

GASTROINTESTINAL FISTULAE

Optimising the treatment of upper gastrointestinal fistulae

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A three stage strategy is generally employed in the management of gastrointestinal fistulae which can form due to surgery, disease, or trauma. The condition is investigated leading to diagnosis, conservative treatment is initiated to stabilise the patient, followed by specific surgical treatment measures in complicated cases, or in the absence of spontaneous closure. Conservative management of fistulae is based on parenteral nutrition and bowel rest, as well as on control of infection, electrolytic disturbances, and local care of the fistula tract. Surgical treatment may be required although generally only in particularly serious cases. Somatostatin-14 has been used in addition to parenteral nutrition to further reduce the volume and enzymatic activity of the fluid output through the fistula tract, generally with good results. The majority of reports have shown a beneficial effect, and randomised studies have demonstrated a reduction in closure time and morbidity. However, due to a combination of the seriousness and rarity of the condition and the difficulties inherent in trial design, data from large scale, double blind, randomised, controlled studies investigating the use of pharmacotherapy in the treatment of established gastrointestinal fistulae are lacking. Nevertheless, preliminary data from initial trials suggest that somatostatin-14 and its analogue octreotide considerably improve the conservative treatment of gastrointestinal fistulae in the absence of distal obstruction. In addition, reduction of the concentration of caustic enzymes in the discharge will benefit both wound healing and nutritional losses. With reduced closure time, the period of hospitalisation will be shortened with potentially considerable economic reductions and improvements in quality of life for the patient.

The formation of a gastrointestinal fistula represents a relatively rare yet serious condition. Despite treatment, morbidity and mortality are particularly high and the potential sequelae include fluid collection, abscess, haemorrhage, sepsis, malnutrition, and death. In addition, fistulae frequently prolong hospital stay and inflict a considerable psychological burden on patients due to the negative impact on the perception of body image. Physical effects notwithstanding, fistulae are associated with complex issues of personal hygiene and wound care, pain, delay in returning to normal activities, and expense associated with prolonged hospitalisation.

In recent years the clinician has acquired a number of useful additions to the armamentarium of therapeutic choices, both surgical and pharmacological, for the treatment of gastrointestinal fistulae. This paper aims to review current management practice and emphasise the benefits and place of pharmacotherapy in association with conservative treatment measures to stabilise patients and shorten recovery time.

AETIOLOGY AND INCIDENCE

The aetiology, epidemiology, and classification of gastrointestinal fistulae are complex. The majority of fistulae develop as a complication of abdominal surgery or trauma, Crohn's disease, intra-abdominal abscess, malignant disease, and radiotherapy. When considering the prevalence of fistulae in various conditions and surgical procedures it is important to note that truly representative epidemiological data are currently lacking. The incidence and aetiology of fistulae are highly dependent on the surgical experience and case load at particular institutions, and on host-patient and disease related cofactors.¹ Moreover, much of the published data relate to experience at specialised centres treating complex cases in particularly unstable patients.

Abdominal surgical procedures

In the majority (75–85%) of cases, fistulae develop through iatrogenic mechanisms as postoperative complications. The

procedures with which they are most commonly associated include operations for cancer, inflammatory bowel disease, and lysis of adhesions. However, surgical treatment of peptic ulcer, pancreatitis, and procedures in an emergency care setting may also lead to postoperative fistulae. In the latter case, additional factors may predispose the patient to further risk, such as insufficient time to prepare the patient for surgery.

In approximately 15–25% of cases, gastrointestinal fistulae form spontaneously. The most common causes include inflammatory bowel disease, radiation therapy, diverticular disease, ischaemic bowel, pancreatic and gynaecological malignancies, erosion of indwelling tubes, and perforation of duodenal ulcers.^{2–9}

Technical failure

Technical failures during surgery that may lead to fistula development include inadvertent full thickness bowel injury and damage to the mesenteric arteries, intestinal entrapment in fascial suture, excessively tight sutures leading to ischaemic necrosis, other suture-line defects, deserosalisation of the bowel, and poor placement of drains. Measures to reduce the risk of fistula formation include performing tension free anastomosis in healthy tissue away from sites of inflammation or disease; preoperative mechanical bowel preparation and the use of intraluminal or systemic antibiotics; meticulous haemostasis; secure closure of the abdominal wall; and maintenance of adequate oxygen carrying capacity and nutritional status during the postoperative period.⁸

Abbreviations: CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; RDA, recommended daily allowance; TPN, total parenteral nutrition; EN, enteral nutrition.

Table 1 Pathology of patients undergoing Whipple's procedure in a consecutive group of 650 patients¹⁰

Condition requiring Whipple's procedure	Proportion of total number of Whipple's operations performed
Pancreatic cancer	43%
Ampullary cancer	11%
Chronic pancreatitis	11%
Distal common bile duct cancer	10%
Neuroendocrine tumour	5%
Duodenal cancer	4%
Cystadenoma	4%
Periampullary adenoma	3%
Cystadenocarcinoma	2%
Other	7%

Pancreatic surgery

Pancreatic surgery presents a considerable technical challenge due principally to the presence of corrosive exocrine secretions. Pancreaticoduodenectomy (Whipple's procedure) in particular represents a significant risk for serious perioperative complications, including fistula development. In recent years, this technique has been used increasingly to resect a variety of malignant and benign diseases of the pancreas and periampullary region (table 1).¹⁰ In the normal pancreas, pancreatic enzymes are compartmentalised both physically and biologically from activating substances—predominantly bile and enterokinase enzymes—present in the intestines. However, surgery alters the anatomical organisation allowing inappropriate contact between pancreatic juice and intestinal activating enzymes. The degree of vascularisation of the periampullary region leads to a high risk of haemorrhage, and the presence of activated proteolytic enzymes accounts for the high incidence of complications following surgery of this nature. Pancreatic fistulae and other postoperative complications are less common following left pancreatectomy where the natural outflow of pancreatic juice to the duodenum via the pancreatic duct is preserved.^{11 12}

ASSESSMENT OF GASTROINTESTINAL FISTULAE

A three stage strategy is generally employed in the overall management of gastrointestinal fistulae, starting with a comprehensive assessment. The condition is investigated, diagnosed, and classified according to anatomical, physiological, and aetiological criteria to achieve an integrated understanding of the fistula and its potential impact on the patient. Conservative treatment is then instigated to stabilise the patient. Finally, in complicated cases, or in the absence of spontaneous closure, specific surgical treatment measures may be implemented.

CLINICAL/PHYSICAL SIGNS

The diagnosis of developing fistulae is generally reliant on the history of the patient and physical examination. The majority of patients will be recovering postoperatively and a slow or unusual course of recovery is often the first indication of arising complications. Patients may present with abdominal pain or tenderness, fever, and leucocytosis. In addition, the wound may develop a cellulitic appearance, with excessive drainage or abscess formation. Patients in whom skin changes around the wound are observed usually present with enteric contents in the wound or dressing within a 24–48 hour period.¹³ Fistulae may drain externally through the skin or internally and the fistula tract may be singular or complex. The characteristics of the effluent can provide an indication as to the source of the fistula, for example the odour, colour, consistency, and amount. Furthermore, as an initial step, clinical recognition

Table 2 Classification of gastrointestinal fistulae according to output

<i>Pancreatic fistulae</i> ^{17–20}	
Low	<200 ml/24 hours
High	≥200 ml/24 hours
<i>Intestinal fistulae</i> ^{21 22}	
Low	<500 ml/24 hours
High	≥500 ml/24 hours

with methylene blue may be useful. The underlying cause of fistula development 7–10 days after surgery is generally a consequence of anastomotic failure but those occurring later, or spontaneously, require further investigation.

Radiological assessment

It is vital to identify the source and route of the fistula tract in addition to aetiological features that may influence the outcome such as the presence of obstructions, abscesses, or pancreatic pseudocysts. Comprehensive determination of the anatomical aspects of fistulae is usually obtained through radiological investigation, utilising contrast studies, computerised tomography (CT) scan, or magnetic resonance imaging. Barium enema may also be beneficial in the investigation of lower intestinal fistulae. In established fistulae, fistulograms may be performed by injecting contrast medium directly into the fistula tract or into previously placed drainage tubes or catheters.¹⁴ Following complete visualisation of the tract, further investigation to delineate associated pockets and cavities may be performed safely using angiographic catheters and guide wires under direct angle fluoroscopic control.¹⁵

In general, barium is considered the contrast medium of choice due to its ability to reveal mucosal surfaces and remain undiluted. However, extravasated barium may induce an acute inflammatory reaction in the thoracic or peritoneal cavity and therefore an alternative—iodinated water soluble medium—should be used where perforations of the oesophagus, stomach, small bowel, or colon are suspected. It is important to note however that as this contrast medium has a lower radiographic density and is inferior with regard to mucosal coating, it may be less reliable in revealing small leaks.¹⁴ Consequently, a negative examination with water soluble agents may be followed by the more sensitive barium contrast medium where warranted.¹⁶

Classification of fistulae by output

Output volume

The most important physiological determinant of a fistula is the daily output of intestinal fluid. Fistula output is often dependent on the anatomical site and high output fistulae are more difficult to treat. Pancreatic and intestinal fistula output may be assigned according to the volume of discharge over a 24 hour period, as shown in table 2.^{17–22}

Fistula output is a predictor of morbidity and mortality and while not an independent indicator of spontaneous closure, 24 hour output generally decreases prior to closure.^{1 23} While fistula mortality rates have decreased over the past few decades from as high as 40–65% to 5.3–21.3%, high output fistulae continue to have a mortality rate of approximately 35%.²⁴

Output enzyme concentration

Laboratory tests to determine the enzyme content of the exudate are also important in diagnosis, especially when pancreatic involvement is suspected. The fistula output will contain a high concentration of toxic bile acids and active digestive enzymes from the pancreas that are highly corrosive and maintain the patency of the fistula tract. Discharge from an external fistula should be analysed for amylase content and if

pleural effusion or ascites are present, both amylase and albumin levels should be determined.¹³⁻²⁵ Skin protection must be provided for enterocutaneous fistula patients, especially those with a high content of corrosive enzymes in the exudate.

The importance of thorough classification

The site and output of a fistula have particular relevance to the likelihood of spontaneous closure⁸⁻²⁶ and consequently a thorough investigation is vital to determine the optimal treatment strategy. Particular anatomical characteristics associated with a poor spontaneous closure rate are summarised in table 3. The length of the fistula tract has a twofold effect on the spontaneous closure rate. Fistulae with a tract length in excess of 2 cm are generally associated with increased flow resistance and reduced output losses in comparison with those of shorter length. In addition, longer tracts are less likely to become epithelialised with bowel mucosa, an event that greatly reduces the possibility of spontaneous closure. Fistulae that develop from bowel wall defects longer than 1 cm in length are also less likely to undergo spontaneous closure. Furthermore, healing of such lesions is frequently accompanied by stricturing, and reoperation may be required. It is important to note however that even in the presence of predictive factors, the ability to determine the likelihood of spontaneous closure is inexact.

CONSERVATIVE MANAGEMENT OF GASTROINTESTINAL FISTULAE

The principal causes of morbidity following the development of enterocutaneous fistulae are malnutrition, electrolyte imbalance, and sepsis. Nutritional disturbances are present in 55–90% of patients with enterocutaneous fistulae,⁵ and are especially prevalent in upper gastrointestinal fistulae due to substantial fluid loss containing pancreatic, jejunal, and biliary secretions plus a high protein and electrolyte content. Pancreatic juice and bile are hypertonic in comparison with plasma and account for excessive bicarbonate and potassium losses, having profound negative effects on the patient and the eventual outcome of treatment. It is therefore vital that measures are taken to reduce fistula output, provide nutritional support, and address fluid and electrolyte imbalance at the earliest opportunity.

Conservative treatment is comprised of supportive measures to stabilise the patient. These include provision of adequate drainage plus cutaneous protection; fluid/electrolyte balance; nutritional replacement and bowel rest via enteral or parenteral nutrition; and wound care and antibacterial therapy in patients with signs of systemic sepsis or local inflammation with pain.

Table 3 Anatomical factors predictive of spontaneous fistula closure⁸⁻²⁶

Unfavourable	Favourable
Complete disruption	Continuity maintained
Lateral fistula	End fistula
Large adjacent abscess	No associated abscess
Adjacent bowel diseased	Adjacent bowel healthy
Distal obstruction	Free distal flow
Fistula tract <2 cm	Fistula tract >2 cm
—epithelialisation	—non-epithelialised
Enteral defect >1 cm	Enteral defect <1 cm
Fistula site:	Fistula site:
• Gastric	• Oropharyngeal
• Lateral duodenal	• Oesophageal
• Ligament of Treitz	• Duodenal stump
• Ileal	• Pancreatobiliary
	• Jejunal

Drainage

Following surgery, drainage is provided to prevent the progressive accumulation of fluid and the development of infection. Furthermore, drainage will not only help prevent pain and potential complications such as ileus, fever, and sepsis, it will also aid early recognition of anastomotic leakage and simplify the diagnosis of a developing fistula in terms of the site and enzymic involvement. The prophylactic use of drainage following surgical procedures with an inherent risk of fistula development is dependent on the type of surgical procedure performed and the experience of the surgeon. Generally, drains are placed near upper digestive anastomoses and sutures with a high risk of fistula formation (for example, oesophagojejunostomy, gastrojejunostomy, duodenal stump, duodenal lateral suture, choledocoduodenostomy or choledocojejunostomy, pancreaticojejunostomy, and pancreatic suture). Sutures with lower risk, such as gastrorrhaphy after gastrotomy, pyloroplasty, and jejunojunostomy are usually not drained.

In the upper abdominal cavity the use of suction drains are currently favoured over passive drains. The new silicone multiperforated drains with a low aspiration pressure are preferable to the classic rigid plastic drains with high suction pressure as they cause less irritation to surrounding tissue.²⁷ Closed suction drains have low infection rates but they often become blocked early in the wound healing process.²⁸ Passive drains are often less efficient and may become contaminated as the upper abdominal cavity has a negative pressure during inspiration.

If anastomotic or suture leaks develop and drainage provided is inadequate, fluid collection with focal or generalised peritonitis may manifest. In most cases, localised fluid can be drained percutaneously with radiographic guidance. However, reoperation may be necessary if percutaneous drainage is unsuccessful or where fluid collection is multiloculated or access to the site of the collection is poor.²⁹ Reoperation is also necessary in cases of generalised peritonitis and systemic toxicity from an intra-abdominal abscess.²⁷⁻²⁹ Passive drainage is utilised where the consistency of the fluid collection is viscous but suction drains are preferred if collection is of a more liquid consistency. Usually, low pressure closed drains are sufficient but in cases with a high volume of fluid or a system open to the air, continuous aspiration will be required.

Established enterocutaneous fistulae drain spontaneously to the skin although some fluid may be retained within the fistula tract leading to abscess formation. In such situations, surgical or interventional management will be necessary, usually with widening of the fistula tract, or placement of drains either through the tract or a new access.

Cutaneous protection

The effects of continuous moisture and enzymic irritation can severely compromise skin integrity and lead to infection and delayed wound healing. In addition to protection of the peristoma area, effectively containing the discharge allows accurate measurement of fluid and electrolyte losses and thus enables timely replacement and maintenance of nutritional balance.³⁰ Provision of optimal skin care may be achieved through assessment of the following four criteria: origin of the fistula, nature of the effluent, condition of the skin, and location of the tract opening.³¹

An output volume of >500 ml/24 hours is usually contained within a pouch system while an output of <50 ml/24 hours may be contained with a dressing and skin barrier. Thick effluent is best contained within a drainable-type pouch while liquid effluent is usually contained using a urostomy-type pouch with a spigot-type closure that may be connected to a larger drainage system. Additional use of a durable skin barrier is required when the effluent has a high proteolytic content or is either excessively acid or alkaline. The method of

containment is also dependent on the condition of the skin surrounding the wound and the location of the fistula tract opening. Severe ulceration and infection create a moist non-adherent surface that causes considerable difficulties with pouch and barrier methods. Furthermore, multiple openings, openings within deep skin folds, on bony prominences, sutures, or open wounds all affect the protection required, as do differences in the contours of the skin around the fistula between the supine and upright position.³¹

Fluid/electrolyte replacement

Gastrointestinal fistula exudate is typically comprised of a rich mixture of sodium, potassium, chloride, and bicarbonate ions, proteins, and other components. Large volumes of gastrointestinal secretions may be lost through fistulae which potentially result in profound disturbances in fluid and electrolyte levels leading to dehydration, hyponatraemia, hypokalaemia, and metabolic acidosis. The degree of the deficit caused by the fistula is directly proportional to volume and composition. To assess fluid and electrolyte requirements, the volume and content of the exudate should be analysed. It is important to note that the composition of the exudate cannot be assumed to correspond with the normal composition for the anatomical position of the fistula. Discharge from the fistula may be a mixture of fluid proximal and distal to the anatomical site of the tract.^{13–23} Blood transfusions may also be required as most patients with fistulae have reticulopenic anaemia, in common with chronic illness.^{32–33}

Fistula losses from patients with pancreatic fistulae are especially hypertonic and rich in bicarbonate and protein. However, sodium content is comparable with serum concentration and therefore saline with supplemented bicarbonate may be used for replacement. The composition of the output from pancreatic fistulae is dependent on the rate of pancreatic secretion, stimulated by oral intake, gastric distension, and cholecystikinin. As a consequence, elimination of oral intake and substitution of alternative nutrition is an important early step in the stabilisation of fistula patients.

Nutritional support and bowel rest

Malnutrition is closely associated with the site and output of a fistula and is a major concern in patients with enterocutaneous upper gastrointestinal fistulae. In particular, hypoproteinaemia leads to delayed gastric emptying and prolonged ileus, increased frequency of wound dehiscence, greater risk of infection, and decreased muscle bulk and function. In addition, fibroblast activity is reduced, delaying wound healing and causing failure of scar contracture. Patients are frequently malnourished prior to the development of the fistula and indeed malnutrition may increase the risk of fistula formation and greatly increase the required healing time.^{34–37} A further important consideration of inadequate nutrition is a decrease in amino acid precursor availability for major brain neurotransmitters. Malnutrition can frequently lead to a state of mental dullness, depression, and apathy, which will have a considerable negative impact on the patient. As complication rates are higher in malnourished patients, nutritional support should be initiated as early as possible in the management of patients with gastrointestinal fistulae.³⁸

There are three potential mechanisms through which a fistula may induce malnutrition: lack of food intake, loss of protein and energy rich fluid in fistula discharge, and hypercatabolism associated with sepsis.¹ Oral food intake in such patients will be limited for obvious reasons and should be totally discontinued where gastric, duodenal, pancreatic, or small bowel fistulae are suspected. The presence of nutrients in the gut, especially solid food, stimulates secretion of digestive juices and therefore increases fistula output, exacerbating poor nutritional status and limiting healing. Small bowel secretions can lead to daily losses of approximately 75 g of

protein and approximately 12 g of nitrogen, comprised of desquamated cells, plus pancreatic exocrine, biliary, succus entericus, and gastric secretions.¹ Under normal circumstances the majority of this nitrogenous material is reabsorbed as free amino acids but in high output upper gastrointestinal fistulae much of this protein is lost. In addition, surgical trauma can induce complex physiological changes that lead to catabolism and loss of body cell mass. This reaction may be exacerbated by previous malnutrition and postoperative complications.³⁹

In general, patients with low output fistulae should receive the full basal energy requirement and between 1 and 1.5 g of protein per kg body weight every day, with a minimum of 30% of the caloric intake supplied as lipid. With high output fistulae, patients should receive 1.5–2 times their basal energy expenditure plus 1.5–2.5 g of protein per kg body weight per day. This nutritional regimen should also include twice the recommended daily allowance (RDA) for vitamins and trace minerals, up to 10 times the RDA for vitamin C, and zinc supplements.⁸ Fistulae from the small intestine that have been established for a number of weeks are often associated with considerable zinc and copper deficiency, and patients may also be deficient in folic acid and vitamin B₁₂.³²

The role of artificial nutrition, provided as either total parenteral nutrition (TPN) or enteral nutrition (EN), is primarily that of supportive care to improve the malnourished status of the patient and provide gastrointestinal tract rest.⁴⁰ In some cases, parenteral nutrition does not need to be total, as patients can have oral intake. Nutritional support is associated with a decrease in fistula output and appears to modify the composition of gastrointestinal and pancreatic secretions and therefore may be considered to have a primary therapeutic role. Indeed, TPN has been the mainstay of conservative management of gastrointestinal fistulae throughout the last three decades. Conservative treatment with TPN has been shown to reduce the maximal secretory capacity of the gastrointestinal tract by 30–50%, induce protein synthesis, and promote favourable conditions for closure.^{41–42} However, the use of TPN can be associated with potentially serious complications such as bacterial translocation, superinfection of central venous access, and metabolic disorders as a result of fistula losses.^{40–43–44} Furthermore, TPN does not suppress basal or cephalic secretions and during long term administration the presence of lipids and amino acids can stimulate gastric and intestinal secretions.^{41–42–45}

The ultimate choice between TPN and EN will depend entirely on whether the latter method is feasible. The decision is dependent on the site of the fistula but EN is preferred wherever possible as the use of the gastrointestinal tract for nutritional support is the safest and most effective method.^{35–38} Generally, TPN is indicated in patients with gastroduodenal, pancreatic, or jejunio-ileal fistulae and EN is provided for fistulae of the oesophagus, distal ileum, and colon. However, if fistula output is increased or patients are intolerant of EN (for example, high gastric residuals, abdominal cramps, or diarrhoea), TPN should be substituted.⁴⁶ The current generation of enteral diets are superior to parenteral formulations available as they contain glutamine, arginine, fish oils, nucleosides, and nucleotides that all support gastrointestinal mucosal growth and function.³⁸ A study by Levy *et al* has suggested that enteral nutrition with appropriate local care may be used in the majority of high output enterocutaneous fistulae. In a total of 335 patients with high output enterocutaneous fistulae (median 1350 ml/24 hours) arising from the small intestine, EN was provided as the exclusive nutritional support in 85% of cases with an acceptable rate of spontaneous closure.⁴⁰

An often undervalued aspect of care, additional to nutritional support, is provision of conditioning and exercise. In many cases, patients are able to use treadmills, exercise cycles, and lift weights, even while nutrition is totally parenteral.³²

Wound care and antibacterial therapy

Regardless of the cause, leakage of intestinal juices often leads to localised and systemic sepsis. Patients with gastrointestinal fistulae are prone to a range of infections, such as sepsis from intravenous catheters, phlebitis, pneumonia, and urinary tract infections, although infections of the surgical wound and the abdominal cavity are most common.⁴⁷ Septic foci may not only contribute to the formation of an enterocutaneous fistula⁴⁸ but may also reduce the likelihood of spontaneous closure.

Infection of the wound following Whipple's procedure occurs in approximately 5–20% of patients. Management measures include removal of sutures or staples in infected areas, with drainage, packing, and antibiotic therapy as appropriate. Perioperative prophylaxis with suitable antibiotics is recommended—for example, bowel preparation with neomycin and erythromycin—and perioperative administration of an intravenous first or second generation cephalosporin.⁴⁹

Gastrointestinal fistulae can also be associated with serious abdominal wall infections. The combination of bacterial infection and caustic erosion from digestive enzymes can result in rapid spread of the infectious process through fascial planes, subcutaneous tissue, and muscle, leading to necrotising fasciitis and gas gangrene. Infections of this nature are potentially life threatening and require aggressive management measures such as surgical incision and drainage, debridement, and appropriate antibiotic therapy.⁴⁷ Good stoma care is therefore vital in patients with gastrointestinal fistulae. Teaching patients practical skills in stoma care not only deals with problems such as leakage from the pouch or sore skin but also the patient's psychological adaptation following stoma surgery.

OPTIMISING CONSERVATIVE TREATMENT: THE ROLE OF PHARMACOTHERAPY

Inhibition of gastrointestinal secretions

Although it has been shown that TPN has substantially improved the prognosis in gastrointestinal fistula patients, long term supportive treatment of between 22 and 45 days is frequently required to achieve spontaneous closure.^{46–50} This treatment period is associated with prolonged morbidity, including psychological stress, risk of mortality, and the high costs of hospital care. As a consequence, it is important to discuss healing times and realistic expectations with patients to provide them with a framework to deal with the condition.³² Furthermore, as morbidity and mortality are associated with fistula output,^{8–26} a strategy to reduce both output volume and the content of corrosive enzymes in the exudate would be likely to decrease the healing time, greatly improving prognosis.

The concept of using the ubiquitous hormone somatostatin-14 to inhibit pancreatic exocrine secretion in the treatment of gastrointestinal fistulae was first introduced in 1979 by Klempa and colleagues.⁵¹ Somatostatin, a 14-amino acid peptide, is a well established inhibitor of gastrointestinal secretion, inhibiting both endocrine and exocrine pancreatic secretion and reducing pancreatic blood flow. Furthermore, somatostatin-14 has been found to exert additional regulatory effects in reducing gastrointestinal motility, gastric secretion, gall bladder emptying, and on secretion of various hormones, including cholecystokinin, vasoactive intestinal polypeptide, secretin, and gastrointestinal polypeptide. It also reduces intestinal motility and delays gastric emptying.⁵² Octreotide is a synthetic octapeptide analogue of somatostatin-14 which has also found application in the management of gastrointestinal fistulae. Octreotide has a similar pharmacological profile to somatostatin-14 (reviewed in detail by Beglinger and Drewe⁵³) although the half life has been increased to approximately two hours compared with <3 minutes for the native hormone.⁵⁴

A number of studies have investigated the effect of somatostatin-14^{20–21–42–50–51–55–57} and octreotide^{58–62} in combination with TPN for conservative management of gastrointestinal fistulae. These trials have been discussed in detail elsewhere in this supplement (Hesse and de Hemptinne, this supplement, page iv11). To date, only one study has reported experience in treating established gastrointestinal fistulae with somatostatin-14 in a multicentre controlled trial setting.⁵⁵ This study demonstrated that somatostatin-14 in combination with TPN accelerated spontaneous closure of postoperative gastrointestinal fistulae, significantly reducing the required period of TPN treatment (time to healing 13.9±1.84 days somatostatin-14+TPN *v* 20.4±2.98 days TPN alone; n=20, respectively; p<0.05) with a consequent reduction in morbidity (35% somatostatin-14+TPN *v* 68.85% TPN alone; p<0.05). Data from several small scale uncontrolled and/or unblinded studies lend support to the findings of this trial. Two randomised, double blind, placebo controlled trials,^{59–60} and one blinded crossover trial⁶¹ investigated octreotide in the treatment of postoperative enterocutaneous fistulae. However, only one of these three studies demonstrated a beneficial effect, reducing fistula output after 24 hours of treatment (53% reduction octreotide+TPN *v* 9% TPN+placebo, n=8 and n=6, respectively; p<0.01).⁶¹ The octreotide trials by both Scott and colleagues⁵⁹ and Sancho and colleagues⁶⁰ failed to demonstrate any significant effect on healing time or reduction in fistula output.

Investigation of pharmacological treatment in the management of gastrointestinal fistulae is complex and the availability of meaningful data is often limited by aspects of study design. As gastrointestinal fistulae are relatively rare, many of the published trials recruited small numbers of patients. Furthermore, the majority of studies included patients with fistulae from different anatomical sites and the varied clinical end points employed to determine the response to treatment make useful comparison difficult.

Optimising the treatment of gastrointestinal fistulae: rationale for somatostatin-14

Although published data in the clinical setting are limited, current evidence suggests that treatment with somatostatin-14 is likely to benefit certain patients with gastrointestinal fistulae as an adjunct to stabilisation therapy, or as a definitive treatment (fig 1). In association with nutritional replacement therapy, somatostatin-14 has been shown to inhibit both basal and stimulated digestive secretion, as well as reducing fluid loss, electrolyte imbalance, and malnutrition, leading to potential reductions in fistula output and time to closure.

When used alone, TPN has been found to reduce maximal gastrointestinal secretion by only 30–50%^{41–63–64} and response to other stimuli persists. In addition, the components of the TPN therapy itself may stimulate pancreatic and gastric secretion, particularly amino acids and lipids.^{41–45} Somatostatin-14 has been found to totally inhibit basal secretion and also to suppress the possibilities of exogenous stimulation.^{52–65} As output losses are associated with a high rate of morbidity and mortality,²⁴ patients with high output fistulae are likely to benefit to the greatest degree. Both somatostatin-14 and octreotide have demonstrated a significant reduction in fistula output,^{55–61} although the evidence for octreotide is less conclusive (Hesse and de Hemptinne, this supplement, page iv11).

It is widely accepted that a fistula should be well defined radiographically before embarking on a prolonged and potentially futile course of treatment. Somatostatin-14 acts pharmacologically and consequently will have no effect as the sole treatment in cases with mechanical obstruction distal to the fistula tract. Complications of this nature require surgical intervention. Nevertheless, while certain well defined factors have been associated with poor spontaneous closure rates and

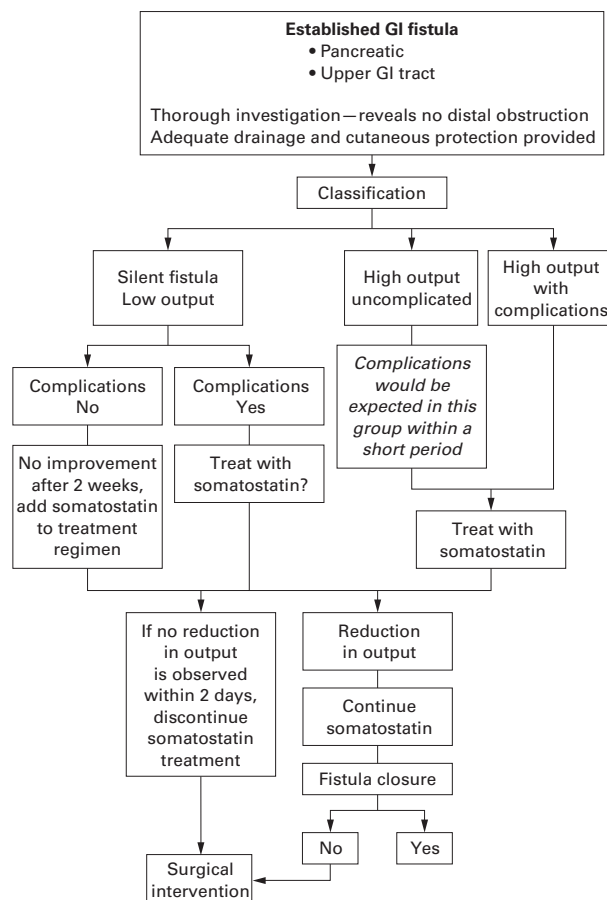


Figure 1 Conceptual algorithm for treatment with somatostatin-14. GI, gastrointestinal.

contraindicate the exclusive use of conservative treatment (table 3), somatostatin-14 may have a potential benefit in the stabilisation of the patient prior to surgery, to allow treatment of septic foci and/or malnutrition.³⁰ Allowing time for improvement prior to surgery may simplify the procedure and consequently reduce the risk of further complications. For example, stabilising a patient while scar tissue forms around a drainage site allows fistulojejunostomy to be performed to provide access to the origin of the fistula, excluding the need for the entire fistula tract to be isolated—a procedure that is generally associated with a greater risk.⁶⁶ Furthermore, as the presence of obliterative peritonitis makes operative dissection particularly hazardous, a sepsis free stabilisation period of approximately six weeks with inflammatory quiescence may allow abdominal adhesions time to resolve, potentially reducing surgical risk.²⁶ In a review of treatment outcome over an 18 year period, the timing of fistula surgery was found to have little impact on the fistula closure rate although better results were obtained when reconstructive surgery was deferred beyond six weeks from fistula onset.⁶⁷

It has been suggested that if fistula output is not decreased within 48 hours of treatment with somatostatin-14 or octreotide, then treatment should be discontinued.⁶⁸ A positive effect on fluid balance charts should also be seen in trials of octreotide, otherwise treatment is withdrawn (50–60% patients). Evidence suggests that a first day response of >50% reduction in output in response to somatostatin-14 in combination with TPN is a prognostic indicator for spontaneous closure.³⁰ As a consequence, the likelihood of success with somatostatin-14 becomes apparent very soon after initiation of treatment and it may be discontinued and surgical intervention provided where good outcome is otherwise

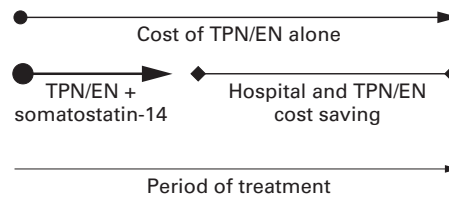


Figure 2 Somatostatin-14 plus nutritional support (total parenteral nutrition (TPN), enteral nutrition (EN)) may considerably reduce treatment costs.

unlikely. This strategy allows optimal management by minimising delay in the provision of surgery where necessary, preventing further deterioration. Moreover, as prolonged conservative treatment is expensive, there are potential economic benefits to be gained. In a study in which 37 patients were treated with TPN and somatostatin-14, 68% of patients responded to treatment after the first day, and the response was found to be independent of prior duration, output, or location of the fistula.⁴² Indeed, due to the degree of response (>50% reduction), the authors recommend that somatostatin-14 may be tried in all fistula patients in the absence of any obvious mechanical obstruction.⁴²

The data available strongly suggest that somatostatin-14 in combination with conservative treatment is associated with a significant reduction in healing time.^{20 21 55 56 69} This reduced hospitalisation period is likely to convey considerable cost savings as prolonged use of TPN is expensive and hospitalisation time is often a major cost driver (fig 2). In fact, considerable cost savings have been demonstrated in patients treated with TPN and somatostatin-14 in comparison with TPN alone, due to the significant reduction in time to closure.²⁰

SURGICAL MANAGEMENT OF GASTROINTESTINAL FISTULAE

Patients who present with factors that are poorly prognostic for conservative treatment (for example, obstruction of the intestinal lumen downstream of the fistula) will require surgical intervention. Surgical treatment will also be required for persistent fistulae that fail to close after prolonged conservative treatment. The primary aim of surgery in such patients is correction of the mechanical anomaly preventing closure. However, failed conservative management can be difficult to define and how to progress should depend on the following considerations⁷⁰: was the conservative treatment optimal; is there a clear anatomical reason to prevent healing; has nutritional status been effectively addressed; has sepsis been controlled; and is the patient fit for surgery?⁷¹ Generally, surgery is indicated in patients with fistulae that fail to close spontaneously after a 30–60 day period of sepsis free parenteral nutrition³² although in some cases surgery can be avoided for at least three months.

Pancreatic fistulae

Surgical management of persistent pancreatic fistulae has been shown to be safe and relatively effective.^{25 66 70 72} In cases where pancreatic fistulae fail to close after 4–6 weeks of conservative treatment, further investigation is required and the type of surgery indicated is dependent on the abnormal anatomy identified. Over recent years, endoscopic retrograde cholangiopancreatography (ERCP) has become more widespread in the assessment of pancreatic duct anatomy, along with CT scan and fistulography. Fistulae emanating from the body or tail of the pancreas and not associated with ductal strictures in the pancreatic head may be treated by distal pancreatectomy. If a pseudocyst or stricture not manageable by resection is revealed, then internal drainage of the pseudocyst or the actual fistula will be required. Pancreatic fistulae arising from the head of the organ are generally also treated through

internal drainage. This is usually achieved with Roux-en-Y pancreaticojejunostomy or cystojejunostomy.⁷⁰

Intestinal fistula

Failure of conservative measures to achieve spontaneous closure is particularly prevalent in patients with ileal fistulae.⁷³⁻⁷⁴ In preparation for the surgical treatment of intestinal fistulae, efforts should be made to ensure a well healed abdominal wall with minimal inflammation. Prior to operation, appropriate antibiotic therapy should be given and tube feeding should be decreased 2–3 days preoperatively to allow antibiotic luminal preparation, with cathartics where appropriate. The operative approach is ideally made through a new incision in the healthy abdominal wall and should be planned to achieve an anastomosis in an area free from any source of infection. End to end anastomosis is recommended as this procedure provides the optimal chance for permanent resolution of the fistula tract. However, previously irradiated bowel may present specific problems and may be better treated with stricturoplasty. Microvascular thrombosis and fibrosis associated with radiation therapy may result in an inadequate blood supply to the bowel wall to support healing anastomosis. Bypassing the fistula containing bowel segment rarely achieves closure and further surgery is often required after the bypass. In contrast, fistula bypass, while providing a route for gastric drainage such as gastrojejunostomy, is the preferred option for the surgical treatment of duodenal fistulae.⁷⁵

After the procedure, gastrostomy and a feeding jejunostomy should be used and secure abdominal closure is vital in the success of surgery. However, the likelihood of failure of surgical intervention in fistula patients with cancer remains high. In patients with large unresectable tumours, intestinal bypass may be performed, which while likely to permit oral nutrition may not entirely correct the fistula.

Biliary fistula

Biliary fistulae generally arise after hepatic resection from the segmental ducts of the surface of the section and from anastomotic leakage following hepaticojejunostomy.⁷⁶⁻⁷⁷ Leakages of this type usually heal with drainage and instigation of conservative treatment. Bile leakage is also an infrequent but serious complication after biliary tract surgery. The subsequent formation of biliary fistulae may be due to bile duct injury or distal bile duct obstruction. Biliary fistulae may require surgical correction with the aim of treatment to facilitate bile flow into the duodenum but endoscopic methods of improving biliary drainage have been found to be successful in the management of postoperative biliary leaks. Postoperative bile leakage can be diagnosed effectively by ERCP. Sphincterotomy alone is the preferred treatment for biliary fistula complicating surgery for gall stone disease although endoscopic placement of an endoprosthesis may be required if the fistula is large.⁷⁸⁻⁷⁹

CONCLUSION

In the majority of cases, gastrointestinal fistulae arise as complications of the surgical treatment of a number of malignant and non-malignant disease states. Established gastrointestinal fistulae are associated with significant morbidity, often over a prolonged period, due to fluid loss, and electrolyte and nutritional imbalance. A three stage strategy is generally employed in the management of gastrointestinal fistulae based on diagnosis and investigation, stabilisation/conservative treatment, and surgical measures. Optimal therapy is reliant on thorough radiological investigation to determine the potential for spontaneous closure, and classification according to anatomical site and nature of output allowing timely instigation of appropriate management measures.

The relatively recent addition of pharmacotherapy to the options available for the conservative treatment of pancreatic and upper gastrointestinal fistulae may have a considerable beneficial impact on the management of these complications. Trials to date strongly suggest that somatostatin-14 and, to a degree, octreotide considerably improve the conservative treatment of gastrointestinal fistulae in the absence of complicating factors. However, due to an association with increased morbidity⁸⁰ and high cost,⁸¹ prophylactic octreotide use should be discontinued if there is no demonstrable health benefit. Pharmacotherapy has been shown to rapidly reduce fistula output and significantly shorten healing time. The reduction in fistula output is associated with many advantages including improvement in nutritional and electrolyte status. In addition, reduction of the concentration of caustic enzymes in the discharge will convey beneficial effects on both wound healing and nutritional losses. With reduced closure time, the period of hospitalisation will be shortened leading, potentially, to considerable improvements in quality of life for the patient and reductions in overall treatment costs. However, due to a combination of the seriousness and rarity of the condition, and the difficulties inherent in trial design, data from large scale, double blind, randomised, controlled studies investigating the use of pharmacotherapy in the treatment of established gastrointestinal fistulae are lacking. While conservative management is preferable, operative treatment is reserved for fistulae that are identified as unlikely to respond to conservative measures, or that fail to heal after a prolonged period of optimised medical management.

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