

GASTROINTESTINAL FISTULAE

The relevance of gastrointestinal fistulae in clinical practice: a review

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Gastrointestinal fistulae most frequently occur as complications after abdominal surgery (75–85%) although they can also occur spontaneously—for example, in patients with inflammatory bowel disease (IBD) such as diverticulitis or following radiation therapy. Abdominal trauma can also lead to fistula formation although this is rare. Postoperative gastrointestinal fistulae can occur after any abdominal procedure in which the gastrointestinal tract is manipulated. Regardless of the cause, leakage of intestinal juices initiates a cascade of events: localised infection, abscess formation and, as a result of a septic focus, fistulae formation. The nature of the underlying disease may also be important, with some studies showing that fistula formation is more frequent following surgery for cancer than for benign disease. Fistula formation can result in a number of serious or debilitating complications, ranging from disturbance of fluid and electrolyte balance to sepsis and even death. The patient will almost always suffer from severe discomfort and pain. They may also have psychological problems, including anxiety over the course of their disease, and a poor body image due to the malodorous drainage fluid. Postoperative fistula formation often results in prolonged hospitalisation, patient disability, and enormous cost. Therapy has improved over time with the introduction of parental nutrition, intensive postoperative care, and advanced surgical techniques, which has reduced mortality rates. However, the number of patients suffering from gastrointestinal fistulae has not declined substantially. This can partially be explained by the fact that with improved care, more complex surgery is being performed on patients with more advanced or complicated disease who are generally at higher risk. Therefore, gastrointestinal fistulae remain an important complication following gastrointestinal surgery.

Gastrointestinal fistulae are usually very serious complications and are associated with high morbidity and mortality rates. They allow abnormal diversions of gastrointestinal contents, digestive juices, water, electrolytes, and nutrients from one hollow viscus to another or to the skin, thus causing a wide variety of pathophysiological effects. Fistulae can also prolong the patient's hospital stay, which has obvious cost implications. Although gastrointestinal fistulae can occur spontaneously in IBD (for example, diverticular disease of the colon), cancer, or radiation enteritis, most gastrointestinal fistulae (approximately 80%) occur following surgery.¹

Due to the high morbidity and mortality associated with gastrointestinal fistulae, effective therapy is of vital importance. However, successful treatment of gastrointestinal fistulae is a continuing challenge. Fistulae, although now treatable in the majority of patients, are incredibly complex to treat, and multiple therapies are typically required. Up until the 1960s, gastrointestinal fistulae were associated with a considerable mortality rate (43%).² The introduction of artificial nutrition and intensive care in the 1970s improved mortality rates but patients still remain in hospital for weeks or even months before their fistulae finally close. Therefore, a treatment that could shorten fistula closure time would be highly beneficial, and could also result in considerable hospital cost savings.³ This review aims to demonstrate the ongoing clinical importance of gastrointestinal fistulae.

DEFINITION AND CLASSIFICATION

External fistulae are pathological communications that connect any portion of the gastrointestinal tract with the skin. This is the most common type of postoperative fistula. Internal fistulae connect the gastrointestinal tract with another internal organ, the peritoneal space, retroperitoneal areas, or the thorax (pleural space or mediastinum).

The absolute definition of what constitutes a fistula is still unclear. For example, some studies have defined a pancreatic fistula as increased amylase/lipase in the drainage fluid for 3–4 days postoperatively with a drainage volume of >10 ml/day.^{4–5} However, other studies have defined a fistula as draining >50 ml/day.^{6–7} This latter definition is probably too high as a lower output volume can still be clinically relevant.

The type of fistula also has important clinical implications. In a lateral (side) fistula, continuity of the intestine is maintained allowing normal progression of intestinal contents beyond the fistula. This is a common type of fistula which usually closes spontaneously if not associated with any other anatomical abnormality. Conversely, with an end fistula, there is complete loss of intestinal continuity beyond the fistula and it generally requires surgery to achieve closure. Complex fistulae refer to multiple fistulae arising from different organs (that is, intestine, colon, and bile ducts)¹³ and pose challenging management problems. Spontaneous closure occurs but rates are much lower than in single organ fistulae. The presence of intra-abdominal abscesses also needs to be determined, as this would have clinical implications.

Various classification systems have been used to define gastrointestinal fistulae, of which fistula output is an integral part. The three schemes shown in table 1 (anatomical, output volume, and aetiological) have been most widely used. Each of these systems carries specific implications with regard to likelihood of spontaneous closure, prognosis, operative timing, and non-operative care planning. These classifications are often used in combination to achieve an integrated understanding of the fistula and its potential impact on the patient.

Abbreviations: IBD, inflammatory bowel disease.

Table 1 Classifications of gastrointestinal fistulae

Scheme	Classification
Anatomical	• Internal • External
Output volume	Pancreatic ^{3 8–10} • Low (<200 ml/day) • High (≥200 ml/day) Intestinal ^{11 12} • Low (<500 ml/day) • High (≥500 ml/day)
Aetiological	Underlying disease

González-Pinto and Moreno González cover classification of fistulae and in particular classification by fistulae output in more detail elsewhere in this supplement (see page iv22).

DIAGNOSIS

The first diagnostic step in a patient suspected of having a gastrointestinal fistula is a thorough examination and medical history. Common symptoms include pain (first localised and then diffuse), illness, and fever, although occasionally a fistula can cause no symptoms. External fistulae are generally easier to diagnose due to the unusual effluent from drainage sites or abdominal incisions (purulent discharge and/or discharge of intestinal contents), cellulitic inflammation, and sepsis.¹³ Internal fistulae are more difficult to diagnose although patients often suffer from diarrhoea, sepsis, and dyspnoea, as well as air, pus, or faeces in the urine.

Once a fistula has been confirmed, the daily output volume should be determined and biochemical (amylase, lipase, bilirubin, pH, etc.) and microbiological evaluations should be performed on the fistula fluid (table 2). Many techniques are available that can be useful in confirming the diagnosis and identifying the intrinsic anatomical and pathological features of a fistula. These are listed in table 2.

AETIOLOGY AND EPIDEMIOLOGY

The majority of gastrointestinal fistulae form following surgery (75–85%), most commonly after operations for cancer, IBD (for example, Crohn's disease, diverticulitis), lysis of adhesions, and pancreatitis.¹ The remaining 15–25% of fistulae usually form spontaneously, most commonly in patients with diverticular disease of the colon and other IBDs (for example, Crohn's disease). Spontaneous fistulae are also reported in cancer patients or those who have received previous radiation therapy. A small number of fistulae form following abdominal trauma such as gunshot wound, stabbing (sharp trauma), or car accident (blunt trauma).

Table 2 Clinical-instrumental methods used for diagnosing gastrointestinal fistulae (adapted from Falconi and colleagues¹⁴)

- Monitor
 - fistula output volume
 - fistula aspect (colour, etc.)
 - water-electrolyte balance
 - biochemical evaluation (amylase, lipase, bilirubin, pH, etc.)
 - infection status
 - nutritional/metabolic status
- Methylene blue test
- Upper or lower gastrointestinal endoscopy
- Digestive tract x rays with water soluble contrast medium
- Fistulography with water soluble contrast medium
- Ultrasonography
- Computerised axial tomography
- Magnetic resonance imaging

Postoperative fistulae

Both local and systemic factors may contribute to postoperative fistula formation,¹⁵ including infection or breakdown of an intestinal anastomosis due to ischaemia, tension, or distal obstruction. They generally form as external rather than internal fistulae¹³ because of the presence of a drain. Technical problems that can lead to fistula formation include inadvertent full thickness bowel injury, deserosalisation of the bowel, suture-line defects, and tight suture causing ischaemic necrosis. Further factors include inadvertent injury to the mesenteric vessels, poor haemostasis resulting in a perisuture haematoma, inappropriate use of drains, and a loop of intestine caught in a fascial suture.¹³ When an abscess cavity is associated with a fistula, infected material tends to collect adjacent to the gastrointestinal tract defect, preventing adequate healing of this defect. Healing is also compromised by malnutrition, immunosuppression secondary to medications, or specific disease states.¹⁶

Fistulae can occur at any time following gastrointestinal surgery. The time elapsed to fistula appearance is an important guideline for management and prognosis. Early fistulae arising in the first 48 hours post surgery can be considered as technical errors and would occasionally require further surgical intervention.^{11 17} Low output well drained fistulae appearing late after surgery have a good prognosis and can generally be treated conservatively. However, in the case of late high output complex fistulae of upper gastrointestinal origin, reoperation would be required in most cases to achieve closure.¹⁸

Spontaneous fistulae

Approximately 15–25% of all gastrointestinal fistulae form spontaneously. Diseases such as pancreatitis and IBD cause local inflammatory processes that can lead to local abscess formation, perforation, and distal obstruction, which are all potential causes of spontaneous fistula formation. Spontaneous oesophagotracheal fistulae can also form in patients with oesophageal cancer. Further causes of spontaneous fistulae include: radiation, diverticular disease, appendicitis, ischaemic bowel, erosion of indwelling tubes, perforation of duodenal ulcers, and pancreatic and gynaecological malignancies.^{1 19–22}

In westernised populations, Crohn's disease is the principal cause of spontaneous fistula formation.²³ As shown in table 3, up to half of Crohn's patients will develop a fistula at some stage during their disease, the majority of which will be external or perianal. Patients with diverticulitis are much less likely to develop a spontaneous fistula (1–12%) (table 3). Although fistulae that develop in the bowel are likely to close without the need for surgery, they often reopen as the underlying problem is still present.¹

Radiation therapy for malignant disease is also associated with fistula development and other complications in approximately 5–10% of patients.³⁰ In a recent review that examined 41 publications, 17% of radiotherapy patients presented with a fistula after a mean interval of 3.4 years following radiotherapy.³¹ The clinical presentation varied from mild disease to debilitating rectal bleeding, diarrhoea, obstruction, and fistula formation. Mucosal ulceration may persist following high dose radiation and indeed, intestinal complications may manifest weeks or even years after radiotherapy.^{1 32} Furthermore, bowel resection and anastomosis in previously irradiated tissue increases the risk of anastomotic failure and, consequently, of fistula formation.

Trauma induced fistulae

Gastrointestinal fistulae can also occasionally occur following a sharp wound, such as that caused by a knife or bullet, or a blunt trauma, such as the impact of a steering wheel during a car accident. Blunt trauma can cause vascular injury, ischaemic problems, or abscess formation, all of which can lead to fistula formation. In one study of 44 consecutive

Table 3 Incidence and type of spontaneous fistulae found in patients with Crohn's disease or diverticulitis

Disease	Spontaneous fistula incidence (%)	Fistula type
Crohn's disease	43 (23–48) ^{24–27}	66% external/perianal, 34% internal (25% ileosigmoid, 23% other ileocolic, 20% ileovesical, 12% ileum/rectum to female genital tract, 11% ileoileal, 9% coloenteric) ^{27 27}
Diverticulitis	1, ²⁷ 12 ²⁸	58% colovesical, 33% colovaginal, 4% coloenteric, 3% colocutaneous, 1% colotubal ^{29 30}

Table 4 Factors that may adversely affect spontaneous closure rates^{1 13 36 38}

Anatomical	Other
• Discontinuity of bowel ends • Complete disruption • Distal obstruction (caused by an obstacle downstream or discontinuity between parts of the gastrointestinal tract) • Intra-abdominal foreign body • Lateral fistula • Complex fistula • Associated abscess • Adjacent bowel diseased • Poor bowel vascularisation • Fistula tract <2 cm • Defect >1 cm • Epithelialisation of mucocutaneous fistula tract • Drainage through large abdominal wall defect (multiple orifices) • Internal fistulae • Fistula site (gastric, lateral duodenal, or ileal)	• Cancer • Chemotherapy • Radiation • Underlying IBD • Uncontrolled sepsis, with or without abscess formation • Fistula fluid infected • Hypoproteinaemia • Large and early leakage of anastomosis • Diabetes patients • Corticosteroids • Renal failure • Output may prognosticate closure^o

^oOpinion is divided on the effect of output on spontaneous closure. According to Martineau and colleagues³⁸ and Rubelowsky and Machiedo,¹³ high output is associated with low closure rates; according to Berry and Fischer,¹ output does not prognosticate closure.

patients with pancreatic or duodenal injuries admitted to a trauma centre over a six year period, an incidence of pancreatic fistulae of 16% was reported in patients with pancreatic injury.³³ Another example of formation of trauma induced fistulae is in response to prolonged intubation with a cuffed tube (tracheotomy or nasotracheal intubation).³⁴

RISK FACTORS FOR POSTOPERATIVE FISTULA FORMATION

Univariate and multivariate (*) logistic regression models have identified the following as risk factors in patients undergoing pancreaticoduodenectomy: soft pancreas, ampulla or duodenum disease (rather than pancreas or bile duct disease)*, advanced age, long duration of jaundice*, high total bilirubin, low creatinine clearance*, shock during operation, long operating time, high intraoperative blood loss*, and low patient volume per surgeon*.^{6 35} Other risk factors that have been suggested, although not proved, for postoperative gastrointestinal fistula formation include malnutrition,³⁶ immunocompromised state, infection, bacterial peritonitis, IBD,¹³ renal insufficiency,³⁷ cirrhosis, mesenteric vascular disease,¹³ previous surgery, low quality suture, low hospital volume, and inadequate surgical training or experience. Patients undergoing emergency surgery may also be more likely to develop a fistula than patients undergoing elective surgery, as patient preparation may have been poor or the patient may be chronically malnourished.¹

Factors affecting spontaneous closure

Fistula closure is considered to be spontaneous if no surgical intervention is required although artificial nutrition and drug therapy may have been administered. Many factors may adversely affect spontaneous closure rates (table 4) although to date, most have not been properly evaluated. The majority of adverse prognostic factors are anatomical, such as the presence of a distal obstruction, diseased adjacent bowel, or an associated abscess.^{1 36 38} It has also been suggested that complex or external fistulae are generally more resistant to healing.^{13 38} The site of the fistula also affects the likelihood of

spontaneous closure—gastric, ileal, and lateral duodenal fistulae may be less likely to heal than oesophageal, jejunal, pancreaticobiliary, or duodenal stump fistulae.¹

Cancer, chemotherapy, and radiation are all thought to reduce the likelihood of spontaneous fistula closure.^{1 13 36 38} However, postoperative fistulae and those caused by appendicitis or diverticulitis are more likely to close spontaneously.¹ The presence of sepsis or local infection can also adversely affect the likelihood of closure.^{13 36} Other factors that can adversely affect prognosis include diabetes,^{13 18} corticosteroid use, and renal failure.¹³ However, opinion is divided on the effect of output on spontaneous closure—high output may^{13 38} or may not¹ be associated with reduced closure rates.

MORBIDITY

A patient with a gastrointestinal fistula will probably suffer much more than severe discomfort and pain. A gastrointestinal fistula is associated with a considerable mortality rate, the knowledge of which can distress the patient greatly. The psychological effect of a drainage bag and malodorous fistula fluid can have an adverse effect on body image, as can pathological changes in the skin at the fistula orifice.¹³ A post-operative fistula will almost invariably lengthen hospitalisation, which increases morbidity as well as the time taken to return to work and social activities. In addition to the morbidity directly associated with the fistula, further complications often occur, such as fluid and electrolyte disturbances, abscess formation or local infection (for example, urinary tract infection, bronchitis), general infection, multiorgan failure, sepsis, and bleeding.

FACTORS AFFECTING MORTALITY

Gastrointestinal fistulae are associated with considerable mortality, most commonly due to sepsis,¹³ although bleeding due to erosion of a large blood vessel can cause acute blood loss which is often fatal very quickly. A number of factors are known to affect mortality rate such as fistula site, underlying disease, low hospital volume and surgeon experience, high intraoperative blood loss, high preoperative serum bilirubin,

Table 5 Incidence of postoperative fistulae in patients undergoing surgery of the oesophagus and/or stomach

Organ	Procedure	Complications (%)	Fistula/leak (%)	Mortality (%)
Oesophagus	Resection	10 ⁴⁸	5 ⁴⁹ 10 ⁴⁸	0 ^{48 49}
	Subtotal oesophagectomy	14 ⁵⁰	1 ⁵⁰	0 ⁵⁰
	Transhiatal oesophagectomy	33 (23–62) ^{51–53}	11 (0–15) ^{51–54}	8 (6–16) ^{51–54}
	Oesophagectomy	44 ⁵⁵	2 ^{55 56}	4 (3–5) ^{55–57}
Oesophagus/stomach Stomach	Oesophagogastrctomy	41 (37–61) ^{58–60}	8 (0–11) ^{49 57–61}	7 (5–22) ^{58–61}
	Total gastrectomy	35 (24–73) ^{62–70 82}	12 (0–28) ^{62 65–73 82}	6 (0–10) ^{57 62 65–67 69–73 82}
	Subtotal gastrectomy	23 (8–90) ^{63 64 74}	ND	30 ^{a 74}
	Distal gastrectomy	18, ⁶⁹ 33 ⁶⁶	5 (0–6) ^{66 69 73}	4 (0–5) ^{66 69 73}
	Lymphadenectomy	37 ⁸¹	9 ⁸¹	10 ⁸¹
	General	17 (9–58) ^{64 66 69 73 75–79}	5 (0–12) ^{63 64 66 69 75 76}	3 (0–11) ^{63 64 75–78}
	Left upper abdominal exenteration plus Appleby's method	57 ⁶⁵	35 ⁶⁵	4 ⁶⁵
	Omental patch closure	68 ^{a 74}	ND	36 ^{a 74}
	Antrectomy	11 ⁸⁰	2 ⁸⁰	2 ⁸⁰

^aHigh risk patients with perforated ulcer.
ND, no data.

large diameter of the pancreatic duct, and the occurrence of complications.³⁹ The effect of advanced age on operative outcome has also been studied.^{40–43} Perhaps surprisingly, operative mortality did not increase with advancing age in any of these studies although the complication rate in patients aged >80 years was higher than those <80 years in one study (57% v 41%, respectively; $p=0.05$).⁴⁰

Hospital volume has been shown to have a significant effect on total in-hospital mortality following pancreatic surgery^{44–46} and other complex high risk gastrointestinal surgical procedures,⁴⁷ although no analysis of the link to fistula formation was made. All of these studies found a significant correlation between high hospital volume and low mortality, although definitions of “high volume” and “low volume” varied considerably. The study by Lieberman and colleagues⁴⁶ also found an association between high volume pancreatic surgeons and reduced perioperative mortality—5% for high volume (>41 cases) surgeons versus 16% for low volume (<9 cases) surgeons ($p<0.001$). Despite these results, it has also been reported that pancreaticoduodenectomy can be successfully performed in low volume hospitals provided the surgeon is adequately trained in the procedure.⁷ In such hospitals, the case load should be restricted to a minimal number of trained surgeons to concentrate the experience.

POSTOPERATIVE COMPLICATION RATES, FISTULA INCIDENCE, AND MORTALITY RATES

As the majority of fistulae are caused by surgery, the remainder of this paper will focus on postoperative gastrointestinal fistulae. Truly representative epidemiological data are difficult to obtain as clinical trials tend to be conducted in specialist centres, which often treat the most complex cases and patients in the worst clinical condition. The frequency of fistulae depends on many surgeon and patient related factors, which are hard to assess for epidemiological purposes. The proposed submission of this paper is as part of a supplement, and more detail with regard to intestinal and biliary fistula is presented by González-Pinto and Moreno González in this supplement (see page iv22).

We examined more than 120 studies in an attempt to provide information on the incidence of postoperative gastrointestinal fistulae following different types of surgery. The studies were found by searching MEDLINE using “complication” as a key word together with each operative procedure. However, it should be noted that the study designs varied widely, as did the definitions used, and therefore the values can only be used as a guide.

Oesophagus and stomach

As can be seen in table 5, oesophagectomy or transhiatal oesophagectomy is associated with a much higher incidence of

complications than resection or subtotal oesophagectomy (23–62% v 10–14%). However, the incidence of fistulae/leaks was higher following resection or transhiatal oesophagectomy (0–15%) than after subtotal oesophagectomy or oesophagectomy (1–2%). The mortality rates after oesophageal surgery varied from 0% up to 16%.

The risk of complications in patients undergoing gastric surgery also varies with operative procedure, with a value of up to 68% in patients with perforated ulcer undergoing omental patch closure. The incidence of fistulae/leaks also varies widely—up to 35% in patients undergoing left upper abdominal exenteration plus Appleby's method. Mortality in patients with perforated ulcer is very high (30–36%) but much lower in other patient groups. The underlying pathology also has an effect on the incidence of fistulae in patients undergoing gastric surgery—those with cancer were more likely to develop a fistula (9% (0–31%))^{62–69 71–74 76 81 82} v 2%⁸⁰).

Liver or biliary tree

In patients undergoing liver surgery, the overall complication rate, anastomotic leak rate, and mortality were generally low (table 6). However, surgery on the biliary tree is much more likely to result in complications, with up to half of all patients suffering at least one complication. The incidence of anastomotic leaks in patients undergoing biliary surgery varied according to the procedure from only 1% in patients undergoing biliary-enteric anastomosis or pylorus preserving pancreaticoduodenectomy to 19% in patients undergoing choledochoduodenostomy. Mortality also ranged from 1% in patients undergoing biliary-enteric anastomosis to 12% in patients undergoing choledochojejunostomy.

Lower gastrointestinal tract

The studies that examined surgery on the lower gastrointestinal tract all used various methods and patient groups and therefore it was difficult to group the results. Table 7 shows that the complication rate varied widely, from as low as 6%⁹² to as high as 69%.⁹³ The incidence of fistulae was low, with the majority of studies reporting rates of 0–7%, although rates as high as 19%⁹⁴ have been found. Similarly, mortality rates were generally low (0–9%), although one study reported 17% mortality.⁹⁵ The presence or absence of cancer did not appear to affect the fistula rate overall (1–19%^{92 94 96–101} v 0–16%,^{29 94–97 102–111} respectively).

Pancreas

It is well documented that pancreatic surgery carries a high risk of fistula formation, principally because of the presence of corrosive exocrine secretions. Due to the high rate of pancreatic fistulae, overall complications, anastomotic leaks, and

Table 6 Incidence of postoperative fistulae in patients undergoing liver or biliary surgery

Organ	Procedure	Complications (%)	Anastomotic leak (%)	Mortality (%)
Liver	Liver transplantation	16 (14–24) ^{83–85}	3 (2–9) ^{83–85}	1 ⁷⁹ 17 ⁸³
	Hepatic resection	8 ⁸⁶	8 ⁸⁶	3 ⁸⁶
Biliary tree	Pancreaticoduodenectomy	4 ⁸⁷	5 ⁸⁷ 8 ⁸⁸	3 ⁸⁷
	PPPD	51 ⁸⁷	1 ⁸⁷	3 ⁸⁷
	Choledochoduodenostomy	11 ^b 89 42 ^a 90	5 ^b 89 19 ^a 90	4 ^a 90 5 ^b 89
	Choledochojejunostomy	2 ⁸⁹	10 ⁸⁹	12 ⁸⁹
	Biliary-enteric anastomosis	13 ⁹¹	1 ⁹¹	1 ⁹¹

^aWound infection, respiratory complications, bile discharge.^bProcedure related.

PPPD, pylorus preserving pancreaticoduodenectomy.

Table 7 The incidence of postoperative fistulae in patients undergoing surgery of the intestine, jejunum, ileum, colon or rectum

Organ	Pathology	Procedure	Complications (%)	Fistula rate (%)	Mortality (%)
Intestine	Mixed	Emergency anastomosis	34 ¹¹²	3 ¹¹²	3 ¹¹²
	Mixed	Elective anastomosis	20 ¹¹²	2 ¹¹²	4 ¹¹²
	Gynaecological cancer	Mixed operations	31 ¹⁰²	6 ¹⁰²	6 ¹⁰²
Jejunum	Mixed	Upper GI surgery with jejunojunostomy	26 ¹¹³	0 ¹¹³	6 ¹¹³
Ileum	Derivative ileostomy	Closure ileostomy	12 ⁹⁶	6 ⁹⁶	0 ⁹⁶
	Crohn's disease	Primary ileal, ileocolonic, and eventual rectal surgery	11 ⁹⁷	2 ⁹⁷	1 ⁹⁷
	Crohn's disease+ enterovesical fistula	Primary ileal, ileocolonic, and eventual rectal surgery	6 ⁹²	2 ⁹²	2 ⁹²
	Crohn's disease with fistulas	Primary ileal, ileocolonic, and eventual rectal surgery	15 ⁹⁸	4 ⁹⁸	0 ⁹⁸
	Crohn's disease + enterovesical fistula	Ileal+eventual sigmoid resection	13 ⁹⁹	1 ⁹⁹	0 ⁹⁹
Colon	Mainly cancer	Elective colectomy	9 ¹¹⁴	5 ¹¹⁴	5 ¹¹⁴
	Cancer (obstructive)	Emergency subtotal colectomy	20 ¹⁰³	0 ¹⁰³	9 ¹⁰³
	Cancer (obstructive)	Emergency left colectomy	52 ¹⁰³	16 ¹⁰³	3 ¹⁰³
	Diverticulitis	Emergency left colectomy	42 ¹⁰⁰	3 ¹⁰⁰	3 ¹⁰⁰
	IBD	Elective total colectomy	27 ¹⁰¹	4 ¹⁰¹	0 ¹⁰¹
	Cancer	Elective left colectomy	27 ¹⁰⁴ 35 ¹⁰⁵	1 ¹⁰⁵ 5 ¹⁰⁴	1 ¹⁰⁵ 7 ¹⁰⁴
	Cancer (obstructive)	Emergency left colectomy	ND	4 (1–7) ⁹⁵ 106–110	6 (2–17) ⁹⁵ 106–110
	Diverticular disease	Colocolostomy (after Hartman resection)	69 ⁹³	3 ⁹³	3 ⁹³
	Cancer	Emergency colectomy	41 ¹¹¹	4 ¹¹¹	14 ¹¹¹
	Diverticulitis with fistulas	Elective colectomy	31 ²⁹	0 ²⁹	0 ²⁹
Rectum	Rectal cancer	Proctectomy	30 ¹¹⁵ 43 ¹¹⁶	<1 ¹¹⁵ 12 ¹¹⁶	1 ¹¹⁶ 3 ¹¹⁵
	Ulcerative colitis, polyposis coli	Proctectomy with ileoanal anastomosis	56 ⁹⁴	19 ⁹⁴	0 ⁹⁴
	Ulcerative colitis, polyposis coli	Proctectomy with Pouch reconstruction	42 ⁹⁶	18 ⁹⁶	0 ⁹⁶

ND, no data.

Table 8 Incidence of postoperative fistulae in patients undergoing pancreatic surgery

Procedure	Pancreatic fistula (%)	Fistula mortality (%)	Overall mortality (%)
Pancreaticoduodenectomy	13 (3–36) ⁸⁷ 117–122	22 ¹²¹	3 (1–8) ⁷ 87 117–119 121 122 124
Left pancreatic resection	16 (4–29) ^{124–127}	0 ¹²⁶	3 (0–6) ^{124–126}
Subtotal pancreatectomy	12 ¹²⁸	0 ¹²⁸	4 ¹²⁸

other fistulae were not included. However, mortality among patients who did develop fistulae was examined in addition to mortality as a result of surgery (table 8). The rate of pancreatic fistulae varied from 3% to 36% in these studies, and fistula mortality from 0% to 22%. Overall mortality was fairly constant in all studies (0–8%).

Due to the high incidence of fistulae following pancreatic surgery, this procedure will be examined in more detail. Tables 9 and 10 show the incidence of fistulae, fistula mortality, and overall mortality according to pancreatic stump management and underlying disease, respectively. The incidence of fistulae varied widely in the different studies, from 0% up to 33% (table 9) and therefore any effect of technique is probably suppressed by variations in study design, surgeon experience, patients, etc.

The effect of underlying disease on fistula incidence is also unclear (table 10). However, it would appear that patients with periampullary carcinoma who develop a postoperative pancreatic fistula are more likely to have a fatal outcome.³⁵ Overall mortality also seems to be increased in patients with carcinoma of the pancreas or periampullary carcinoma.⁴ 107 112 134 137

BARTOLI ET AL META-ANALYSIS¹³⁹

A meta-analysis carried out during 1975–1989 examined the effects of stump management and underlying pathology on pancreatic fistula and mortality rates following pancreaticoduodenectomy (Whipple's procedure) in 2684 patients.¹³⁹ The results of this analysis provide some interesting information and will therefore be included here.

Table 9 Pancreatic fistulae, fistula mortality, and overall mortality rates with different pancreatic remnant treatments after pancreaticoduodenectomy

Treatment of pancreatic stump	Pancreatic fistula (%)	Fistula mortality (%)	Overall mortality (%)
Pancreaticojejunal end to side anastomosis	12 ¹²⁹	ND	ND
Pancreaticojejunal end to end anastomosis	25 ¹²⁹	ND	ND
Pancreaticojejunosomy	12 [2–33] ^{6 124 130–135}	28 [0–50] ^{124 130–132}	9 [0–50] ^{124 130–135}
Pancreaticogastrostomy	9 [0–12] ^{6 130 131}	0 ^{130 131}	0 ^{130 131}

ND, no data.

Table 11 Incidence of pancreatic fistulae with different pancreatic remnant treatments after pancreaticoduodenectomy¹³⁹

Treatment of pancreatic stump	Fistula (%)
Ligation	59 ^a
Total anastomosis	13 ^b
Pancreaticojejunal end to side anastomosis	16 ^c
Pancreaticojejunal end to end anastomosis	12
Wirsung-jejunal end to side anastomosis	11
Pancreaticogastrostomy	1
Occlusion	7 ^d
Closure+anastomosis	8 ^e

^{a–b}, ^{a–c}, ^{a–d}, ^{a–e} $p < 0.001$; ^{c–d} $p = 0.009$.

The widely used Wirsung-jejunal end to side anastomosis, the pancreaticojejunal end to side anastomosis, and the pancreaticojejunal end to end anastomosis were associated with fistula formation rates of 11–16% (table 11). However, the now obsolete ligation procedure was associated with a much higher incidence of fistulae (59%) (table 11).

When comparing outcomes of pancreaticoduodenectomy for cancer or for a benign disease such as chronic pancreatitis, the structural alterations present in the pancreas greatly affect fistula incidence.¹³⁹ Significantly fewer pancreatic fistulae form after surgery for chronic pancreatitis than for cancer (5% *v* 14%, respectively; $p < 0.001$) (table 12) as pancreatitis causes a particular change in the consistency of the pancreatic tissue. A chronically inflamed pancreas is fibrotic and is therefore usually easier to suture¹⁴⁰ whereas the soft normal tissue after tumour resection gives rise to less stable anastomoses. The location of the cancer also affects the incidence of fistulae. Bile duct cancer does not obstruct the pancreatic duct system and therefore anastomosis with the remaining pancreas is difficult. However, pancreatic cancer blocks the pancreatic duct which makes the suture easier to perform. Therefore, pancreaticoduodenectomies for bile duct cancer are associated with a significantly higher incidence of fistulae than for ampullary ($p = 0.002$) or pancreatic ($p = 0.003$) cancer (table 12).

Examining the effect of disease on fistula mortality, it was found that subjects with bile duct cancer had the highest

Table 12 Pancreatic fistula incidence and mortality by underlying illness in 2684 pancreatic resections¹³⁹

Underlying illness	Fistula incidence (%)	Fistula mortality (%)
Bile duct cancer	33 ^a	70 ^f
Ampullary cancer	15 ^b	31 ^g
Pancreatic cancer	12 ^c	27 ^h
Total carcinomas	14 ^d	21 ⁱ
Chronic pancreatitis	5 ^e	9 ⁱ

^{a–b} $p = 0.002$; ^{a–c} $p = 0.003$; ^{d–e} $p < 0.001$; ^{f–g} $p = 0.045$; ^{f–h} $p = 0.028$; ^{i–j} $p = 0.047$.

mortality rate (70%) followed by patients with pancreatic and ampullary cancer (table 12).¹³⁹ The difference in mortality for pancreaticoduodenectomies for cancer versus chronic pancreatitis was significant (21% *v* 9%, respectively; $p = 0.047$). Although these mortality rates were higher than would be expected now due to improved patient care, they still give a good indication of the increase in mortality according to the underlying illness.

THE CHANGING POPULATION OF GASTROINTESTINAL FISTULA PATIENTS

Although the total number of patients with fistulae has not fallen over time, mortality and morbidity rates have improved. In an extensive review spanning 30 years, 404 patients with gastrointestinal cutaneous fistulae were studied.¹⁴¹ During the first period (1946–1959), mortality was very high (44%) as the only available treatment was antibiotics. During the second period (1960–1970), parasurgical care was dramatically improved—respiratory support, perfection of antibiotic use, preliminary introduction of nutritional support, and improved patient monitoring. These measures resulted in a decrease in mortality to 15%. During the third period (1970–1975), parenteral nutrition was introduced but the mortality rate did not decrease further (21%).¹⁴¹ This is probably because, during this period, patients accepted for surgery were older, sicker, had more advanced cancer, underwent more complex operations, and were generally at higher risk.¹⁴²

Table 10 Pancreatic fistulae, fistula mortality, and overall mortality rates by underlying illness

Underlying condition	Pancreatic fistula (%)	Fistula mortality (%)	Overall mortality (%)
Bile duct cancer	18 ¹²⁹	ND	ND
Ampullary cancer	18 ¹²⁹	ND	ND
Periampullary carcinoma	16 ^{35 28} ¹³⁴	19 ³⁵	6 ^{112 9} ¹³⁴
Carcinoma of pancreas or periampullary carcinoma	30 [23–41] ^{30 43 51}	0 ³⁰	7 [0–10] ^{30 43 51}
Pancreatic adenocarcinoma	13 ⁸⁷	0 ⁸⁷	3 ⁸⁷
Pancreatic cancer	22 ¹²⁹	ND	ND
Neoplastic disease	10 ¹²⁴	0 ¹²⁴	0 ¹²⁴
Endocrine tumour	12 ¹²⁴	0 ¹²⁴	0 ¹²⁴
Malignancy	6 ¹³⁸	0 ¹³⁸	0 ¹³⁸
Chronic pancreatitis/ inflammatory disease	20 [9–34] ^{4 124 138}	0 ^{4 124}	0 ^{4 124 137}

ND, no data.

In a later review of patients undergoing Whipple's procedure, mortality fell from 18% during 1970–1979 (n=2133) to 7% during 1980–1989 (n=1474).¹⁴³ Morbidity was also reduced, from 49% (n=1049) to 35% (n=521) during the same time periods. However, these changes cannot be attributed to a reduced fistula rate, as the incidence of pancreaticojejunostomy leak only fell slightly, from 12% (n=1049) to 9% (n=521).

In a more recent study, mortality rates were examined in 312 patients undergoing partial pancreaticoduodenectomy.¹⁴⁴ Hospital mortality decreased from 4.9% during 1983–1992 to 1.4% during 1995–1996. The complication rate also decreased, from 60% to 41%, as did hospital stay, from 24 days to 16 days. These improvements were attributed to better surgical techniques and increased surgeon experience.

CONCLUSION

Gastrointestinal fistulae, the majority of which form after operative procedures, are a major cause of morbidity and mortality. Their effects on the patient are wide ranging—pain, complex wound care, psychological effect on self image and self esteem, reduced quality of life, delayed return to social and work activities, and anxiety about future operative procedures and possible death. Complications such as nutritional problems, abscesses, and sepsis may also occur. Furthermore, a postoperative fistula increases hospital stay which obviously increases hospital costs.

Despite numerous medical advances—improved diagnostic techniques, patient care (parenteral nutrition, antibiotics, intensive care, and wound care), perioperative management, and surgical techniques—the overall number of postoperative fistulae has not fallen. This may be because these factors have also led to an increase in the number of operations carried out, particularly in patients at high surgical risk (old, malnourished, or catabolic tumoral patients). Furthermore, improved surgical techniques have led to more complex surgery being performed which again has increased the risk of fistula formation despite improved care.

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