RECOMMENDATIONS OF ASSOCIATION OF POLISH SURGEONS AND POLISH SOCIETY OF ONCOLOGICAL SURGERY
GASTROINTESTINAL FISTULAE IN PATIENTS TREATED FOR MALIGNANCY
- DIAGNOSTICS AND TREATMENT

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Postoperative gastrointestinal fistulae occur more often in patients undergoing surgical treatment for
oncological reasons than non-oncological reasons. Fistula is associated with a number of serious sequelae
and complications: fluid and electrolyte abnormalities, acid-base abnormalities, local and systemic infec-
tion and progressive cachexia that increase morbidity, treatment duration and mortality. Development of
fistula additionally delays or prevents specific treatment in oncology. For a patient, a fistula is associated
with both physical and mental suffering resulting from concern over further therapy.

Although the introduction of advanced surgical techniques, intensive postoperative care, total paren-
teral nutrition and modern enteral nutrition, resulted in decreased postoperative mortality, however
the number of patients with gastrointestinal fistulae hospitalized in the departments of surgery is not
decreasing. This may result from the fact that many patients still present for treatment in the advanced
phase of their malignancy (clinical stage III/IV according to International Union Against Cancer – UICC)
and consequently in worse general status, which poses a high risk of postoperative complications and
requires more extensive procedures in progressively older patients. Thus gastrointestinal fistulae still
remain a serious clinical problem. Main components of treatment of fistulae include: adequate drai-
nage, fighting of infections, artificial nutrition and drugs that decrease gastrointestinal secretion (e.g.
somatostatin) that are intended to create conditions for spontaneous fistula healing. Some cases may
require an early or late surgical intervention.

Key words: carcinoma, digestive tract, fistula

Gastrointestinal fistulae are usually serious complications of medically or surgically treated
diseases. They are often associated with poor general condition of the patient and high mor-
tality (1). Fistulae lead to abnormal translocation of gastrointestinal contents, digestive jui-
ces, water, electrolytes and nutrients, from one organs that contain a lumen to other organs or to the skin and to the outside, causing various sequelae. Furthermore, fistulae result in marked prolongation of patient hospitalization which significantly increases the treatment costs. Although gastrointestinal fistulae may form spontaneously in inflammatory bowel and pancreatic disease, diverticulosis of the colon, gastrointestinal malignancies or radiation-induced enteritis, majority of gastrointestinal fistulae (approximately 80%) are a consequence of surgical activities (2).

The most common cause of postoperative fistula is a leaky intestinal anastomosis as a result of: ischemia of the anastomosis, infection, excessive tissue tension or mechanical blockade beyond the site of anastomosis. Most often they result in an external fistula and the discharge is evident due to the drains left in the wound. Early fistulae that manifest within 48 hours after the procedure, are considered technical errors. Although early fistulae are believed to require an early surgical intervention, experience in treated fistulae indicates that many of them can be successfully managed medically, unless there are signs and symptoms of peritonitis. Low-output fistula, effective draining and to some degree, late manifestation of a fistula after an operation (after 5-6 days), are believed to indicate good prognosis and possibility that the fistula will close with conservative treatment (1).

Due to a large number of complications and high mortality in gastrointestinal fistulae, successful and effective treatment is of utmost importance. Despite considerable progress of knowledge that has been made recently, treatment of gastrointestinal fistulae is still an important challenge for the surgeons worldwide. Until 1960, mortality in gastrointestinal fistulae was very high, approaching 40-85% (3, 4, 5). Introduction of artificial nutrition techniques, in particular total parenteral nutrition (TPN) and intensive medical care, reduced mortality and improved the rate of spontaneous fistula closure to approximately 60-80% (5-9) however the time to fistula closure still remains long and patients still remain hospitalized for weeks or even months, before the fistula closes (6, 10). Thus it is obvious that a treatment that has a potential to shorten the fistula closure time, would be very beneficial for the patient since it would shorten the hospitalization and concurrently decrease the treatment costs (11, 12).

This paper presents clinically relevant details that are important for the management of patients suffering from malignancies that developed gastrointestinal fistulae.

According to the state of the art, conservative treatment of fistulae is considered the first line therapy. It should include adequate draining, nutritional support and somatostatin or its analogs.

Main reasons for failure of conservative treatment include lack of patency of the gastrointestinal tract below the fistula and/or anatomical conditions that prevent the fistula form healing (5, 13-17).

In some cases, additional early (up to 24 hours) or delayed (> 24 hours) surgical intervention may be required, depending on clinical situation and general condition of the patient. Usually an early surgical intervention should be undertaken when a fistula is accompanied by signs and symptoms or peritonitis or complication such as: abscesses, leakage or hemorrhage.

It is believed that a delayed surgical treatment is indicated when the volume of fistula discharge does not decrease within four weeks or the discharge decreases without spontaneous fistula closure. However, the choice of timing of surgical treatment is dictated by multiple factors. The most important factors include: general condition of the patient, extensity of inflammation in the abdominal cavity and nutritional status (5, 18-22).

**DEFINITION AND CLASSIFICATION OF GASTROINTESTINAL FISTULAE**

A fistula is a complication of treatment or disease that prolongs the hospitalization and markedly increases treatment costs and significantly worsens the quality of life. Its initial symptoms include: abnormal postoperative course (pain, fever, bloating, leucocytosis, inflammatory infiltration around the wound) and discharge of intestinal contents from the wound and/or drain, most commonly 5-7 days after the surgical procedure.

From the pathophysiological point of view, a fistula is an abnormal communication between epithelialized surface of the intestine or ductal epithelium of a parenchymal organ of the alimentary system (e.g. pancreas) and the skin (an external fistula – fig. 1), or with another epithelium of an organ located in the abdomi-
nal cavity or in the chest as well as peritoneal, pleural cavity, extraperitoneal space or the mediastinum (an internal fistula – fig. 2).

Basic criteria of fistula classification include anatomical location, etiology, location of an external orifice, output of the discharge and morphological presentation.

Most commonly fistulae are classified according to their anatomical location, into: esophageal, gastric, duodenal, jejunal, ileal and colonic fistulae. Based on their relation to the viscus from which they arise, they are divided into lateral or end fistulae. Based on their external orifice, they are classified as external fistulae and internal fistulae.

Etiology of gastrointestinal fistulae is presented in tab. 1.

Based on etiology, gastrointestinal fistulae can be divided into spontaneous (approximately 20%), resulting from an inflammatory pathology (e.g. pancreatitis, inflammatory bowel disease, particularly Crohn’s disease and advanced malignancy) or iatrogenic (approximately 80%), i.e. resulting from external factors (e.g. radiation-induced fistulae which are a consequence of ionizing radiation in the course of radiotherapy, post-traumatic and most commonly – postoperative).

Based on morphological criteria, gastrointestinal fistulae can be divided into: simple – direct communication (only one canal) with some other visceral organ that has a lumen or a space (e.g. pleural cavity) in case of internal fistulae or body surface (skin), directly or indirectly in case of external fistulae, and complicated (fig. 3) – with multiple canals and communicating with more than one organ or intraabdominal space or body surface (15, 18). Based on the fistula canal, fistulae are classified as uncomplicated, in which the fistula canal connects gastrointestinal lumen with atmosphere, and complicated, in which the canal goes through an abscess, between intestinal loops, its external orifice is located in an extensive defect of abdominal wall and multiple fistulae.

Based on the volume of the discharge, fistulae are classified as high-output (> 200 ml/24 h) or low-output (< 200 ml/24 h) fistulae.

**CONSEQUENCES OF GASTROINTESTINAL FISTULA**

Gastrointestinal fistulae, in particular post-operative fistulae, pose numerous clinical
problems. A fistula occurs usually early after an operation, in the period of neuroendocrine disturbances, catabolism and decreased immunity. It is accompanied by an infection, manifesting as a limited or diffuse peritonitis and/or infection of post-operative wound that exacerbate metabolic abnormalities and catabolism of the post-operative period and fluid loss which composition and volume depend on the fistula location and size. Peritonitis that develops in some patients, requires an early re-operation of the fistula, but in majority of patients the infections undergoes self-limitation to the area immediately adjacent to the fistula. Intraperitoneal abscesses result in approximately 30% of patients from contamination of peritoneal cavity with intestinal contents (5).

The volume of fluids discharged through a fistula within 24 hours can be as high as 9 liters. Concentration of electrolytes and pH of the fluid discharged through a fistula, depend on its location and functional status of the gastrointestinal tract. Because bile and pancreatic juice are hypertonic with respect to blood plasma and majority of digestive juices contain more potassium than plasma, loss of electrolytes is relatively higher than loss of water. Until recommendations for treatment of fluid and electrolyte and acid–base disturbances were prepared, they were one of the most common cause of death in patients with fistulae.

Increased protein loss and increased protein and energy demand in face of lack of possibility of effective nutrition through the natural pathway, lead to rapidly progressing cachexia that occurs in more than half of patients.

Along with a discharge excreted through a fistula, patients also lose not clearly known enterohormones. They are missing in the further parts of the gastrointestinal tract which disturbs or eliminates a natural inhibition of gastrointestinal secretion. Thus some Authors administer the contents discharged by fistulae to the portion of the gastrointestinal tract located below the fistula. This results in decrease of the fistula discharge by approximately 30% and decreased intensity of hepatic disturbances, which are probably caused by interruption of the heptointeretic circulation of bile acids, in particular in the case of duodenal and intestinal fistulae (23). Such management is not commonly used due to technical difficulties.

Hemorrhage is among the most dreadful and most common complications of fistulae. Bleeding from the gastric and duodenal mucosa is most commonly caused by hemorrhagic inflammation of the mucosal membrane in the course of septic state or multi organ failure. Coexisting peptic ulcer is a rare cause of bleeding. Ulcer caused by a rigid probe in the stomach can be a source of esophageal bleeding. Hemorrhages from the peritoneal cavity or wound margins can be caused by a blood vessel injury by a drain or digestive juices. Most of the hemorrhages require surgical treatment. Less common complications include mechanical obstruction of the gastrointestinal tract below the fistula that may cause fistula and prevent it from healing.

According to the literature, until 1970 the most common causes of death in patients with fistulae included:
- cachexia,
- fluid and electrolyte and acid–base disturbances,
- septic complications (24).

Preparation of principles of treatment of fluid and electrolyte and acid–base disturbances and introduction of nutritional support enable effective treatment of fistulae and concurrent maintenance of improvement of patient’s nutritional status (8, 25). Infections remain a number one problem. Although septic complications are the most common cause of death, majority of reports do not specify an exact etiology of infection. In an early period, these most probably include peritonitis and less commonly intraperitoneal abscesses and infection of the fistula region or bacterial translocation from the excluded portion of the gastrointestinal tract.
tract below the fistula. Uncontrolled infection prevents effective treatment and some of these patients die as a result of septic shock immediately after occurrence of the fistula; some patients develop a multi-organ failure.

**DIAGNOSTICS OF THE GASTROINTESTINAL FISTULAE**

The most common symptoms of a fistula include: pain (initially limited, thereafter diffuse) and fever, although a fistula may also cause no fulminant symptoms, and manifest as increased white blood cell count or worsened general condition.

External fistulae are easier to recognize through visible sites of atypical discharge: spontaneous or resulting from surgical incisions that drain pus and/or intestinal contents.

Internal fistulae are a more difficult diagnostic problem but the following symptoms are frequently observed in these patients: diarrhea, symptoms of sepsis, respiratory disturbances and sometimes air, pus or stool in the urine. If a fistula is confirmed, a volume of 24-hour discharge should be assessed and biochemical assessment (amylase, lipase, bilirubin, pH, electrolytes) and microbiological assessment (culture) of the fluid discharged from the fistula should be performed. To obtain necessary information about a patient who develops a gastrointestinal fistula (most commonly intestinal), a standard diagnostic management should included the following (one or several) diagnostic modalities and monitoring and assessment of parameters of the fluid discharged from the fistula.

The following clinical and instrumental diagnostic modalities are recommended in the gastrointestinal fistulae (19, 26, 27).

**Monitoring of clinical parameters:**
- volume of the fistula discharge,
- fistula characteristics (color, smell),
- fluid and electrolyte balance and assessment of other metabolic abnormalities,
- assessment of biochemical parameters (amylase, lipase, bilirubin, pH, urea),
- microbiological assessment (culture),
- assessment of nutritional status (predominantly biochemical and immunological parameters).

**Imaging investigations:**
- an examination with methylene blue to confirm the presence of a fistula; currently is rarely used. Positive result does not definitely confirm the presence of a fistula,
- upper or lower gastrointestinal endoscopy although recommended, should not be used in the post-operative period due to possibility of anastomotic dehiscence.

Thus the principle diagnostic modalities in fistulae are still: gastrointestinal examinations with water soluble contrast agents and fistulography with water soluble contrast agents which are aimed at confirming the presence of a fistula and determination of its location, patency of the gastrointestinal tract below the fistula as well as location of drains that drain the fistula. Some authors suggest that such examinations should be performed 3-5 days, while others 3-4 weeks after a fistula formation. Ultrasound, computed tomography or magnetic resonance imaging is performed to rule out abscesses.

**TREATMENT OF GASTROINTESTINAL FISTULAE**

The main goal of treatment is to cure the patient and restore alimentary autonomy. One of the available strategies to achieve this goal is to obtain spontaneous fistula closure. Fistula healing is believed to facilitate nutrition promoting healing, infection control, decreased secretion and promote conditions that support healing by draining the fistula canal and stimulation of peristalsis below the fistula. Shortening of a healing time decreases the risk of infection and shortens the hospitalization and reduces the treatment costs and costs of hospitalization (12).

Some fistulae may close spontaneously but the rate of spontaneously closed fistulae varies depending on fistula type and location. The incidence of spontaneous healing is low in fistulae related to Crohn’s disease and to malignancy as well as in fistulae with external orifice located in an extensive defect of abdominal wall.

Table 2 summarizes factors that hamper a spontaneous fistula closure.

An adequate fistula draining is of utmost importance: it leads to prevention of many complications in the course of medical treatment, facilitates healing (closing of the canal margins) and ensures precise monitoring of the amount of lost fluids and electrolytes and better protection of the skin against the detrimental effects of digestive substances (27).
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Fig. 4. Intestinal fistula with intestinal narrowing below the fistula

Fig. 5. Intestinal fistula with total lack of continuity between the ends of the intestine

Table 2. Factors that hamper a spontaneous closure of gastrointestinal fistula

- Infection
- Malnutrition/cachexia
- Coexisting:
  - Crohn’s disease
  - irradiation
  - malignancy
- Anatomical problems:
  - foreign body
  - intestinal narrowing below the fistula (fig. 4)
  - total lack of continuity between the ends of the intestine (fig. 5)
  - chronic abscess around the site of the fistula (fig. 6)
  - mucoso–cutaneous continuity (fig. 7)
  - external orifice in an extensive defect of abdominal wall

The timing of a fistula treatment, in particular first 24-48 hours after its diagnosis, especially in high gastrointestinal fistulas, is of utmost importance (1, 11). At this time, the principle goal of treatment is to control the shock, correct fluid and electrolytes and acid-base abnormalities, supplement blood and protein, ensure effective drainage and protect the skin, drainage of the gastrointestinal tract by insertion a nasogastric probe to the stomach or gastrostomy. A decision must be made whether to operate early (that may be required in case of diffuse peritonitis, leakage of the gastrointestinal contents and abscesses). In the latter case, possible percutaneous drainage under US- or computed tomography-guidance should be considered. If the decision to operate early is made, the following issues should be taken into account:

- healing of a fistula is rarely possible unless the underlying cause is eliminated (correction of a technical error or suturing of a missed injury of intestinal wall can solve the problem, while in the case of coexisting diffuse peritonitis, pronounced inflammatory reaction, severe patient’s condition or disturbed gastrointestinal patency below the fistula, fistula can recur even if the opera-
tion has been performed perfectly from the technical point of view),
– breaking the continuity of the gastrointestinal tract and formation of an end-stomy and mucosal fistula is an immediate life-saving procedure,
– if breaking the continuity of the gastrointestinal tract and formation of an end-stomy is impossible, one must limit his/her actions to creating conditions that facilitate fistula healing (adequate drainage, decompression of the anastomosis).
When a decision is made to manage a patient conservatively, the standard management of the gastrointestinal fistula usually includes (1, 11):
– nothing per os,
– decompression of the gastrointestinal tract by inserting a nasogastric suction probe to the stomach (or in the area of the anastomosis) or gastrostomy,
– reduction of gastric secretion (H2-blockers, proton pump inhibitors, somatostatin),
– optimization of fistula drainage – suction drainage is recommended, adjusted to a fistula type on an individual basis,
– skin protection around a fistula,
– correction of fluid and electrolyte abnormalities and improvement of patient’s nutritional status,
– antibiotic therapy (first de-escalation, then targeted),
– nutrition treatment (parenteral and/or enteral),
– respiratory and motor rehabilitation.
Figure 8 summarizes the sequence of events related to formation and treatment of a gastrointestinal fistula.

CLINICAL PROBLEMS RELATED TO THE TREATMENT OF GASTROINTESTINAL FISTULAE

The circumstances found during the fistula treatment, facilitate development of infections, e.g. by:
– NPO (nothing per os) diet that decreases the volume of fistula effluent and limits inflammation in the skin at the fistula orifice but exacerbates malnutrition;
Fig. 8. Sequence of events related to formation and treatment of a gastrointestinal fistula. According to M. Falconi, P. Pederzoli The relevance of gastrointestinal fistulae in clinical practice: a review; Gut, 2002; 49 (Suppl IV), 2-10 (1).
insertion of a nasogastric probe decreases the volume of fistula effluent, but concurrently increases the risk of respiratory system infections (pneumonia due to poor ventilation);
- use of H2-blockers, proton pump inhibitors or somatostatin results in decreased volume of discharged gastric contents, prevents hemorrhagic complications (gastric, duodenal ulcer) (5). However, increased gastric pH results in increased incidence of fungal infections. Thus it is of utmost importance to monitor bacterial flora in patients treated for intestinal fistulae;
- drain-induced injury and bleeding from a fistula may result – they often require surgical intervention;
- intensive fluid-replacement therapy with correction of electrolyte abnormalities (Na, K, Ca, Mg), depending on the level of the fistula, sometimes leads to volume overload and circulatory failure;
- parenteral nutrition through a catheter inserted to the vena cava may result in catheter-associated sepsis, resulting from improper handling of the venous line. Incorrectly chosen parenteral nutrition may result in various metabolic complications, that in turn may facilitate other clinical complications;
- enteral nutrition may also result in complications, especially when the gastrointestinal tract is obstructed below the fistula and when there is no hemodynamic reserve that would allow splanchnic blood flow to increase.

Many literature data indicate that surgical intervention is indicated in patients in whom the fistula does not spontaneously close even after 30-60 days of nutritional support free of septic symptoms and the volume of fistula effluent does not decrease. The decision to undertake a delayed surgical treatment to heal the fistula should be taken only when the following factors indicate that the operation can be successful:
- inflammatory infiltration in the abdominal cavity has resolved,
- patient’s nutritional status has improved,
- patient has been mobilized.

Otherwise a delayed surgical treatment even by several years should be considered. During this time parenteral or enteral nutrition should be undertaken at home (20).

Furthermore, the following criteria should be met before definitive corrective surgery:
1. Gastrointestinal patency and efficiency below the fistula should be demonstrated.
2. Optimal antibiotic regimen should be selected basing on results of the culture.
3. Indications to temporary anastomosis decompression should be reviewed (temporary lateral fistula, insertion of a silicone drain) (22, 28).

Artificial nutrition and metabolic management

Conservative treatment of duodenal fistulae located outside the path of food passage, based on oral feeding and suction of the fistula contents, was used by Cameron as early as in 1920’s (29). Learning about the pathomechanism of fluid and electrolyte and acid – base abnormalities associated with a discharge of large volumes of digestive juices through a fistula, preparation of guidelines for their treatment and introduction of total parenteral and enteral nutrition based on ready diets, allowed conservative treatment of other fistulae as well. Since the progressive cachexia was considered one of the most important causes of mortality in patients with fistulae, nutrition, especially parenteral nutrition, started to be utilized commonly in the fistulae treatment and first reports were enthusiastic with regard to its effects on the treatment outcome. The spontaneous closure rate increased to 70-80% with accompanying drop of mortality rate to 6-10%. Many Authors confirmed beneficial effects of parenteral nutrition by comparing results of fistula treatment in patients receiving parenteral nutrition with results obtained before its introduction. Deitel (30) achieved drop in mortality rate from 40% to 9% by using parenteral nutrition or enteral nutrition, Himal et al. (31) from 33% to 8%, Kaminsky and Deitel (32) from 40 to 12.5%, Fujita et al. (33) from 55% to 40%, Thomas (34) from 60% to 26%, Riboli et al. (25) from 87.5% to 25%, and Wretlind and Sudžijan (36) from 85% to 33%.

Subsequent studies, conducted in larger groups of patients, provided more varied results. According to Campos et al. (37) (188 patients with fistulae), spontaneous fistula closure was detected only in 31% of cases, and excluding pancreato-biliary fistulae: only in 26%. Li et al. (38) (1168 patients) achieved spontaneous fistula closure in 37% of cases,
Hollingon et al. (39) (277 patients) – in 20%, and Haffejee (40) (147 patients) in 75%. Undoubtedly, spontaneous closure rate depends on type and location of fistulae and probably on other treatment methods, used concurrently (suction, fistulae with orifice in abdominal wall defect, coexisting conditions, general care and predominantly ability to prevent treatment complications). Assessment of prognostic factors with a regression analysis demonstrated the following factors of poor prognosis: high score on APACHE II scale, low albumin concentration (7), early discharge of large volumes of intestinal contents through a fistula and coexisting conditions (41) and coexisting other complications and metabolic abnormalities, advanced age, malnutrition before the initial operation and delayed nutritional treatment, infection that could not be controlled and no patient immobilization (5). The poor prognostic factors for a fistula healing included, besides infection that could not be controlled, fistula orifice in a large abdominal wall defect (5). It must be emphasized that the volume of the fistula effluent was a significant factor only in one of the three studies.

It has been found that although after introduction of parenteral nutrition and enteral nutrition, more patients require surgical treatment than previously thought, due to nutritional treatment the surgical treatment can be started later, after a few weeks or even months of conservative treatment, without the risk of worsening of patient’s general status (20, 25, 28).

Enteral nutrition should be used whenever possible. It can be the only method of nutrition in low-output fistulae, provided that adequate fluid supply is ensured. Usually parenteral supplementation is required in high-output fistulae and is conducted until the volume of fistulae effluent is reduced. Enteral nutrition can be administered through a nasogastric tube (or gastrostomy) introduced below the fistula (e.g., in case of esophageal fistulae and other fistulae of the upper gastrointestinal tract). Enteral nutrition is also indicated in high intestinal fistulae if a tube can be introduced below the fistula and efficient peripheral portion of the gastrointestinal tract can be utilized (e.g., to the peripheral intestinal loop through a fistula or to the mucous fistula canal after disconnecting the anastomosis).

Levy et al. (42) used only enteral nutrition in 85% of 335 patients with intestinal fistulae, after a brief initial period of parenteral nutrition, administering diets that depended on the fistula location, above the fistula or through the fistula. Spontaneous fistula closure was achieved in 38% out of 234 patients treated conservatively with enteral nutrition and mortality was 19% in this group. However, mortality in the whole group was higher and was as high as 34% (42).

Both parenteral and enteral nutrition should supply dose of protein and energy adjusted to the needs and abilities of the patient. Adequate water and electrolyte and trace element supply must be provided, in particular when they are being lost through the fistula. The nutrition has to be complete, i.e. must include all required nutritional substances. However, excessive supply should be avoided, in particular in septic patients. Although effects of glutamine supplementation have not been studied in patients with fistulae, indications to its administration as well as to administration of omega-3 fatty acids, are dictated by the condition of a patient and intended treatment goals. In summary, nutritional treatment creates conditions for the fistula to heal and allows to delay the definitive surgical treatment until the time when patient’s general and local condition suggest that the reoperation will be successful. The precondition of safe parenteral nutrition is adequate care for venous line that allows for long-term treatment without septic complications (catheter-related sepsis – approximately 10% of cases).

One of the principles of treatment of patients with fistulae is NPO diet although there is no scientific evidence that such management increases the probability of fistula healing. It is feasible in the early period of treatment while other factors should be considered later. Probably, when a fistula is located in the lower portion of the gastrointestinal tract, drinking 250-300 ml of fluid per day would do no harm. Oral hydration could even decrease the volume of fistula effluent. The same is true for fistulae located outside the path of passage of the gastrointestinal tract, e.g. duodenal fistulae. Currently we utilize such management when it does not increase the volume of fistula effluent. Similarly, when we prepare a patient for operation in whom there is no chance of fistula healing and there is no risk of gastrointestinal content leakage, we allow him/her to consume nutritional supplements (e.g., Nutridrink).
Pharmacological blockade of the fistula effluent

Low-output fistulae heal faster and probably more often. The lower the fistula output, the easier it is to care for the area of the fistula orifice, to control the fluid balance and the patient’s well-being is better. Thus decrease of the fistula output with specific medications seems an easy and feasible management. The parenteral nutrition itself reduces gastrointestinal secretion (43). Further reduction of secretion can be achieved by administering medications that reduce gastric secretion. Cimetidine and ranitidine are most commonly used in this indications. They (especially cimetidine) can be added to the nutritive mixtures. Proton pump inhibitors that are also commonly used, cannot be added to the nutritive mixtures (5, 44). Such management reduces the risk of acute ulcer and serious complications such as gastrointestinal hemorrhage (5). Use of agents that reduce the secretion of other digestive juices is more interesting. Somatostatin – 14 belongs to such medications. This is a natural hormone that inhibits secretion of the gastric and pancreatic juice. Furthermore somatostatin reduces splanchnic blood flow, delays gastric emptying and prevents gallbladder contraction, decreases intestinal motility, reduces absorption of nutrients and stimulates absorption of water and electrolytes. Due to its short half-life, somatostatin requires continuous intravenous infusion. The dosage of somatostatin-14 administered concomitantly with total parenteral nutrition should be: 250 µg (bolus) and then a continuous intravenous infusion at a dose of 250 µg/h until the fistula is closed, and then 3 mg/day (125 µg/h) for another 48 hours to prevent re-opening of the fistula.

Several somatostatin analogues have been syntetized; octreotide is the most commonly used somatostatin analogue in the treatment of gastrointestinal fistulae. Due to its longer half-life, it is administered subcutaneously, usually three times daily. Newer analogues with prolonged activity are also available. Octreotide and somatostatin have similar but not identical properties with regard to their interaction with a specific receptor, so their activities are not identical. Analysis of published randomized clinical trials conducted on small groups of patients with gastrointestinal fistulae that used somatostatin or octreotide, demonstrates that both medications reduce the volume of fistula effluent and somatostatin treatment shortens the time needed by the fistula to heal. One prospective study that enrolled patients treated with somatostatin, demonstrated significant reduction of spontaneous healing, although patients with biliary and pancreatic fistula constituted more than half of the study population (41). The only available comparison of somatostatin and octreotide demonstrated higher healing rate among somatostatin-treated patients; this group also contained more patients with pancreatic fistulae as compared to the control group (47). According to Draus et al. (28), decreased volume of fistula effluent is observed in approximately 1/3 of patients with fistulae, while according to Scott et al. (48), treatment with octreotide has no effect. Basing on available data we can assume that somatostatin infusion (probably this does not apply to octreotide) reduces the volume of fistula effluent and shortens the time to fistula heal. Lloyd et al. believe similarly (41).

The advantage of somatostatin is possibility of adding its daily dose to the nutritive mixture. Studies confirming stability of somatostatin in the nutritive mixtures used in Poland, have not been conducted yet.

Although somatostatin-14 is an expensive treatment, it reduces treatment time and number of complications, probably resulting in decreased mortality in patients treated for the gastrointestinal fistulae and thus reduces treatment costs by shortening hospitalization.

Pancreatic fistulae

Increased number of patients undergoing surgical treatment for pancreatic malignancy and chronic pancreatitis, improved results of treatment of early stage of severe acute pancreatitis and improvements in procedural endoscopy, lead to the increase of number of patients with pancreatic fistulae (PF) (49-53). Incidence of PF after pancreatoduodenectomy ranges from 0 to 27%, after left pancreatectomy from 5 to 28.6% and after pancreatic injury from 9.6% to 13.5% (49, 50, 53). An estimated mortality rate related to PF after PD is 6-10% (49, 51). Postoperative PF result in increased morbidity and mortality, prolong hospitalization and increase the treatment costs (49-53). They will be discussed separately due to variable etiology, anatomical variations and digestive activity resulting from the nature of the fistula.
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Definition

Classic definition of PF (abnormal communication between epithelium of the pancreatic duct and other epithelialized surface, containing fluid with enzymes of pancreatic origin) does not cover all postoperative PF. Discrepancies in the definitions of postoperative PF found in the current literature (26 definitions were found in papers included in Medline from the recent 10 years (54)) result in difficulties in comparing study results and variable incidence of PF in the same case series, depending on utilized definition. Thus The International Study Group of Pancreatic Fistula proposed a new definition of postoperative PF and PF classification system that involved 3 groups depending on clinical implications and treatment costs (54, 55). According to this definition, postoperative PF is a discharge through a drain inserted during or after the operation through percutaneous puncture of any measurable volume, in which concentration of amylase is three times higher than in the serum, detected on day 3 after the operation or later (54). Classification criteria of postoperative PF according to Bassi et al. (54) are presented in tab. 1.

Etiology and pathophysiology

Pancreatic fistula results from the disruption of continuity of the pancreatic duct or leakage of its anastomosis with the gastrointestinal tract. As a consequence, pancreatic juice leaks outside (external fistula) or inside the abdominal cavity. External fistulae most commonly occur after the surgical procedures or percutaneous drainage of pancreatic cyst. Such fistula may occur also after endoscopic procedures or fine needle biopsy and in the course of acute and chronic pancreatitis and pancreatic injury (49-54).

Internal fistulae may drain into the peritoneal cavity (pancreatic ascites or pseudocyst). Until pancreatic enzymes become activated, pancreatic ascites does not cause peritonitis. Internal fistulae may also drain into pleural cavities, mediastinum and bronchi. Some patients do not present with abdominal symptoms and complain of cough and shortness of breath. PF may also drain into the extraperitoneal space, intestinal mesentery and lumen of any part of the gastrointestinal tract, biliary tract and vessels, e.g. the portal vein (49, 50, 52, 53).

Fistulae can also be classified on the basis of volume of the fistula effluent and anatomically lateral and end; the latter include fistula resulting from disruption of the pancreatic duct throughout the cross-section inside the pancreas (56). Such fistulae are believed to have no chance of healing under conservative therapy (49, 57). Lateral fistulae and fistulae of the pancreatic tail usually heal under conservative therapy, provided that there is good draining of the pancreatic juice into the gastrointestinal tract (50, 57).

Postoperative fistulae are most commonly located at the anastomotic site or in the operated region. Fistulae resulting from acute pancreatitis are most commonly located at the site of bending of Vrisung’s duct, at the border of pancreatic head and neck and fistulae occurring in patients with chronic pancreatitis can occur in any part of the pancreas (49, 50, 51, 53).

Pancreatic fistula results in loss of fluid and bicarbonate, and in some patients in metabolic acidosis, malabsorption resulting from lack of pancreatic enzymes in the gastrointestinal tract, infection and hemorrhages. The consequences depend on whether proenzymes in the pancreatic juice underwent activation or not;

| Table 1. Classification of postoperative pancreatic fistulae according to Bassi et al. (54) |
|---|---|---|---|
| Clinical status | Group A | Group B | Group C |
| Special treatment* | good | often good | looking sick / poor |
| US / CK result | negative | negative/positive | positive |
| Drainage > 3 weeks | no | usually yes | yes |
| Reoperation | no | no | yes |
| PF-related death | no | no | possible |
| Signs and symptoms of infection | no | no | yes |
| Sepsis | no | no | yes |
| Rehospitalization | no | nie | nie |

* Partial or total parenteral nutrition, antibiotics, enteral nutrition, somatostatin analogues and/or active drainage.
their activation requires contact with gastrointestinal contents or atmospheric air. PF with activated enzymes are more irritating, have greater penetrating ability and cause more local complications. The cornerstone of skin protection is drainage through a drain instead of stomy bag.

Diagnosis

The appearance of PF effluent may be variable, depending on whether it contains solely pancreatic juice, whether pancreatitis or infection coexists. It can be clear, turbid, green, yellow and blood stained or be purulent (49, 50, 51).

PF diagnosis is based on detection of high activity of pancreatic enzymes in the fistula effluent; it is believed that it should be at least 3 times higher than that of serum (51, 53). Imaging studies are selected basing on the fistula type and aim of the examination. Fistulography is the modality of choice in the canal fistula (51). In the other cases the diagnosis is based on computed tomography, magnetic resonance cholangiopancreatography that better visualizes the pancreatic duct and its possible disruption and endoscopic retrograde cholangiopancreatography (ECPW), conducted to visualize the fistula, pancreatic duct and its duodenal draining which is the base for the decision to proceed with endoscopic or surgical treatment (50). It is especially important in the case of internal PF (49, 50, 58). It is believed that ECPW should be performed within 2 weeks of the fistula formation (57).

Prevention

Narrow pancreatic duct and soft pancreatic tissue are the most important risk factors of the postoperative PF after pancreatectomy. Many methods were proposed, aimed at reducing the risk of PF, however neither of them proved successful. Prophylactic treatment with somatostatin or its analogues is still a matter of debate (59). Metaanalysis of 8 prospective clinical studies did not demonstrate any significant effect of somatostatin or its analogues on the risk reduction of the postoperative PF (60). However, another metaanalysis of 7 studies demonstrated significant risk reduction of the postoperative PF (61). Majority of European studies demonstrated benefits, contrary to studies conducted in USA. Two small studies demonstrated beneficial effects of somatostatin in the PF prevention, while prophylactic administration of octreotide reduced the incidence of complications without any effect on incidence of PF (50).

Treatment

The principle treatment of PF is conservative therapy. Endoscopic or surgical treatment is undertaken when there is no healing, at the earlier stage in patients in whom PF triggers life-threatening complications (hemorrhage, pancreatic ascites, pseudocyst, pancreatopleural fistula, mediastinal fistula and others) (49, 50, 51, 53, 59, 62). The poorest prognosis is associated with PF draining into the intestinal mesentery or extraperitoneal space.

When patient’s condition worsens, usually due to infection, urgent intervention is required to improve drainage. In majority of internal fistulae, US-guided percutaneous drainage is usually successful, targeted to peripancreatic fluid collection or pseudocyst; in the remaining cases early surgical treatment is indicated (49, 51, 52).

The precondition of PF healing is good drainage of the pancreatic juice via natural pathway. When a fistula does not heal, the reason should be determined basing on imaging studies, and treatment plan should be established thereafter. The available options include surgical procedure, endoscopic procedure or delayed procedure in the event of marked inflammation in the abdominal cavity or coexisting malnutrition. In the latter case, a drain is left in the fistula canal, the skin is protected around the fistula, method of nutrition is arranged and a patient is discharged home. When there is a chance that a fistula will heal, usually enteral nutrition is utilized, while in the remaining cases oral nutrition plus supplementation of pancreatic enzymes.

Conservative treatment

Basic principles of conservative treatment are similar to those in other gastrointestinal fistulae: cardiovascular and respiratory stabilization, hydration and correction of electrolyte and acid-base abnormalities and control of the fistula effluent. In pancreatopleural fistula, a drain should be inserted or sequentional decompressive puncture should be performed. Decompression of pancreatic ascites may also be indicated (58). In the event of coexisting infection, ongoing effective
Gastrointestinal fistulae in patients treated for malignancy - diagnostics and treatment

Drainage is required plus targeted antibiotic therapy (49, 50, 53).

Some patients receive artificial nutrition at the time of PF formation and usually parenteral or enteral nutrition, administered below the pancreatic area, is continued in the hope of obtaining healing. In the remaining patients oral nutrition should be stopped and parenteral nutrition should be started, to decrease secretion of the pancreatic juice and facilitate healing. Another indication to start artificial nutrition is disease-related malnutrition, which is exacerbated by disturbances of absorption due to lack of pancreatic enzymes in the gastrointestinal lumen.

Control of secretion

Parenteral nutrition reduces pancreatic secretion by 50 - 70% more than enteral nutrition (5, 14). In the low-output fistula, oral nutrition does not exacerbate secretion.

Somatostatin and its analogues, e.g. octreotide, dosed as in the intestine fistulae, reduce pancreatic secretion. After one day of somatostatin administration, the volume of PF effluent was reduced by 82% (63) and by 69% after octreotide administration (64). Somatostatin is administered as an infusion, while octreotide as three single doses, which results initially in reduction of pancreatic juice secretion, and increase after 4 hours (14). Somatostatin therapy reduced duration of PF treatment (63).

Brunaud et al. achieved healing of all 15 fistulae treated with somatostatin or its analogues, although in half of the patients with PF after a pseudocyst drainage, the pseudocyst recurred (64). Leandros et al. demonstrated that somatostatin was more effective than octreotide (47). Octreotide exerted also beneficial effects in the treatment of postoperative PF and pancreatic ascites (65). Octreotide reduced the volume of fistula effluent by 3-9-fold; 7 out of 12 fistulae were healed (66). Saari et al., using somatostatin and parenteral nutrition, achieved healing of 13 out of 19 (68%) PF (67). In all reports authors emphasize that good draining to the duodenum was the precondition of the fistula healing (47, 66, 67). Howard et al. did not found improvement of results with somatostatin (57).

Endoscopic treatment

Unless no result is achieved after 6-8 weeks of conservative treatment of PF, endoscopic treatment should be considered. Improvement of the pancreatic juice drainage creates conditions for the PF to heal. Sphincterotomy was being performed at the beginning of interventional endoscopy. Currently drainage through a naso-pancreatic tube or pancreatic duct stenting is an intervention of choice, effective in the event of pancreatic ascites, some pseudocysts, some postoperative PF of the pancreatic tail and body and even pancreateopleural fistulae (50, 68-71). Endoscopic drainage of a cyst is an option here (most commonly – endoscopic cystogastrostomy). Prosthesis allows outflow of pancreatic juice through the narrowing, allows for closure of a lateral fistula and sometimes even outflow from a split peripheral fragment which makes possible to delay the treatment. Prosthesis obstruction is a problem; it manifests as pain, fever, pancreatitis or fistula recurrence. To avoid early obstruction, initial insertion of nasopancreatic cannula is recommended, which thereafter can be replaced with a stent, if indicated, which length and diameter have to be individually chosen. Usually they are left for 4-6 weeks. If they are to be retained for longer, stent exchange is indicated every 6-12 weeks. Endoscopic intervention is estimated to allow for PF healing in 75-100% treated patients (49, 50), even with pancreateobronchial, pancreateopleural fistulae and totally disrupted pancreatic duct (70, 71). Tissue glues, most commonly a fibrin glue, have been used in isolated cases to obstruct the fistula canal and thus it is difficult to present any evidence-based recommendations in this area (49, 53).

Usually endoscopic interventions are undertaken through transampullar approach. When the Vater’s ampulla is inaccessible, transgastric endoscopic drainage could be possible, provided that an enlarged pancreatic duct is visualized under endosonographic guidance (50).

The chances of PF healing are high; according to the literature, conservative treatment, in some patients supported by endoscopic intervention, results in fistula healing in 70-90% patients (49, 57, 62, 63).

Surgical treatment

Surgical treatment is used when ECPW is impossible, prosthesis cannot be introduced to the pancreatic duct, the pancreatic duct has been completely disrupted or some fragment of the pancreas is missing and when conserva-
tive treatment has not resulted in PF healing. Choice of an operation depends on etiology and localization of a fistula, condition of the pancreas and outflow of the pancreatic juice to the duodenum. Depending on local conditions and the fistula localization, Roux loop pancreatojejunal anastomosis can be performed, peripheral resection of the pancreas with possible anastomosis of the remaining pancreas with Roux loop and anastomosis of the fistula canal with jejunal loop or stomach (49, 51, 52, 53, 72, 73). The authors believe that one should always undertake all efforts to maintain the pancreas. Therefore, when chronic pancreatitis coexists with enlargement of the pancreatic duct, Puestow operation is recommended. In the event of complete pancreatic split, closure of the proximal part and its anastomosis with a jejunal loop is recommended plus anastomosis of the distal part with the jejunal loop after ensuring that it is not damaged and that there is no second fistula. In fistula of the pancreatic tail, it is preferable to anastomose the tail with an intestinal loop then to resect it, unless a small part around the fistula can be resected and the remaining part can be safely closed. However, one must be sure that the outflow to the duodenum is preserved. When a fistula drains into the head of the pancreas, depending on local conditions, one must choose between anastomosis of the jejunum with the pancreas with the fistula coverage and pancreatojejunal anastomosis after enlargement of the fistula region (as in Pustow operation).

Although resection of the head of the pancreas is considered difficult due to pronounced inflammatory reaction, when malignancy is suspected or anastomosis with the jejunum cannot be performed, resection of the head of the pancreas with or without the duodenum can be the only option available.

Anastomosis of the jejunal loop or stomach with the wall of a pseudocyst cures a symptomatic cyst, however is associated with high rate of complications and recurrence (53). The authors believe that indications to this operation should be limited to exceptional situations in which none of the above mentioned operations can be performed and simple endoscopic intervention is impossible due to severe general condition of the patient.

In patients with PF of the pancreatojejunal anastomosis and symptoms of pronounced infection, surgical treatment can be indicated immediately after occurrence of PF or many days afterwards. In such situation the remaining part of the pancreas is resected or the fistula region is drained. Literature reports are conflicting and no data are available to suggest superiority of either method (49, 74). Drainage surgery is associated with requirement of long-term PF therapy.

Treatment of PF should be selected on an individual basis. Cooperation of a surgeon, endoscopist and radiologist is required. Majority of fistulae heals with conservative treatment and parenteral or enteral nutrition plus an agent that decreases pancreatic secretion (somatostatin) and endoscopic treatment when a fistula and pancreatic duct are visualized. Surgical treatment is undertaken when conservative treatment fails, with the exception of patients in whom emergency surgery is indicated due to life-threatening condition, such as infection or hemorrhage.

### SUMMARY

Available data indicate that the basic components of treatment of gastrointestinal fistulae, whatever their etiology, include:

1. Correction of acid-base and water and electrolyte abnormalities.
2. Effective fistula drainage.
3. Infection control (abscess drainage – surgical or percutaneous, antibiotic therapy).
4. Artificial nutrition.
5. Somatostatin, in particular in pancreatic and biliary fistulae.

Supportive components include:

1. Prophylaxis/treatment of thromboembolic complications.
2. Psychotherapy,
3. Rehabilitation.

Conservative treatment results in healing of most of the fistulae.

Early surgical treatment is indicated in the event of diffuse peritonitis, abscesses or hemorrhages. Under such circumstances extensive, curable operations should be avoided; staged operation is preferable. Initial treatment should be conducted in the department of surgery, according to presented recommendations. The decision to transfer a patient to a specialist fistula center should be made basing on risks and availability of treatment in the department of surgery.
Definitive reconstructive operation should be undertaken after improvement of patient’s general status and resolution of inflammation in the abdominal cavity, after systemic and local preparation of the patient.

REFERENCES


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