Nutritional Support in Gastrointestinal Diseases — Topic 12

Module 12.3

Nutrition and Gastrointestinal Fistulas

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Learning Objectives

- To learn about the general management of patients with gastrointestinal fistulas;
- To learn about the nutritional management of patients with patients with gastrointestinal fistulas;
- To learn about the metabolic and nutritional complications of patients with gastrointestinal fistulas.

Contents

Key Messages

- The development of enterocutaneous fistulas is a major gastrointestinal complication with significant morbidity and mortality requiring staged specialised treatment;
- Treatment focuses on controlling sepsis, optimisation of nutritional status, wound care, anatomical evaluation of the fistula, timing of surgery, and surgical strategy;
- 55-90% of the patients with an enterocutaneous fistula becomes malnourished, because of a combination of illness and starvation;
- Nutritional screening and subsequent assessment provide important information regarding nutritional status and requirements;
- Enteral nutrition has advantages over parenteral nutrition and where possible, is the preferred route of nutrition;
- Short bowel syndrome, ileus, high fistula output leading to malabsorption, are indications for parenteral nutrition;
- The duration of convalescence prior to reconstructive surgery must be at least six weeks (more commonly 6 months) to control sepsis, to clear inflammatory activity and regain normal body composition and function (normal nutritional status);
- The majority of patients do not require additional artificial nutritional support after fistulas closure.

1. Introduction

An enterocutaneous fistula (ECF) is an abnormal connection (fistula) between the intestine (enter) and the skin (cutis)(1). It can develop spontaneously, for example in patients with cancer, inflammatory bowel disease or after radiotherapy, but develops most often postoperatively as a result of iatrogenic intestinal lesions or leaking anastomoses. An Enteroatmospheric fistula (EAF) with visible mucosa and the absence of overlying soft – tissue within an open abdomen form a special subset of ECF's.
The treatment of patients with an ECF has proven to be extremely challenging and has resulted in the past a mortality rates of 40%. Mortality has mainly resulted from sepsis, malnutrition, and electrolyte imbalances and treatment is complicated by wound infections, high output fistulas and the need often prolonged safe nutrition requiring multi-disciplinary approach. Successful treatment is also specialist centres to which these patients can be referred.
Improvement of several aspects of treatment have led to the development of a guided approach by a multi-disciplinary team involving surgeons, gastro-enterologists, radiologist, dieticians, and nurses skilled in nutrition, wound care, fluid balance and psychology, which has reduced mortality from 40% to <% (2, 3). Welch (4) and somewhat later Chapman (5) a created the foundation for the structured approach to patients with an ECF. This was further developed by many groups adhering to similar principles, including management of sepsis and skin care, nutritional support, definition of intestinal anatomy, and development of a plan for a definitive surgical procedure when fistulas persist (5-7).
The incidence of ECF has been estimated to be below 0.5 patients per 100,000 inhabitants[6] and thought to complicate 0.8-2% of abdominal operations (8) and thus is one of the orphan diseases (9). This emphasizes the necessity to establish tertiary referral centres where in particular the severe cases can be treated (10). The following introduction provides an overview of the treatment guideline for patients with an ECF as it has evolved over the past decades and includes a discussion of the major complications observed in these patients.

2. Historical Summary

In 1960 Edmunds *et al.* were the first to study and describe a large cohort of patients with an ECF (4). They reported that mortality in their population was related to electrolyte imbalance, malnutrition and generalized peritonitis in 78, 61 and 67% of cases, respectively. Although antibiotic treatment had been available during this period, the reported overall mortality rate was 40%. In 1964 treatment of ECF patients evolved after Chapman and colleagues introduced a structured guideline for treatment of these patients (5). The guideline was based on treatment of the main complications, in order of their impact on survival. It primarily involved control of the fistula output, treatment of sepsis and maintenance of adequate nutritional status. A significantly lower mortality rate (12%) was observed in adequately intravenously nourished patients compared to the suboptimally fed group (55%). The authors concluded that adequate nutritional therapy could be decisive for survival. The introduction of parenteral nutrition consisting of glucose, lipid and amino acids in the late sixties has enabled supplementation of adequate amounts of macro- and micronutrients when enteral nutrition (EN) fails to reach requirements due to fistula output or poorly functionig bowel (11, 12). The effect of introducing PN was evaluated by Soeters et al. They retrospectively assessed outcome of ECF patients that received PN or not in the Massachusetts General Hospital between 1970 and 1975 (3). There was no significant difference in mortality between patients with PN (24.7%) and without PN (16.3%). Furthermore, outcome did not differ from the mortality rate (15.1%) of patients treated between 1960 and 1970 receiving no PN. The authors suggested that these results were related to 1) better patient monitoring including correction of electrolyte disturbances, support of respiratory and cardiac insufficiency and 2) the application of sound surgical principles. Finally, patients in the PN group had higher fistula output and were more ill than the patients that did not receive/need PN. Sepsis remained the main cause of death in both periods. Since then, several groups refined the treatment protocol, off which the focus revolves around the control of sepsis, optimisation of nutritional support, wound care, establishment of the anatomy of the fistula, timing of surgery and surgical strategy, abbreviated to SOWATS. Below, the guideline will be described in more detail.

3. Aetiology of the ECF

The ECF may lead to intestinal failure. Intestinal failure is defined as the reduction of gut function below the minimum necessary for the absorption of macronutrients and/or water and electrolytes, such that intravenous supplementation is required to maintain health and/or growth.and, if left untreated, leads to malnutrition, dehydration and deficiencies (14). Three types of intestinal failure are distinguished. Type I intestinal failure resolves within one month and mainly includes postoperative ileus or obstruction, requiring only short-term PN. Type II intestinal failure by definition extends one month and includes patients with complex inflammatory bowel disease, intestinal fistulas (ECF) and abdominal sepsis. They often require long-term PN and operative resolution. Type III intestinal failure results in dependency on PN. These patients mostly suffer from short bowel syndrome and require home PN (15).
A minority of ECF's develop spontaneously (10-25%) as a result of Crohn's disease, cancer or radiation damage and diverticulitis (**Table 1**) (2, 16-18). The majority of ECF's (75-90%) develops after surgery mainly because of iatrogenic lesions or anastomotic leakage in patients with malignancy of the digestive tract, Crohn's disease or infectious diseases of the bowel (2, 16, 19). In these patients, intestinal content from the damaged intestine enters the abdominal cavity which leads to abscess formation. This abscess may rupture spontaneously to areas of diminished resistance like the recently closed wound or finds its way to the skin after surgical or radiological drainage. In this way a connection is formed between the inside of the damaged bowel to the skin, forming an enterocutaneous fistula.

Table 1
Common causes of fistula formation

Formation	Cause
Spontaneous	Crohn's disease
10-25%	Cancer Diverticulitis Radiation enteritis
Surgical	Iatrogenic lesion (sutures)
75-90%	Anastomotic failure Abdominal wall dehiscence Mesh rupture Drain puncture
Traumatic	Diagnostic intervention (puncture)
<5%	(Traffic) accident

4. Management of ECF

4.1 Treatment Strategy

Patients with an ECF present intermittently with a low incidence and form a very heterogeneous population. Most patients receive initial treatment at the hospital where the complication occurred, but where the managing team will have limited exposure to these relatively rare patients. Due to the lack of centralisation and complexity of patients with ECF's randomised controlled trials of different treatment options in patients with ECF's are virtually impossible to perform. Consequently, establishment of optimal treatment is largely based on cohort series and expert opinion. A major factor in the lack of specialist centres is difficulties in re-imbursement as ECF management is not specifically coded, yet requires considerable resources (20). A number of expert centres have contributed to the optimisation of the care of these patients by development of treatment guidelines (10, 18, 21). Although the text of guidelines differs among institutes, there is general agreement on the priority of treatment steps. In order of priority the treatment strategy consists of, treatment of sepsis, optimisation of nutritional status, wound care, anatomical evaluation, timing of surgery and surgical procedure (20) (SOWATS; **Table 2**). Recognition of the presence of an ECF is the first step towards adequate fistula management. The treating physician should inform the patient about the general outline of treatment, duration of treatment and the possibility of a (further) surgical intervention (10).

Table 2
Treatment of patients with ECF according to the SOWATS guideline

Step	Considerations and action
Sepsis control	Signs of sepsis Radiological drainage of abscesses Relaparotomy on demand
Optimization of nutritional status	Rehydration and electrolyte supplementation Parenteral/enteral nutrition
Wound care	Wound care with woundmanager Sump suction
Anatomy of the bowel and fistula	Contrast fistulography MRI or CT enterography Fistula tract Visualisation of the length of the intestine and fistulas tract Stenosis, obstruction, fluid collection
Timing of surgery	Clinically stable Normalisation of laboratory values > 6 weeks after fistula development Defensive
Surgical strategy	Restore continuity Careful access to the bowel Cover sutures with omentum Stay away from compromised area

4.2 Treatment of Septic Complications

4.2.1 Diagnosis of Abdominal Infection and Sepsis

Throughout the past decades sepsis has been the main cause of mortality in patients with an ECF. Diagnosis and then treatment of sepsis has the highest priority. Most fistulas are established after a period of sepsis (see earlier). Sepsis is therefore at the origin of fistula formation. Nevertheless, other causes may lead to sepsis and accompany the development of a fistula (3-5, 22, 23), including infection of the central venous catheter, pneumonia and wound infection.

Clinical signs of sepsis include fluid retention and oedema, fever and organ failure. Patients show alteration in laboratory parameters that reflect inflammation and infection, including increased white cell counts and CRP and reduced plasma albumin levels (24). A central venous catheter infection must always be suspected and if found treated according to local protocols. When sepsis arises after surgery, intra-abdominal infection and abscesses should be suspected and excluded. In these cases CT or ultrasonic guided drainage of abscesses has proven extremely valuable to control the infection (25). When there are multiple collections and/or the radiologist is unable to place the drain inside the collection, an operative procedure is indicated. A minimal invasive procedure is the first choice but if needed to control sepsis, a complete laparotomy should be performed (**Fig. 1**). There is no difference in clinical outcome between a relaparotomy on demand or planned relaparotomy but an on demand strategy results in lower costs of treatment (26).

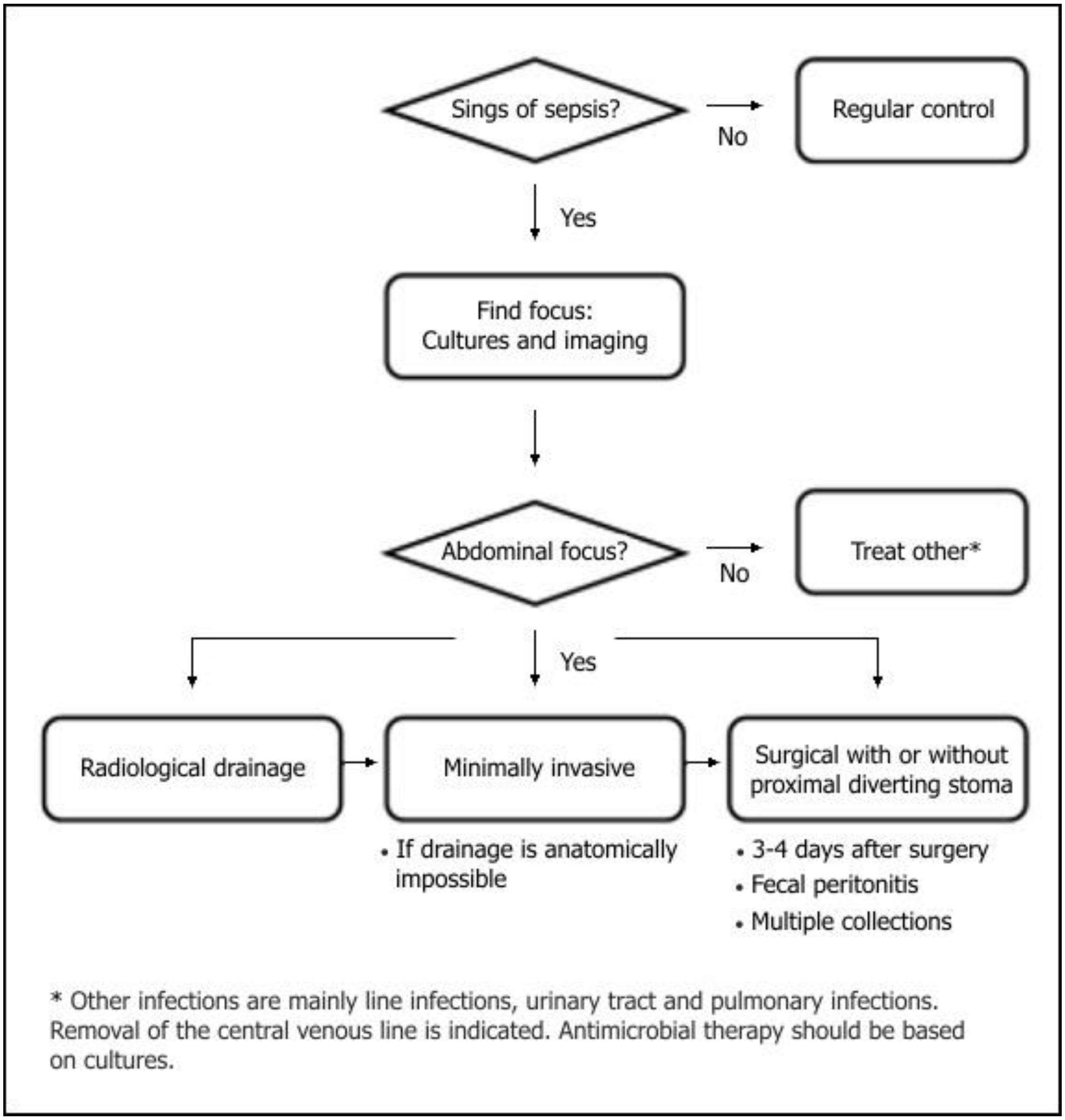

Fig. 1 Flow chart of sepsis treatment

4.3 Optimisation of Nutritional Status

4.3.1 Malnutrition

The pathophysiology of malnutrition consists of a combination of varying degrees of undernutrition (negative nutrient balance) and inflammatory activity, leading to changes in body composition and diminished function (27). Patients with an ECF suffer from inadequate food intake, exclusion of the intestine distal from the fistula and excessive loss of gastrointestinal contents in combination with inflammatory activity due to infection causing catabolism and increased energy expenditure (14). Subsequently, 55-90% of patients with an ECF become severely malnourished (4, 28, 29). Malnutrition decreases healing capacity and increases the susceptibility to infection even further. Edmunds *et al.* and Chapman *et al.* demonstrated that malnutrition in patients with fistulas resulted in an increase in morbidity and mortality (4, 5).

4.3.2 Nutritional Screening and Assessment

Nutritional screening and assessment provides information about the risk of malnutrition and basic energy requirements. Weight loss, body mass index, food intake and disease severity are easy screening measures during treatment. The Nutritional Risk Screening 2002 combines these parameters and can be used easily (30). Other validated tools include the Malnutrition Universal Screening Tool (31) and the Subjective Global Assessment tool (32).
In patients who appear at risk according to nutritional screening, a detailed assessment of body composition and energy requirement is advised in order to develop a nutritional plan. Individual energy requirements can be calculated with a number of different validated equations, or measured via indirect calorimetric analysis using the ventilated hood in cases where precise measurement is crucial.

4.3.3 Enteral Nutrition

EN, either oral, intragastric or intrajejunal, has several advantages over parenteral nutrition. It reduces the inflammatory response (33), maintains the enterohepatic circulation (34), maintains gut function and structure (35), decreases bacterial overgrowth (36), avoids intravenous access complications (37), blunts the hypermetabolic stress response (38) and has been claimed to decrease organ failure (39). However, in multiple organ dysfunction syndrome, bowel function may be compromised and EN is not always tolerated. Also, EN may severely complicate wound management in patients with fistulas in open wounds and intestinal failure precludes adequate nutritional support. However, when adequate wound care can be provided enteral nutrition should not be withheld (40). Complications associated with EN include aspiration, diarrhoea, misplacement of the nasogastric tube, nausea and vomiting, obstruction (ileus) and require special attention. Especially patients with a high output small bowel fistula (>500mL/day) need PN support. Alternatively, nutritional formulas can be infused into the intestine distal to the fistula: fistuloclysis. In a group of 12 patients who were prepared for a restorative procedure, 11 patients could be weaned of PN by fistuloclysis (41). A more recent paper has updated the concept of collecting the proximal fistula output and re-infusing this fluid into the disconnected distal bowel (42).

4.3.4 Parenteral Nutrition

Patients who are not able to meet nutritional requirements via the enteral route alone depend on parenteral supplementation in order to maintain or improve nutritional status (**Fig. 2**). Particularly in patients with high output small bowel fistulas, the intestine distal to the fistulous tract is not involved in the absorption process resulting in malabsorption. As discussed by Soeters (3) and emphasised by Fazio (43), PN has allowed postponement of surgical intervention in severely ill patients in whom re-operation would be extremely hazardous. PN can maintain or even improve nutritional status during this period provided infection is adequately treated.

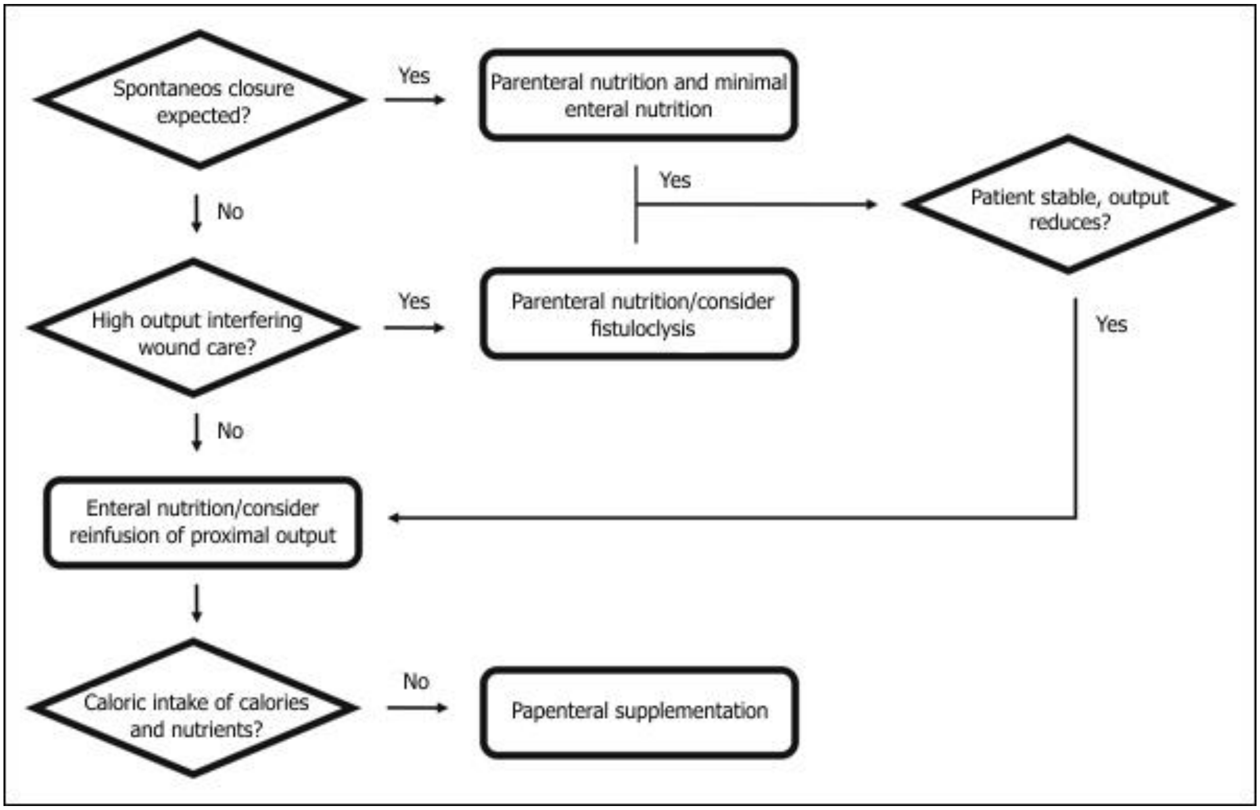

Fig. 2 Flow chart of nutritional management

The beneficial effect of PN for the treatment of patients with ECF is difficult to establish because of the simultaneous introduction of other treatment options (3). In addition, the beneficial effect of adequate nutritional support by PN in patients that cannot be adequately fed by the enteral route is so obvious that randomized trials including a non-treatment arm would be unethical. As a result of this benefit, more patients survived the initial disease and complications that had been lethal in the past. This resulted in a change in ECF population with more sick, elderly patients and consequently the outcome of treatment in terms of mortality did not alter in the last decades (3, 43). Earlier studies did suggest that in suitable cases postponement of surgical repair enabled by PN allowed for some spontaneous closure (44, 45).

4.3.5 Parenteral Fatty Acids

Patients most commonly receive PN formulas containing triacylglycerols, containing long chain fatty acids (LCFA). LCFA provide essential fatty acids and a caloric source and when included as source of FA currently provide the lowest prized lipid emulsion. However, the clearance of LCFA containing fat emulsions is not always optimal causing hypertriglyceridemia (46, 47). Free fatty acid overload can lead to steatosis and steatohepatitis by as yet not fully elucidated mechanisms. Abundant fatty acids have proinflammatory effects and produce reactive oxygen species leading to insulin resistance (48). There is no established method to interrupt this cycle or reduce hypertriglyceridemia. Several lipid solutions have been developed to prevent this complication but their value in clinical practice is not yet fully established. Of all RCTs on PN and lipid emulsions in humans, only a subset reported plasma triglyceride concentrations as a potential indicator of steatosis. In these studies, soy oil (SO), fish oil (FO), olive oil (OO), MCT/LCT mixtures, structured lipids (STG) and SMOFlipids were compared in various combinations. However, there were no differences observed between these lipid emulsions (FO vs SO (49, 50), MCT/LCT/FO vs SO (51), OO vs SO (52-55), OO vs FO (56, 57), OO vs MCT/LCT (58), STG vs SO (59-62), STG vs MCT/LCT (63), SMOF vs SO (64-68) and various (69)). Only two reports (by Sandstrom and colleagues (70) comparing STG with LCT and Schlotzer and colleagues and Schlotzer and colleagues comparing SMOF with LCT (65)) showed a reduction in triglyceride concentration in favor of the non-LCT groups, but this was measured after an infusion period of only 6 hours.

4.3.6 Immunonutrition

Immunonutrition can be defined as nutrition in which specific nutrients are included in amounts exceeding quantities normally present in food and that have beneficial effects on the immune response. For than two decades, such beneficial immunological effects have been ascribed to glutamine. The potential positive effect of glutamine is still a matter of debate and studies in patients with ECF are not performed (71, 72).
Enteral supplementation of substances such as arginine, omega-3 fatty acids, and nucleotides in critically ill patients and infants resulted in a decrease in infectious rate and reduction in hospital stay but no reduction in overall mortality (72-74). The effect of immunonutrition regimens has not been studied in patients with ECF.

4.3.7 Intestinal Failure Associated Liver Disease

Intestinal failure associated liver disease (IFALD) occurs as a complication in patients with intestinal failure. It occurs in 5 to 50% of patients with intestinal failure such as short bowel syndrome (SBS) and enterocutaneous fistula (ECF) (75, 76), potentially resulting in patients with chronic intestinal failure in end-stage liver disease (77). Several factors have been associated with its development such as parenteral nutrition, sepsis and the external loss of secreta of stomach, liver, pancreas and small bowel (78). Whereas the first two have been studied more thoroughly the value of loss of small bowel fluid has been less well established. An early study showed that collecting intestinal fluid that was lost through the ECF and reinfusing it into the distal intestine, normalized liver test abnormalities and albumin level (19). It was suggested that in particular loss of bile acid would play an important role in the development of cholestasis and IFALD. Support for this theory can be found in studies linking bile acids such as chenodexycholic acid (CDCA) and cholic acid (CA) with the farnesoid X receptor (FXR) (78, 80). The FXR is located in the liver, intestine, kidney and adrenals. Binding of bile acids with the FXR in intestine and liver induces a negative feedback loop of regulating the enterohepatic circulation. Moreover, the FXR regulates lipid, carbohydrate and glucose metabolism (81). Conversely, loss of bile via the ECF may lead to

reduced activation of the FXR, subsequent disturbance in bile homeostasis, and inflammatory signs in liver and intestine.
The importance of the FXR for lipid metabolism has been highlighted by animal studies showing that reduced stimulation of the FXR leads, amongst other genes, to increased expression of sterol regulatory element binding protein-1c (82-85), fatty acid synthetase (82, 86), acetyl-coenzyme A carboxylase (83, 87) promoting hepatic lipid accumulation leading to steatosis and in some patients to steatohepatitis (88, 89). Equally important in the development of liver damage may be intestinal damage and intestinal bacterial overgrowth caused by lack of bile acids and subsequent reduced expression of FXR (90-92). Bacterial endotoxins can now reach the liver by the portal circulation and have a detrimental effect on the liver, leading to systemic inflammation with increased levels of TNF-alfa (93). This further represses FXR expression (82, 94), but also stimulates hepatic fat deposition directly (94). Information about these mechanisms has been obtained from cholestasis, steatosis and FXR knock out animal models. Studies from non-cholestatic biliary drainage models that more adequately reflect patients with an ECF are lacking.

4.4 Wound Care

4.4.1 The Problematic Wound

ECF can produce large amounts of fluid. A high output fistula is conventionally defined as more than 500 ml fluid loss per 24 hours. An output volume between 200 ml and 500 ml per 24 hours is regarded by some authors as a moderate output fistula. When fluid loss is less than 200 ml per 24 hours, the fistula is defined as alow output (1, 96). In addition to fluid, electrolytes and nutrients, the fistula output contains proteolytic enzymes and bile salts that may damage the skin or other tissues like bowel in dehiscent abdominal wounds, surrounding the external opening. Subsequently, this area becomes inflamed and painful and liable to become infected. The wound can become macerated, granulation tissue may become macerated and newly epithelialized layers may desquamate. Skin, bowel and wounds should be healthy and not infected to allow proper healing of anastomoses and successful abdominal closure during the restorative procedure.

4.4.2 Treatment of Wound Surfaces

A dedicated team of wound care specialists is of great value for proper wound and stoma care, collection of fistula output and wound discharge, and protection of the skin. An endless array of products are available, including powders, pastes, adhesions materials, barriers, wound bags, etc. Dearlove reported the important elements that should guide wound care: origin of the fistula, nature of the effluent, condition of the skin and location of the fistula (97). As mentioned by Irving and Beadle (98) fistulas with a single orifice and intact skin can be properly treated with a silicone barrier surrounding the fistula after cleaning and drying of the skin. The hole in the adhesive disc must fit closely to the margin of the fistula, adequately covering the skin around the fistula. In high output fistulas it may be advantageous to use a wound managers either or not in combination with negative pressure. Single or multiple drain tracts passing through the abdominal wall and exiting in the skin close to bony prominences, scars, and so on, can be treated by filling the grooves with paste after which a large stomal appliance or wound manager system is placed over the abdomen. Fistulas residing in an abdominal wall defect constitute the biggest challenge and their incidence has substantially increased during the past decades (23, 99-101). Fistulas situated in a small abdominal wall defect can be treated with a large plate adhesive disc after which the edges are protected with filler paste. A wound manager is usually necessary to collect the output of the fistula. Fistulas in a laparostomy wound are treated most effectively with a wound manager, with or without negative pressure. Placement of a low pressure suction drain causes a slight vacuum in the bag resulting in constant drainage of fluid from the wound, preventing intestinal continents from damaging skin or bowel exposed in an open wound as well as possible (**Fig. 3**).

Fig. 3a and **3b**
3a. Enterocuteneous fistula in an abdominal wall defect and
3b. Appropriate wound care by use of a wound manager system.

4.4.3 Supportive Methods in Wound Care

Somatostatin analogues are not routinely advised for patients with an ECF. It can be used to reduce output (102, 103), aiming to facilitate wound care, but there is no advantageous effect on outcome, including the promotion of spontaneous closure of the fistula (103, 104). The vacuum assisted closure technique should be applied with caution since it may induce renewed fistulisation, thus complicating treatment even further. As summarized by Fischer these new fistulas may be associated with increased mortality (105).

4.5 Anatomical Evaluation

4.5.1 Macroscopic Analysis of the Abdomen and Discharge

Macroscopic diagnosis of an ECF in a dehiscent abdominal wall with the intestine including the fistula directly at sight does not pose great problems (**Fig. 4**). Fluid from the small intestine has a low viscosity and a green-yellowish color caused by the relatively high amount of bile salts and bilirubin. Fluid from the large intestine has a more brownish aspect, is more odorous, and has a higher viscosity. Also, output volume from the large intestine is, with few exceptions, lower than 500mL/day (106). However, macroscopic scrutiny of fluid discharge will not always be conclusive, especially when fluid discharge from the fistula is low or when the fistula connects with an abscess cavity or with a defunctioned loop (**Fig. 4**).

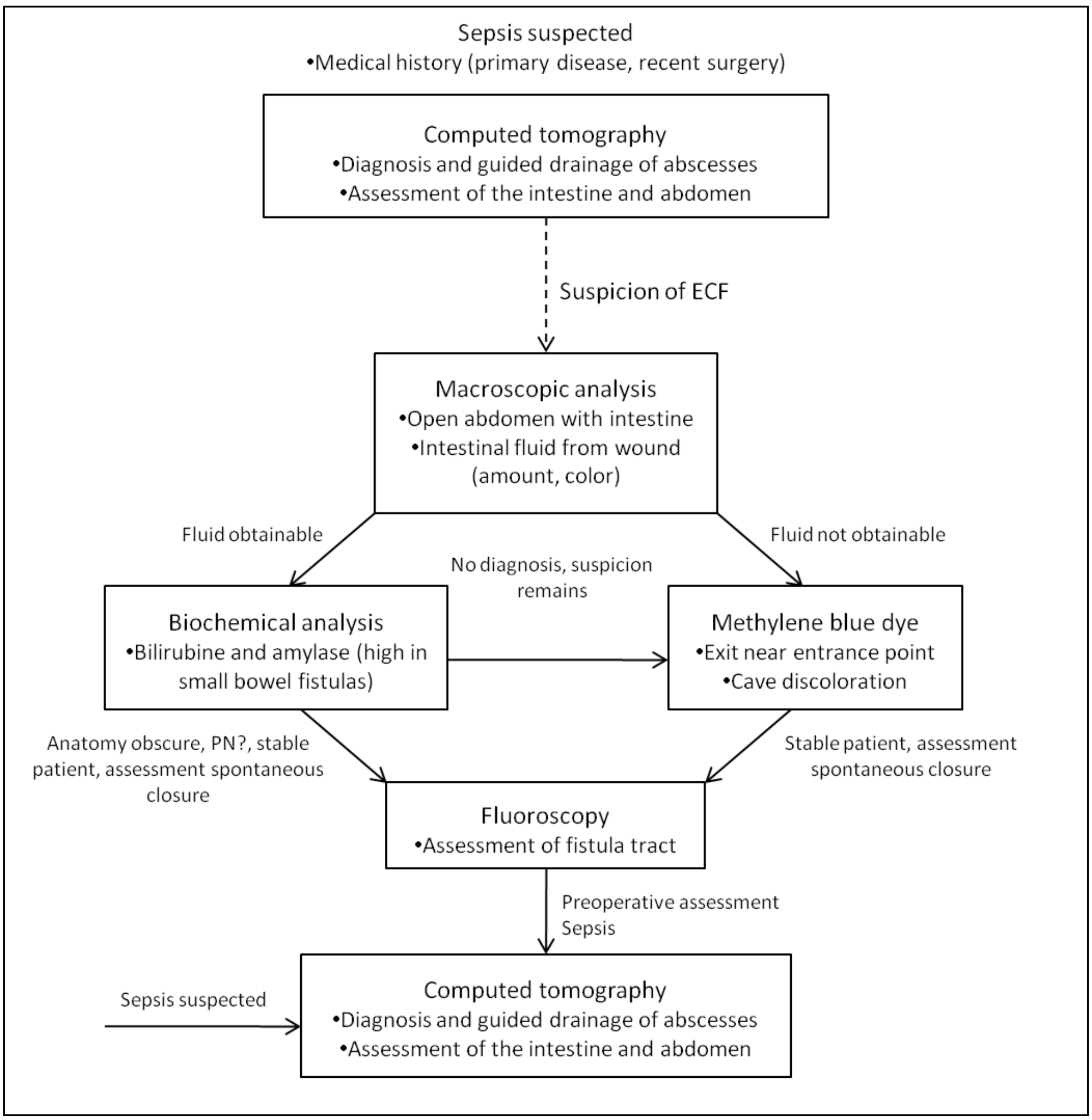

Fig. 4 Flow chart of establishing the anatomy of the fistula

4.5.2 Methylene Blue Dye

When macroscopic analysis of intestinal fluid provides insufficient information, methylene blue can allow detection of an ECF (107). The ECF can be visualized after oral ingestion of methylene blue or by rectal enema. When the methylene blue is dark and appears quickly after supplementation, the intestinal defect is most likely situated near the entrance point of the blue dye. However, false negative results may occur when the ECF drains directly into an abscess cavity or resides in a defunctionalized loop. It should also be considered that methylene blue can be reduced to the colorless leucomethylene in high concentrations of bacteria (>10*E9 colony forming units/mL), leading to false negative results (108). It implies a high false negative outcome when the distance between the entrance point the dye and the fistula is long, and when the ECF resides in the colon, containing >10*E11 colony forming units/mL. Additionally, intestinal bacterial overgrowth can easily occur in patients who depend on parenteral nutrition and/or with enteral starvation (109). Methylene blue is rapidly absorbed and will, if given in large amounts, slightly color serous fluids and more strongly urine. This should be taken into account when fluid secretions show a light blue color hours after instillation into a fistula. Nevertheless, administration of methylene blue is easy, cheap and can provide in some cases quick results and provides, in some cases, rapid confirmation of the presence of an ECF (107).

4.5.3 Biochemical Analysis

A third method to diagnose the ECF involves biochemical analysis of intestinal fluid discharging from the wound. Measurement of bilirubin and amylase in the intestinal fluid discharge is easy, cheap and provides quick results and is more informative about the anatomy of the ECF than methods described above. Although this method is frequently practiced there are no studies providing information on cut-off points to discriminate small from large bowel fistulas.

4.5.4 Radiological Imaging

The aforementioned diagnostic procedures will in most cases provide useful information about a single uncomplicated fistula. When spontaneous closure is expected, simple diagnosis of the ECF and its anatomy will suffice. However, the diagnostic procedures described above will occasionally fail to furnish definitive information and radiological imaging techniques will be needed to characterize the ECF, especially preoperatively. Radiological imaging not only allows to define the exact anatomical origin of the ECF, but also to assess the exact course of the ECF, the length of the intestine proximal and distal to the fistula, and the presence of stenoses or obstructions that possibly impede spontaneous closure or postoperative suture healing. More importantly, abscesses can be detected and subsequently drained under radiological guidance (25, 110). This may prevent invasive operative procedures and associated development of complications especially in patients suffering from active infection (111). Hereby, it constitutes an important adjunct to the first phase of fistula management, controlling sepsis.
Contrast medium is used to visualize the fistula tract. Barium is a suitable medium to provide detailed information on mucosal surfaces as it remains undiluted (112), but when

leaking into the peritoneal cavity may cause chemical peritonitis (113). Therefore, iodinated water-soluble contrast medium should be used instead. Nevertheless, when examination with an aqueous contrast medium provides no conclusive results the intestinal defect is probably too small and application of barium-contrast is recommended (114). Filling the fistula canal in combination with oral and rectal infusion of contrast medium provides the most complete information regarding the anatomy of the fistula and the intestine (115). Insertion of a small catheter into the external opening of the ECF followed by gentle injection of water soluble contrast medium directly into the tract most often achieves complete filling of the tract. Fistulography can be performed with fluoroscopy and CT-scanning, and in rare cases with ultrasonography or magnetic resonance imaging (MRI).

4.5.4.1 Fluoroscopy

Water soluble contrast medium is injected into the cutaneous opening of the fistula for a dynamic follow through providing a two dimensional image (**Fig. 5**) (116). However, fluoroscopy does not provide information about the complete fistula tract, the gastro-intestinal tract (including stenoses and obstructions), and abdominal abscesses. Furthermore, narrow fistula tracts do not always fill with contrast medium impeding fluoroscopic visualization (and other imaging). A supplementary CT-scan is indicated for these patients.

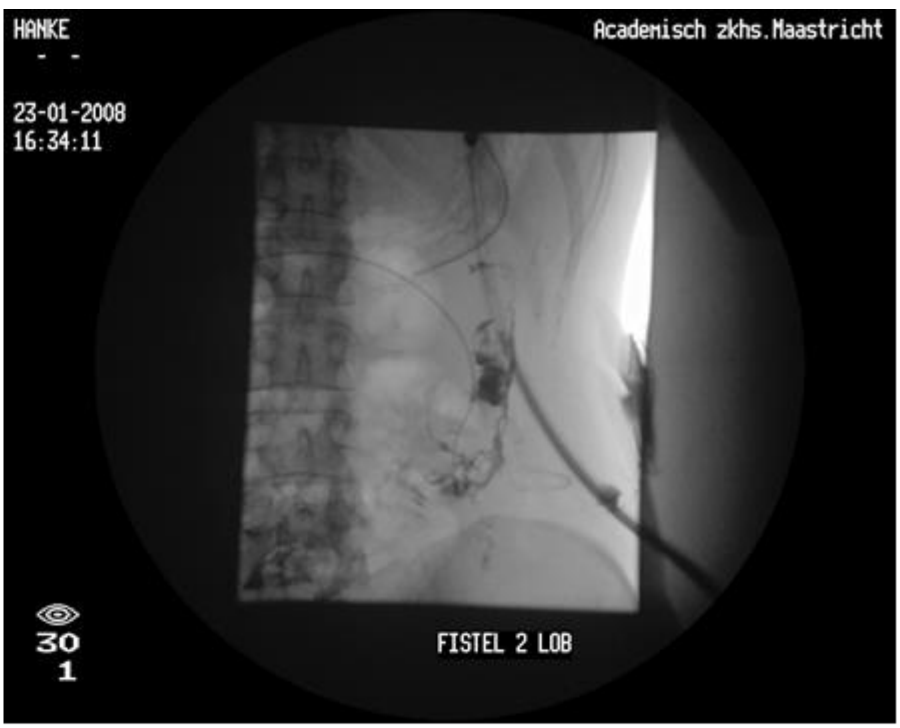

Fig. 5 Fluoroscopic image of the ECF.
A catheter is inserted in the external opening of the skin and filled with contrast fluid.
Fluoroscopic image shows filling of the intestine with contrast fluid.

4.5.4.2 Computed Tomography

A CT-scan is recommended when a patient displays any sign of sepsis or poor clinical progression. Thin slides provide a clear three dimensional image, properly differentiating separate bowel loops (**Fig. 6**). Before the examination the intestine needs to be filled with water-soluble contrast medium to distinguish bowel from extra-intestinal fluid collections. During the examination, administration of intravenous contrast is helpful to diagnose abscesses. Pre- and post hydration is necessary to prevent contrast nephropathy, even more so in patients with compromised renal function. In addition CT-scanning exposes patients to higher amounts of radiation than conventional radiology like intestinal follow through or barium enema. CT scanning has the added advantage that it allows radiology guided drainage when an abscess is detected (110, 117). The introduction of radiological drainage has enabled postponement of surgical intervention in patients with an ECF partially accounting for the improved outcome in these patients (13).

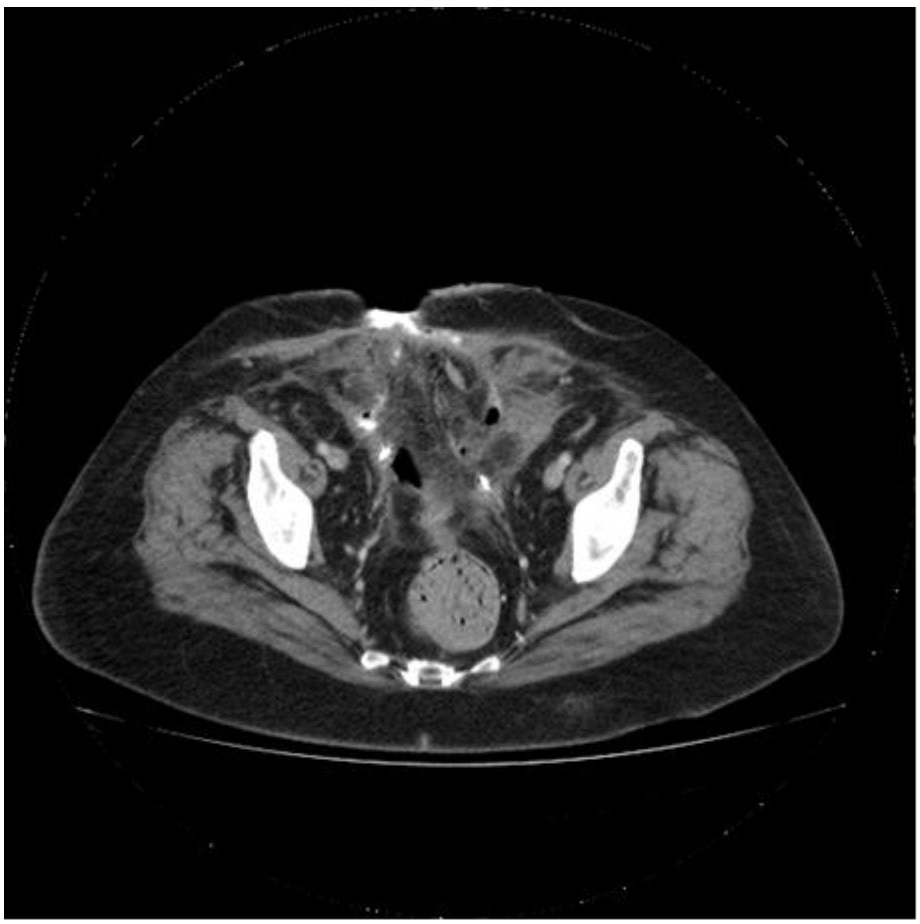

Fig. 6 Computed tomographic image of the ECF.
Computed tomographic images of a female patient with an enterocutaneous fistula originating from the small intestine.

4.6 Monitoring and Timing of Re-intervention

4.6.1 Spontaneous Closure

Spontaneous closure ranges from 20 to 70% (17, 18, 44, 118). It occurs more frequently in fistulas originating from the stomach and duodenum than from other parts of the intestine (13, 119). Spontaneous closure rarely occurs when anatomical properties are unfavourable such as intestinal obstruction, complete discontinuity, presence of a foreign body, a fistula in the intestine involved in the inflammatory disease, presence of undrained sepsis and radiation enteritis (120, 121). Fistula located in an abdominal wall defect have shown reduced tendency for spontaneous closure (**Table 1**) (99, 122). In a multivariable analysis, Campos *et al.* reported a spontaneous closure rate of 31% and concluded that non-surgical cause, high output, referrals from other hospital and infectious complications negatively and independently influenced spontaneous closure of gastrointestinal fistulas including biliary and pancreatic fistulas (118). Studies published in more recent years found reduced tendency for spontaneous closure in high output fistulas, presence of co-morbidity, jejunal fistulas and fistulas in a open abdominal wall after multivariable analysis (123-125). Additionally, increasing the period of convalescence allowed an increase of spontaneous closure from 16 to 29% (126). The TNF-alfa inhibitor infliximab showed to significantly increase in spontaneous closure within 54 weeks of analysis compared to a placebo group in patients with Crohn's disease (127). A report from the large GETAID group from France showed that up to a third of simple Crohns fistulae had healed with Infliximab therapy. Caution was advised as to excluding complex fistulae, distal stenosis and intra-abdominal sepsis. A report of three non-Crohn patients also showed spontaneous closure with infliximab (128). EAF never close spontaneously.

4.6.2 Timing of Surgery

When spontaneous closure does not occur, an operative procedure will be required to close the fistula. The majority of ECF will need operative closure. Before reverting to the restorative procedure the patient must be in a stable health state. This is considered from a medical as well as a (more subjective) psychological point of view. The patient must be mentally willing to proceed to the restorative procedure and be confident that outcome will be successful. The patient should be mobile with interest in his/her surroundings and eager to return home.

Clinical signs of improvement include reduction of oedema, a negative fluid balance and increased muscle strength. Infection parameters must normalise and the plasma albumin level must increase to normal or near-normal level (129, 130). Abatement of sepsis allows improvement of the nutritional status when properly nourished. Before the introduction of parenteral and sophisticated enteral nutrition the restorative procedure was performed after a relatively short period of convalescence to shorten the period that patients were suboptimally nourished (5). Since the introduction of parenteral nutrition and enteral forms of artificial nutrition it has been possible to postpone surgical intervention until sepsis has been adequately treated and patient's health status is stabilised (131).

Low albumin level as a measure of inflammatory activity is associated with negative outcome and should normalise before commencing the restorative procedure (28, 125, 129, 132, 133). However, in a prospective study (126) it was demonstrated that in a significant amount of patients (20%) it was not feasible to increase albumin levels above 25 g/L (the pre-set target for the restorative procedure)in the time frame discussed. In these cases patients were either too ill and had to undergo an emergency operation or had a stable albumin concentration after a period of convalescence that showed no tendency to increase. In contrast, a multivariable analysis showed a significant decreased risk of recurrence when period of convalescence was prolonged (126). In a recent systematic review it was possible to estimate an ideal time for surgery. These authors suggest a time interval between 6 and 12 months in order for optimal patient physiology to take place and reduce operative mortality and morbidity as well as reducing fistula recurrence (134). Martinez and colleagues did not study the relation between period of convalescence and recurrence rate but did show that recurrence rate was associated with high output fistula and non-resection surgical option (132). Additional variables that negatively influence success of surgical outcome include location of the fistula in the jejunum, presence of multiple fistulas (28), high output fistulas (118), co-morbidity (124) and increased age (133).

4.7 Surgical Strategy

At present, 60 to 80% of patients will usually require a restorative procedure which is successful in 85 to 90% of these cases (18, 28). The restorative operation should be performed with care and patience. Most reviews come from specialist centres who can have experienced surgeons operating together, the prolonged theatre time and often postoperative intensive care facilities required regularly required. The procedure requires careful adhesiolysis and removal of obstructions/stenoses distal to the ECF. Subsequently, the fistula tract including the diseased part of the bowel is resected. The number of anastomoses should be minimized, sometimes requiring resection of a larger section of intestine when two or more ECFs are widely apart from each other or when renewed bowel lacerations have been made during the dissection. This allows to limit the number of anastomoses. The location of the anastomosis should preferably be positioned in such a way that it is covered with healthy surrounding tissue and thus protected from other sutures, abscesses and meshes. The abdominal muscle/fascia layers are closed with two-three layers of absorbable vicryl mesh when the fascia cannot be approximated.

5. Recovery

After the restorative procedure, full recovery requires a long period of rehabilitation to regain a satisfactory quality of life which means that they should be physically, mentally, cognitively and immunologically healthy. The chronic inflammatory state inevitably leads to a substantial loss of muscle mass which can generally not be fully restored before surgery. The restorative operation generally is a major procedure that all by itself leads to a catabolic state from which patients only fully recover after six weeks to three months. Thus nutritional guidance is needed in the immediate postoperative phase and patients need to rehabilitate actively either themselves or with the help of physiotherapists. A minority of patients becomes dependent on home PN because of insufficient intestine left to ensure adequate absorption of nutrients. These patients require life-long guidance and specialised support.

Mortality has reduced from 40% to 10-20% over the past decades (1-3). Recent studies suggest that overall mortality has stabilized at 10-20% (123, 124, 126). However, there appears to be a reduced postoperative mortality rate (135, 136). This shift can be attributed to a better preoperative selection of patients fit for surgery. However, considering the overall stable mortality rate it also implies that a certain subset of patients are significantly ill and will succumb to the disease irrespective of an attempt of surgical repair.
Long-term health related quality of appeared to be satisfactory in patients with an ECF (137). On average patients were able to perform daily activities without much hindrance. Nevertheless, quality of life seems to equal those of patients admitted to the ICU.

6. Summary

Patients with an ECF experience a high morbidity and mortality rate, making their treatment challenging. The introduction of antimicrobial therapy, parenteral nutrition and CT-guided drainage of abscesses have been important medical advancement in the treatment of these patients. Treatment should occur according to guidelines by a multi-disciplinary team. Several groups have described the basic focus of the guideline all revolving around the control of sepsis, optimisation of nutritional status, wound care, establishment of the anatomy of the ECF, timing of surgery and surgical strategy, the SOWATS guideline. The severity of disease in patients that have developed fistulas, the complexity of their treatment and their rarity makes it advisable to treat these patients in centres (often termed Intestinal failure units) where sufficient patients are treated to acquire enough experience and expertise to achieve good result minimizing morbidity and mortality.

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