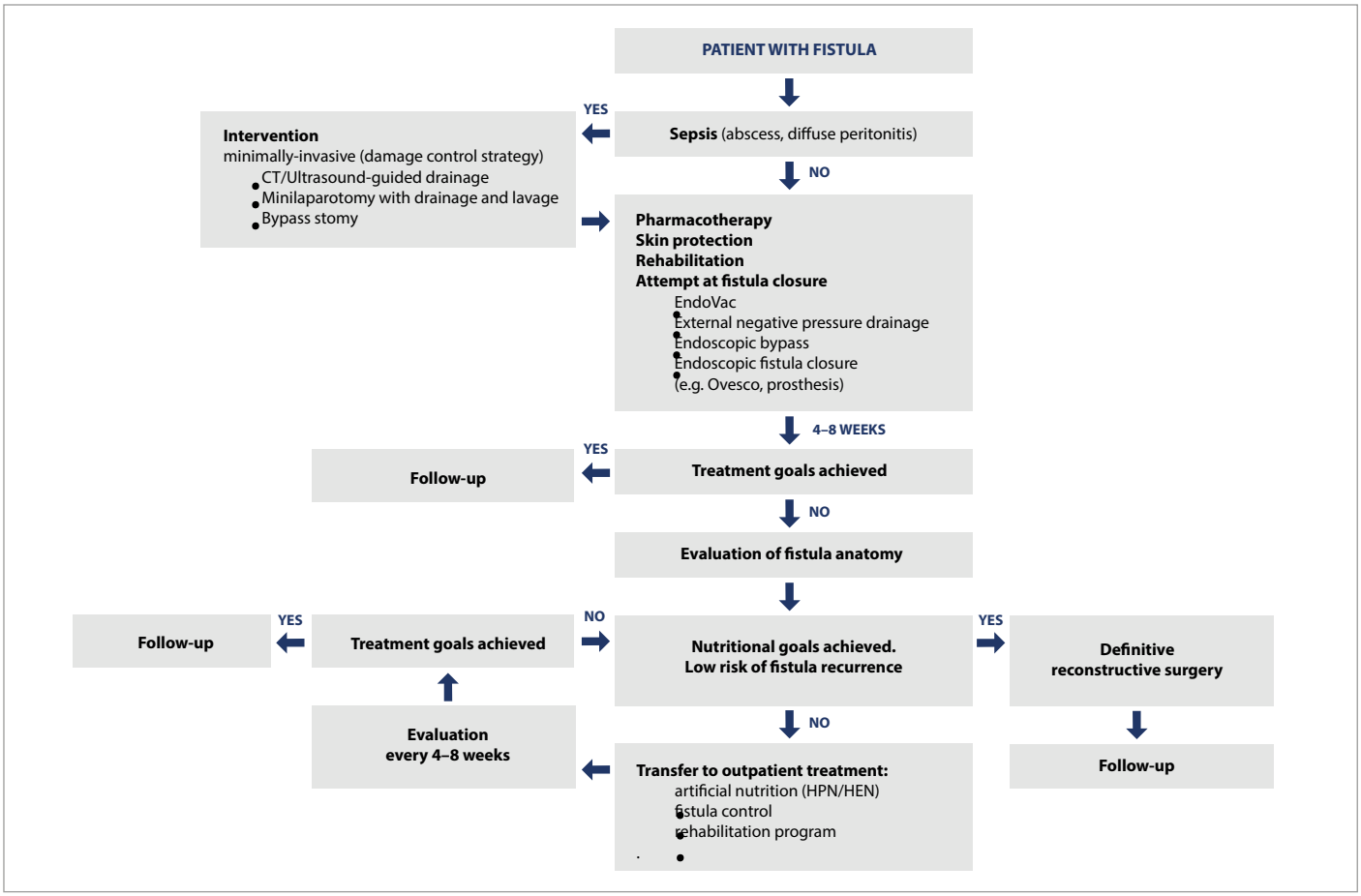

Fig. 2. Algorithm for management of gastrointestinal fistulae.

Thoughtless attempts at surgical treatment without patient preparation are cases of malpractice and are not recommended. Multiple laparotomies and attempts at primary surgical repairs are not only unlikely to be successful but they put patients at risk of developing severe complications and increase the risk of disability in the form of short bowel syndrome. Elective surgery should be postponed until optimal general and local conditions are achieved. Patients with type 1 and 2 fistulae usually meet optimal metabolic status for effective healing after 3 months of intensive multimodal treatment. In case of type 3 and 4 fistulae, such readiness may be achieved in no less than 3 months after spontaneous skin closure or, if the wound has not healed, in 9 months from the beginning of treatment. Local inflammation resolves over time, increasing the chances for successful surgery and reducing the risk of repeated bowel resections.

Diagnostic tests and anatomical assessment prior to making a decision about surgery are key to a successful intervention. Advanced fistulae (grade 3 and 4) require extensive abdominal surgeries consisting of digestive tract and abdominal wall reconstruction and sometimes also involve the urinary system. Moreover, these procedures require an experienced multidisciplinary team (GI surgeon, urologist, plastic surgeon) and may require step procedures over several months. Results of treatment conducted in specialized centers with a multidisciplinary approach are characterized by: low mortality (approximately 3%), less than 25% of complications and low risk of fistula recurrence.

The volume of fistula (stoma) discharge should be kept at the level of less than 500 mL per day and it absolutely should not exceed 1000 mL per day. This equals to a loss of 12 g of protein, 600 kcal and a significant amount of electrolytes, vitamins and trace elements, as well as bicarbonates and bile salts. Greater fluid loss may hinder meeting nutritional goals and lead to metabolic and septic complications.

Keeping nasal tube for enteral nutrition for longer than 4 weeks is not recommended due to both poor quality of a patient's life and local complications related to enteral access. We advise placement of PEG, gastrostomy, surgical jejunostomy or a feeding tube inserted in the fistula's tract. Enteral nutrition restores anatomical and functional integrity of the gastrointestinal wall, reduces inflammation, prevents bacterial translocation, restores normal gut microbiota and limits antibiotic-resistant bacterial growth. Stimulating the gastrointestinal tract with nutrition increases hormone production, affects lipid metabolism, reduces the feeling of hunger and limits gastric secretions. Moreover, nutrition improves the mechanical strength of the intestinal wall and increases the diameter of the intestine, which greatly facilitates definitive surgical reconstruction. Enteral nutrition supports the resolution of diversion enteritis and restoration of normal bowel motility and intestinal transit. All these factors contribute to reduced risk for anastomotic complications and faster recovery after surgery. Patients receiving initially exclusive parenteral nutrition benefit from a combination of enteral and parenteral nutrition for 4 weeks prior to surgery, however this approach require significantly more efforts.

Before final surgical repair, patients with significant abdominal wall defects may require specialized rehabilitation, an individually tailored program of physical exercises for rebuilding the remaining muscles and fasciae, as well as other special procedures (e.g. expanders).

Experts' comments

- (TB:) prior surgical treatment may be considered in the following cases: rapidly progressing malnutrition, inability to provide nutritional support, presence of a stoma or fistula which is difficult to manage and does not allow for discharge from hospital despite patient's good metabolic condition. In such cases, corrective surgery ("improving" the situation) is acceptable;
- (JS:) in case of progressing malnutrition, metabolic losses should be limited and nutrition optimized. Urgent approach to surgery in these cases increases mortality.

Recommendation 9.

Surgical treatment should be carefully planned and preceded by a detailed anatomical evaluation. It is recommended to conduct reconstructive surgical procedures in reference centers.

Thorough anatomical assessment of the fistula is crucial in making a decision about the timing and strategy for elective surgical intervention [73–75]. Factors preventing fistula healing include: distal intestinal obstruction (ileocecal valve stricture, abdominal adhesions etc.), fistula tract lined with mucousa, neoplasm or infection in the fistula tract, active inflammatory bowel disease (Crohn's disease), foreign body (hernia mesh, drain in the fistula lumen), emaciation, history of radiotherapy, short fistula tract, large gastrointestinal or abdominal wall defects, immunosuppression, intestinal ischemia. Factors responsible for treatment failure are abbreviated as FRIENDS (Foreign body, Radiation, Inflammation, Epithelialization, Neoplasm, Distal intestinal obstruction, Steroids).

Preoperative anatomical assessment should answer numerous questions, including:

- How many fistulae are active?
- Which intestinal segment does the fistula origin from?
- What is the patency of the intestinal segment below and above the fistula?
- Which intestinal segments are suitable for reconstruction?
- How long is the fistula tract?
- Is the fistula tract lined with epithelium? Are there any other factors which could possibly affect healing?
- Is the intestinal segment below the fistula patent?
- What is the anatomy of the abdominal wall? Will abdominal closure be possible?

Patient eligibility criteria for surgical fistula closure include:

- no perspective for spontaneous fistula healing,
- absence of systemic or local infection,
- optimal metabolic condition, normal BMI,
- functional improvement – better physical fitness,
- improved functional performance of all organs and systems,
- abdominal closure at the surgery is feasible,
- absence of other diseases limiting the perspective of survival for the next several months.

Expert's comment

- (TB:) prior to surgery, sphincter function should be evaluated and fecal masses flushed out of the bowel.

CONCLUSIONS

Therapeutic goals in gastrointestinal fistula treatment include: reduction of mortality, preventing complications and facilitating fistula healing by conservative treatment or performing successful reconstruction surgery after adequate preparation. These goals are not achieved easily, as fistula treatment often takes several weeks, especially in malnurished patients.

Fistula treatment is a complex process including: bypassing the intestinal segment with fistula, individually adjusted nutritional treatment, pharmacological reduction of fistula secretion, negative pressure therapy, physical therapy and psychological support. Decision about surgical intervention should be preceded by metabolic and local improvement and optimization (resolution of inflammation) aimed uncomplicated healing. Emergency surgical procedures should be reserved for cases of uncontrolled sepsis or haemorrhage. Minimally invasive techniques are preferred to reduce metabolic stress. Endoscopic procedures (clipping, stents, vacuum endotherapy, PEDS) significantly accelerate healing of fistulae [4, 76]. The algorithm presented in Fig. 2. summarizes the major principles of treating gastrointestinal fistulae.

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