REVIEW ARTICLE

Defining post-operative pancreatitis as a new pancreatic specific complication following pancreatic resection

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Abstract

Introduction: Post-operative pancreatic fistula has been well defined. However the underlying aetiology remains poorly understood. The aim of this review was to investigate whether the underlying aetiology for a proportion of patients suffering from post-operative pancreatic fistula was due to post-operative pancreatitis.

Method: A systematic literature review according to the PRISMA guidelines. The date range was from 2005 to 2016. The search strategy included the terms: post-operative pancreatitis, pathophysiology, post-operative pancreatic fistula, pancreaticoduodenectomy, ischaemic pancreatitis, microcirculation and pancreatitis, serum and drain amylase and lipase. The data was summarised without quantitative or qualitative analysis.

Results: There exists significant physiological, biochemical, clinical and histological evidence in the literature that a proportion of post-operative pancreatic fistula is due to post-operative pancreatitis. A new definition of post-operative pancreatitis based on the presence of biochemical evidence for pancreatic inflammation (urinary trypsinogen-2 >50 ug/L or serum amylase/lipase > upper limit of normal) between post-operative days 0–2. Predicted severity is based on C-reactive protein with a cut-off of 180 mg/L at post-operative day 2. The proposed grading of severity is in line with previous work by international study group of pancreatic surgery.

Conclusion: Post-operative pancreatitis should be recognised as a separate pancreatic specific complication following pancreatic resection. Improved recognition may allow better understanding of potential methods of prevention, treatment and prediction of severity.

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Introduction

Breakdown of the pancreaticoenteric anastomosis remains the major cause of morbidity and mortality following pancreaticoduodenectomy (PD) (Fig. 1).[1] Following a landmark paper in 2005 the International Study group for Pancreatic Surgery (ISGPS)[2] standardised the definition of this complication as post-operative pancreatic fistula (POPF). In the decade since this definition, little progress has been made in reducing the incidence of pancreatic fistula. Contemporary rates of clinically relevant (grades B/C) POPF remain between 8 and 17%.[1,3] In an effort to reduce the severity of the morbidity and mortality associated with POPF numerous anastomotic techniques have been described[4] but no single technique has been shown to eliminate anastomotic leak with any degree of reproducibility between surgeons.

Traditionally, the definition of a fistula is an abnormal track between two epithelial surfaces. It was acknowledged by the authors of the ISGPS in 2005[2] that most prior definitions related to the concept that the complication being defined was leakage of pancreatic fluid due to communication with the pancreatic duct if the anastomosis failed to heal, or leakage from an iatrogenically-created raw surface of the pancreatic parenchyma.[2] The final broad definition of a pancreatic fistula consisted of the following; persistent drainage of amylase rich fluid (3x > than upper limit of normal serum value) for greater than 3 days.[2] At

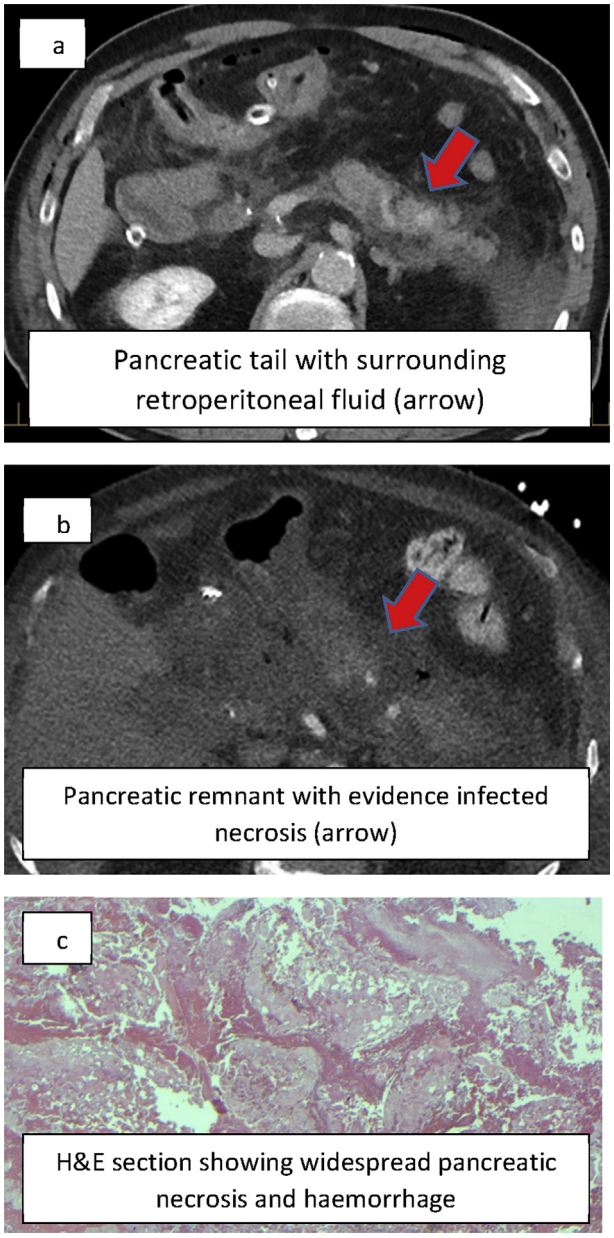

Figure 1 A 71 year old man who underwent pancreaticoduodenectomy (PD) for T1 N0 duodenal carcinoma. Anaerobic threshold unknown. Intrathecal morphine was used. No somatostatin analogues or perioperative NSAID's were administered. Standard dissection for PD was performed. Fistula risk score was six. Pancreatic neck was transected by ligasure. Binding pancreaticogastrostomy was performed. Post-operative day (POD) 1 patient was confused, tachycardic, serum amylase 7 x > upper limit normal. Urinary TRP2 was not measured. POD 1 CT scan showed evidence of post-operative pancreatitis (Fig. 1a). POD 2 CRP was 359 mg/L. POD 17 patient became increasingly unwell. Repeat CT showed evidence of infected pancreatic necrosis (Fig. 1b). POD 17 operative findings were of intact anastomosis but segmental pancreatic necrosis. Partial pancreatectomy by debridement (anastomosis taken down) and wide bore drainage to remnant pancreatic bed. Initial clinical improvement followed by clinical deterioration at POD 27. Completion pancreatectomy performed. Histologically confirmed pancreatic necrosis within the remnant (Fig. 1c)

this time the concept of the possibility that POPF may result from pancreatitis within the remnant was not considered, or at least not clearly stated.

The biochemical diagnostic criteria for acute pancreatitis are defined as three times increase in upper limit of normal serum value of amylase or lipase in association with upper abdominal pain or confirmatory radiological imaging.[5] In addition urinary trypsinogen activation peptide (U-TAP) and trypsinogen-2 (U-TRP2) have been shown to be accurate early biochemical markers of acute pancreatic inflammation and although they can predict severity, accuracy remains problematic.[6,7] Although cross-sectional radiological criteria for acute pancreatitis exist, the presence of necrosis cannot be usually detected for several days,[8] although this has recently been challenged.[9] Early biochemical prediction of necrosis remains difficult and is not related to the extent of serum lipase or amylase rise.[5] C-reactive protein (CRP), haematocrit rise, procalcitonin blood urea nitrogen have all been associated with severity although the specificity remains poor.[5,10] These criteria have not been widely tested in the setting of post-operative pancreatitis or incorporated into the definition of POPF.

With a further decade of experience it is timely to reconsider the underlying pathophysiology of POPF. The aim is to achieve superior clarity in terms of definition, standardisation of reporting and potentially prevention of this significant complication. The underlying concept of this paper was to test the hypothesis that the grade of POPF following pancreaticoduodenectomy represents a spectrum of severity of acute pancreatitis within the pancreatic remnant.

Method

A PubMed search was performed combining the terms post-operative pancreatitis (POP), pathophysiology, post-operative pancreatic fistula, pancreaticoduodenectomy, ischaemic pancreatitis, microcirculation and pancreatitis, serum and drain amylase and lipase. Exclusion criteria included studies not involving humans. The search was limited to papers published after 1st January2005 given the watershed following establishment of the ISGPS definition of POPF. The exception was for studies focussing on anatomical or physiological aspects that were relevant but not the sole focus of this review. Articles with abstracts that were deemed relevant to the topic were then sourced and included for further review. Outcomes of the search were recorded via the PRISMA flow chart (Fig. 2). The last search date was 2/3/16. It was planned that a descriptive review of the

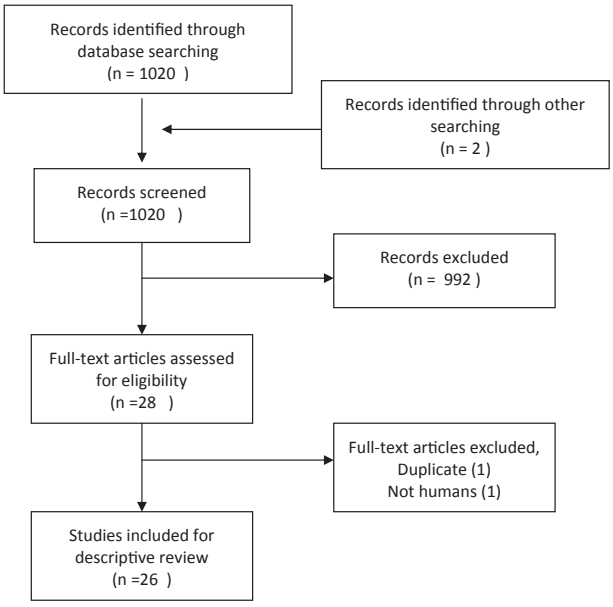

Figure 2 PRISMA flow diagram

available data would be undertaken. No qualitative or quantitative analysis was planned.

Results

Anatomy of pancreatic blood supply and pathophysiology of acute pancreatitis

The pancreatic arterial blood supply comes from the splenic artery and branches of the hepatic artery (Fig. 3). The pancreatic head is supplied by the pancreaticoduodenal arcades which are formed by the anterior and posterior superior (terminal branches of duodenal component of the gastroduodenal artery) and inferior pancreaticoduodenal arteries (origin from superior mesenteric artery).[11] Three major branches arise from the splenic artery to supply the pancreatic body and tail.[11,12] From anatomical right to left these are the dorsal, pancreatic magna and caudal pancreatic arteries.[12] The dorsal pancreatic artery passes inferiorly and to the right of the splenic artery for 5 mm when it enters the pancreas 2–3 cm to the left of the portal vein.[12] Within the pancreas, while passing inferiorly to the left of the portal vein, the dorsal pancreatic artery splits into three further branches (superior and inferior right and left).[12] The superior right branch crosses the neck (surgical transection line for PD) to anastomose with the posterior superior pancreaticoduodenal arcade.[11] Further distally the inferior right branch crosses the pancreatic neck to anastomose with the inferior pancreaticoduodenal arcade.[12] The terminal branch of the dorsal pancreatic artery (left branch) courses to the left along the inferior border of the pancreas to become the transverse pancreatic artery anastomosing with more distal pancreatic branches from the splenic artery including the pancreatic magna and caudate pancreatic artery.[12] These anastomoses are variable and can be absent, in such situations ligation of the left branch can result in pancreatic infarction.[11] The origin of the dorsal pancreatic artery is however highly variable following the previously described course in only 40% of individuals.[12] Importantly it can arise from the either of the foregut or midgut vessels or their tributaries such that it may be at risk of division during PD. Thus there are two scenarios that may occur following division of the pancreatic neck during PD with regard to pancreatic ischaemia. Interruption of the aforementioned anastomoses may result in watershed area of ischaemia within the remaining pancreatic neck to the right of the dorsal pancreatic artery.

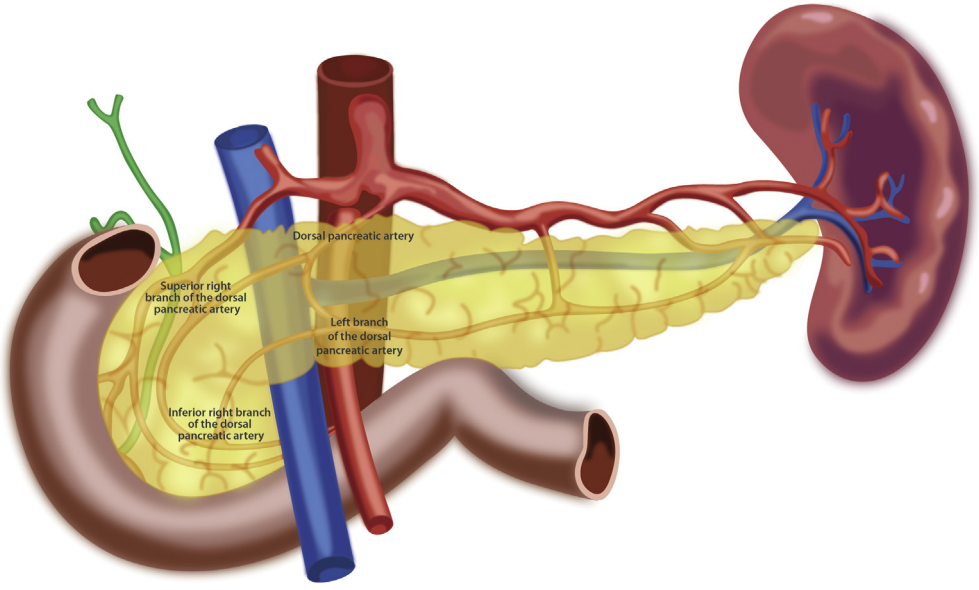

Figure 3 Anatomy of pancreatic blood supply demonstrating course of dorsal pancreatic artery and its branches through the pancreatic neck

Alternatively if the dorsal pancreatic artery is anomalous in its origin, its division may interrupt the anastomoses with the pancreatic body and tail resulting in pancreatic ischaemia within the whole pancreatic remnant. Venous drainage of the tail of the pancreas occurs via multiple small tributaries into the splenic vein.[11] There are no veins that drain directly into the SMV or splenic vein from the pancreatic neck.[11] The pancreatic head drains via pancreaticoduodenal tributaries into the right side of the portal vein.[11] The pancreas is exquisitely sensitive to both arterial and venous ischaemia and importantly, infarction is not a prerequisite for pancreatic necrosis.[13] Transient hypo-perfusion can be enough to induce the cascade of changes associated with acute pancreatitis.[13] In 2006 Cuthbertson and Christophi performed a systematic review of microcirculatory changes associated with acute pancreatitis.[13] A summary of the authors' findings is presented visually in Fig. 4. The authors described how each pancreatic lobule is supplied by an end artery which supplies a continuous network of capillaries.[13] Autoregulation of blood flow occurs through hormonal and neural mechanisms to maintain normal perfusion of the pancreas across a range of physiological conditions.[13] This ensures the gland is evenly perfused with blood, with flow being linked to exocrine secretion.[13] Blood flow can be reduced by somatostatin and increased by cholecystokinin.[13] Ischaemia and hypoperfusion have been shown to induce pancreatic necrosis.[13] Venous occlusion has been demonstrated to induce and worsen the severity of pancreatitis.[13] Changes to the microcirculation can occur within minutes of induction of pancreatitis and architectural changes can occur within 30 min.[13] Vasoconstriction occurs first, leading to stasis of the circulation, exacerbating tissue ischaemia.[13] The proportion of capillaries perfused is reduced leading to progressive capillary exclusion.[13] By three hours there can be complete capillary malperfusion.[13] Of importance the changes are not homogenous meaning that total pancreatic blood flow does not correlate with regional pancreatic blood flow.[13] The presence of pathological shunts leads to significant tissue hypoxia due to capillary stasis.[13] This is an important contributor to the formation of pancreatic necrosis.[13] The endothelial disruption that occurs leads to increase in capillary permeability such that leakage of fluid and activated proteases into the surrounding tissue and lymph leading to further local tissue destruction and distant organ dysfunction.[13] Reperfusion injury is also thought to be a major contributor to severity and leads to acinar cell destruction and release of activated enzymes.[13]

Biochemical evidence for early onset post-operative pancreatitis following pancreatic resection

If the concept that POP contributes to POPF holds true then it would expected that there would be biochemical evidence of acute POP in the immediate peri-operative period. In the absence of gross technical error it would also be expected that the commonly used pancreatico-enteric anastomoses be watertight preventing "leakage of amylase rich fluid into the peritoneal fluid from ductal epithelium". Therefore any drain fluid in the early post-operative period should not have elevated levels of pancreatic enzymes.

Valle *et al.*[14] reported on 98 patients who underwent PD and had a post-operative day (POD) 1 serum lipase measured. No normal range was provided for the serum lipase, but 85 of the 98 patients had an elevated serum lipase. In patients who did not develop POPF (n = 56), the median POD 1 serum lipase was 25 IU/L vs. 89 IU/L for those who developed POPF, $p < 0.001$. The degree of elevation of serum lipase did not correlate with severity of POPF. Elevated serum lipase at POD 1 also predicted other pancreatic specific complications including delayed gastric emptying. Others have reported rises in serum amylase in the immediate perioperative period. Palani Velu *et al.*[15] describe 185 patients who underwent PD of whom 64 (35%) developed POPF of which 43 (23%) were CR-POPF. Serum amylase was measured at least 4 h post pancreatico-enteric reconstruction. The mean serum amylase in those with No POPF or Grade A POPF was 92 IU/L vs. 217 IU/L in those who developed CR-POPF, $p < 0.001$. Serum amylase levels at POD 0 were significantly elevated in those with high risk pancreatic remnants. The authors concluded that this early elevation of serum amylase potentially represented a marker of "trauma" to the functioning pancreas rather than a fistula in evolution. Winter *et al.*[16] retrospectively studied 2323 patients undergoing PD. An amylase >100 U/L occurred in 1142 (49%) patients. Of these patients 179 (16%) developed a POPF as compared with 41/1181 (4%) patients with an amylase <100 IU/L, $p < 0.001$. An amylase >292 IU/L was shown to be independent predictor of POPF, intra-abdominal abscess and delayed gastric emptying. Of particular interest was the combination of a soft pancreas and serum amylase >400 IU/L had a 30% incidence of POPF with odds ratio of 25 as compared to hard pancreas and normal amylase. Okabayashi *et al.*[17] also described similar findings in 50 patients who underwent PD. An elevated serum amylase of 1.69 × the upper limit of normal increased the risk of POPF 2 fold.

U-TRP2 has high specificity and sensitivity for pancreatitis irrespective of aetiology.[7] U-TRP2 and serum amylase were measured at POD 1 and 3 in 130 patients undergoing PD.[18] At POD 1 of the 19 patients who developed a POPF 11 (58%) had evidence of hyperamylasaemia (3x upper limit of normal) vs. 26/111 (23%) who did not develop POPF, $p = 0.005$. On POD 3, 14/19 (74%) patients who developed POPF had U-TRP2 levels >50 ug/L vs. 29/111 (26%) patients without POPF, $p < 0.001$. Importantly, U-TRP2 also correlated with elevated serum amylase POD 1 ($p = 0.009$), elevated amylase drain levels POD 1 ($p < 0.001$), elevated CRP POD 1 ($p = 0.003$), POD 3 ($p < 0.001$), POD 7 ($p = 0.002$) and all grades of POPF. Following multivariable analysis U-TRP2 was shown to be an independent predictor of POPF. The authors made some very

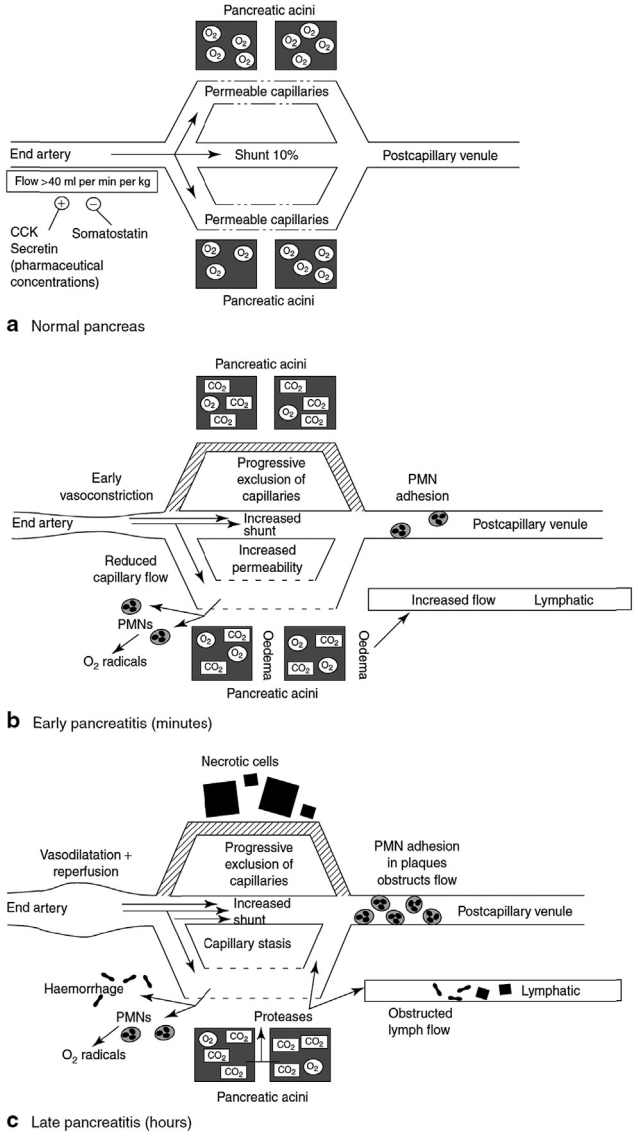

Figure 4 Microcirculatory changes that occur during acute pancreatitis (CCK, cholecystokinin, PMN, polymorphonuclear cell). Reproduced with permission from Fig. 1. Physiology and pathophysiology of microvascular changes in acute pancreatitis. Cuthbertson CM and Christophi C. Disturbances of the microcirculation in acute pancreatitis. Br J Surg 2006; 93:518–530, John Wiley & Sons Ltd, Copyright © 2006

important observations with regard to the time dependant profile of the pancreatic enzymes, amylase and trypsinogen, in serum, urine and peritoneal drains. This was highly suggestive the source of the elevated U-TRP2 was release of trypsinogen 2 from the acinar cells due to POP as opposed to reabsorption from the peritoneum of leaked pancreatic juice. In a study by Raty *et al.*[19] 50 patients undergoing pancreatic resection (43 PD) were followed measuring serum amylase and CRP POD 4, 6, 10, drain amylase at POD 4 and 6, routine contrast enhanced CT scan at POD 2 and 6, daily U-TRP2 strip test (positive if > 50 ug/L). POP was diagnosed on the basis of CT changes including focal or diffuse enlargement, contour irregularities, non-homogenous attenuation and enhancement of the pancreatic remnant and inflammatory changes in the left anterior pararenal space. No patient had CT evidence of pre-operative pancreatitis. Thirteen of the 50 patients developed CT evidence of POP, of which 12 were evident by POD 2. All thirteen patients had a positive U-TRP2, 12 by post POD 1 and all by POD 2. Three of 37 patients without CT diagnosed POP had a positive U-TRP2 test. In addition a positive U-TRP2 was associated with higher CRP and serum amylase at POD 4. Of the 12 (7-CR POPF) patients diagnosed with POPF by ISGPS criteria, 11 had positive U-TRP2, while 2 of 3 patients with positive U-TRP2 test and no CT evidence of POP had a POPF. As a control group, patients undergoing total pancreatectomy showed no elevation in U-TRP2.

In a novel study, de Reuver *et al.*[20] demonstrated an intra-operative association of raised peritoneal amylase levels with the development of POPF. In a study of 62 patients undergoing PD, following reconstruction of the pancreatic anastomosis the area was irrigated with saline and then suctioned. New fluid samples were obtained from adjacent to the peripancreatic space. A peritoneal amylase value of >200 IU/L predicted POPF with an AUC of 0.93. Strikingly in those patients without POPF the median peritoneal amylase level was 34 IU/L vs. 618 IU/L for those who developed POPF, $p < 0.01$. Raised intra-peritoneal amylase levels also correlated with delayed drain amylase levels and the development of other complications, in particular delayed gastric emptying. Unfortunately, corresponding data on serum amylase levels were not provided.

Other authors have also recognised that intraperitoneal changes are occurring within the pancreas earlier than initially thought. A meta-analysis by Giglio *et al.*[21] identified 13 studies involving 4416 patients of whom 4079 underwent a PD. All studies showed a strong association with elevated drain amylase levels at POD 1 and development of both grade A and clinically relevant (CR) POPF (Grade B/C of ISGPS definition). However, no data was provided with regard to serum amylase or lipase measurements.

Further evidence to support the concept of localised tissue hypoxia precipitating pancreatitis comes from a study by Ansorge *et al.*[22] The authors used microdialysis to sample fluid close to the pancreaticojejunal anastomosis in the immediate post-operative period. Microdialysis can be used to calculate lactate to pyruvate ratio (L/P ratio) which is a well-established method for assessing tissue hypoxia, while glycerol concentrations can be used as a marker of cell death.[22] In addition authors, measured trypsinogen activation peptide (TAP) and glucose levels. A total of 48 patients underwent PD. Seven of the 48 patients developed POPF. In those patients who developed POPF there were significant increases in the L/P ratio across POD 1–5 as compared with those patients that had other surgical

complications or no complications. Strikingly, intra-peritoneal TAP levels on day 1 were detectable in 6/7patients who developed POPF vs. 2/33 patients with no surgical complications. Similarly, elevated levels of plasma pancreatic amylase (although not at levels diagnostic of acute pancreatitis) were observed in those with POPF but not in those with no surgical complications. Peak glycerol levels in those patients who developed POPF had intra-peritoneal levels >800 umol/L – a level far in excess of previously described associated with infarction in pigs. The author's conclusion was that the profiles of changes were consistent with activation of trypsin and lipase as the initial step in POPF formation, followed by local ischaemia and reduced tissue perfusion resulting in reduced substrate delivery leading to pancreatic necrosis.[22] Importantly the authors noted that peritoneal samples were more sensitive at detecting changes of pancreatitis and tissue hypoxia than serum samples.[22] Other non-specific but potentially supporting evidence is found in a study by Kinaci et al.[23] in which 85 patients undergoing PD had early markers of inflammation analysed. Although neutrophil/lymphocyte ratio, platelet/lymphocyte ratio or serum lactate were not associated with subsequent development of CR-POPF, acidosis at end of the procedure as measured by pH was. A pH of <7.31 associated with CR-POPF with a positive likelihood ratio of 2.4. However the underlying aetiology of the acidosis was not able to be elucidated from the study.

If the proposed hypothesis holds true then there should also be a correlation between early markers of severity of acute pancreatitis and the development of clinically relevant POPF especially grade C. Hiyoshi *et al.*[24] studied 176 patients undergoing PD, 30 (17%) who developed CR-POPF. Elevated CRP POD 1–4 and body temperature POD 2–5 were shown to be independent predictors of CR-POPF. Using data from POD 3, a drain amylase >750 IU/L, a CRP ≥200 mg/L and body temperature ≥37.5 °C demonstrated a positive likelihood ratio of 47 and negative likelihood ratio of 0.2 with regard to predicting CR-POPF. Palani Velu *et al.*[25] have published a follow up study to their previous work[15] with regard to POD 0 serum amylase predicting CR-POPF. In this series[25] 230 patients underwent PD of whom 54 (24%) developed CR-POPF. A POD 2 CRP >230 mg/L was most closely associated with CR-POPF, but a POD 2 CRP >180 mg/L was the best predictor of pancreatic specific complications ($p < 0.001$), need of invasive post-operative intervention ($p = 0.017$). Importantly, raised CRP was not associated with non-pancreatic infectious complications. Following multivariable analysis, independent predictors of pancreatic specific complications were soft pancreatic texture ($P < 0.011$), serum amylase POD 0 >130 IU/L ($p = 0.001$), CRP POD 2 >180 mg/L ($p = 0.026$), independent predictors of POD 2 CRP >180 mg/L were small pancreatic duct ($p = 0.025$) and serum amylase POD 0 >130 IU/L ($p = 0.003$). The combination of serum amylase POD 0 >130 IU/L and POD 2 CRP >180 mg/L was associated with 66% incidence of a pancreatic specific complication, 23% incidence of reoperation and 9% 90 day mortality. This concept of early systemic inflammatory response as marker of severity of pancreatitis is further supported in a large retrospective analysis of Grade C POPF by McMillan *et al.*[26] In this study post-operative findings of elevated white cell count, fever, tachycardia by POD 6 were warning signs of impending Grade C POPF. Other clinical signs reported that are consistent with POP are the observation that loss of drain fluid clarity or sinister effluent within the drain[26,27] in the early postoperative period is a predictor of grade C POPF.

Clinical evidence for altered intraoperative pancreatic perfusion

In 1998 Strasberg and McNevin[12] described 40 patients who underwent PD. Following sharp transection of the pancreatic neck 16 of the 40 patients failed to show evidence of brisk bleeding. This was reported to correspond to the absence of a Doppler signal following hand held Doppler flow probe assessment. The authors followed this up with a further prospective study in 2002 of 123 patients undergoing PD, 38% whom required the pancreatic neck to be cut back to achieve brisk arterial bleeding from the cut surface. Given this paper was prior to the ISGPS definition of POPF the outcomes are not presented but these studies are included to document the physiological observation of altered intraoperative pancreatic perfusion.[28] More recently a case report using indocyanine green dye and a near infrared capable laparoscope confirmed similar observations with an area of ischaemia not visible to the naked eye present in the pancreatic neck.[29] It is unclear whether this corresponded with clinical improvement in bleeding from the cut surface or indeed how deep the penetration of assessment into the gland near infrared can detect. It is well known that a firm pancreas has significantly lower risk of POPF but until recently it has been difficult to objectively assess this phenomenon. In a recent study of 20 patients undergoing pancreaticoduodenectomy Sugimoto *et al.*[30] analysed preoperative pancreatic perfusion and correlated this with histological assessment and clinical outcomes. In those patients who did not develop POPF there were lower levels of arterial flow (ml/min/100 mls) and reduced mean transit time (seconds) while histologically there was an increase in fibrosis and higher vessel density (mm^2). How these features may contribute to transient pancreatic ischaemia following transection is yet to be elucidated.

Clinical evidence for POP post PD

Nentwich *et al.*[31] analysed 20 of 521 patients who underwent PD and required completion pancreatectomy. In 7 of these patients the reason given was pancreatic necrosis within the remnant. It was not clear what differentiated POPF (N = 14) from POP. Rudis and Ryska[32] recently describe 14 patients who developed grade C POPF by ISGPS definition. Of these 14 patients, 7 died. Autopsy of the pancreas revealed acute pancreatitis with necrosis in 4 patients. The authors noted that clinically it was difficult to distinguish clinically from POPF due to anastomotic leak or POP

based on post-operative CT or intra-operatively when re-operated on. However there was an association with higher CRP POD 3–5 and serum amylase POD 1–3 with POP.

Further evidence supporting this theory has been elegantly demonstrated by McMillan *et al.*[33] indicating that preoperative somatostatin analogues increase the severity of POPF particularly in those patients identified as high risk by the fistula risk score.[34] The basis of this finding has been thought to be due to hypoperfusion of the pancreatic remnant via splanchnic vasoconstriction.[33] Somatostatin has been shown to act as a splanchnic vasoconstrictor especially of the foregut vessels.[35,36] However the effect is highly variable across individuals and in some patients an increased flow in midgut vessels has been observed.[35] The reason for such variation has not been elucidated but may include variable receptors within the vessels walls or metabolites interacting with somatostatin receptors subtypes.[35] This may partly explain the apparent discrepancy with a large recent randomised trial of Pasireotide.[37] In this well performed trial there was a reduction in incidence and severity of POPF including in subgroup analysis of high risk pancreatic remnants with the use of Pasireotide.[37] Pasireotide is a somatostatin analogue with a significantly longer half-life than octreotide and thus may avoid rebound hypersecretion that occurs between doses of short acting somatostatins.[37] Pasireotide has a different binding profile and affinity to the somatostatin receptor subgroups as compared with octreotide.[38] No data exists with regard to Pasireotide's effect on splanchnic blood flow although it has been shown to reduce exocrine secretion.

Should the proposed hypothesis hold true it would be expected that POPF associated with PD would have a different incidence and severity than following distal pancreatectomy (DP). McMillan *et al.* have looked at this in detail.[39] The authors analysed the outcomes of over 2000 patients undergoing PD or DP. The incidence of POPF was higher after DP (35%) than PD (27%), $p < 0.001$. The incidence of CR-POPF was also higher following DP (15%) vs. PD (11%), $p = 0.019$. However it is important to acknowledge that the patients were not risk adjusted for factors associated with POPF such as obesity. There was a higher use of octreotide and prophylactic drains in the PD group. These factors may have therefore altered both incidence and grade of POPF. Perhaps most striking was the difference of severity of the burden of the CR-POPF with grade C POPF following PD being an order of magnitude greater than that observed for patients undergoing DP. For example there was significantly increased likelihood of intensive care admission, degree of multi-organ failure, hospital stay and mortality associated with grade C POPF following PD vs. DP. This fits with clinical practice in that although patients may require reoperation after DP for POPF rarely is it associated with multi-organ failure or death. This may be suggestive of a different underlying aetiology for POPF after PD vs. DP such as POP compared to true leakage from a cut surface of pancreas.

Discussion

There exists significant physiological, biochemical, radiological and clinical and histological evidence to support the hypothesis that the pathophysiology of a significant proportion of POPF following PD is due to POP. This appears to be induced intra-operatively and can be detected in the immediate peri-operative period. Manifestations range from self-resolving inflammation to fulminant pancreatitis with associated multi-organ failure and pancreatic necrosis. Understanding this raises significant possibilities with regard to treatment options but also highlights the importance of standardising the reporting of risk factors beyond the nature of the remnant or type of surgical reconstruction.

Given the evidence and potential benefits of recognising POP as a separate entity to POPF a modification to the ISGPS definition of POPF is proposed (Table 1). This is based on the findings from this review and the modifications to ISGPS grading as suggested Hackert *et al.*[40] A predicted severity is also proposed because if validated to be accurate it opens the possibility for early intervention and "down staging" of the "level of burden"[39] associated with POP. Clearly validation and refinement will be required but this combined with a standardised minimum reporting dataset for PD and DP that describes patient, therapeutic and technical factors will help elucidate the true underlying aetiology and treatment options for POP and POPF. However a key point of understanding is that the rise in the serum levels of amylase and lipase in the post-operative period may be significantly less than that traditionally associated with the diagnosis of acute pancreatitis. U-TRP2 is suggested as it is an easy bedside test to do with commercially available test strips and been shown to be predictive of pancreatitis in the post-operative setting.[7,18] However in the future it may be that urinary TAP may also be useful.

With the exception of Strasberg *et al.*[28] almost all surgical techniques looking to reduce POPF have focused on the pancreatico-enteric reconstruction.[3] Strasberg *et al.*[28] describe in detail dividing the pancreas along the medial longitudinal margin of the SMV with a scalpel. If pulsatile bleeding on the superior and inferior borders of the pancreatic remnant requiring suturing was not encountered the pancreas was further mobilised (1–2 cm) and re-divided. Yet this alone may not be enough. From the understanding of the timing of the microcirculatory changes that occur within the pancreas during induction of acute pancreatitis[13] further consideration may need to be given to the order of pancreatic dissection. For example, traditionally during pancreaticoduodenectomy the pancreas is transected late in the resection phase. The vascular inflow and outflow control of the pancreatic head is performed early potentially leaving a prolonged period with in-situ pancreatic parenchymal ischaemia. Should the pancreas be divided early prior to circulatory disruption? Are the new sealing devices better or worse than sharp transection of the pancreatic neck? Currently the answers are unknown and may be difficult to study in a

randomised and controlled fashion. However given the burden to both the patient and the health systems of CR-POPF it would seem appropriate that answers to these questions are sought. As a minimum these factors should be considered as part of a standardised dataset when reporting intraoperative techniques.[4]

There is experimental evidence that various pharmacological agents can alter the pancreatic microcirculation following the induction of acute pancreatitis.[13] Many are used in the peri-operative period including heparin, anti-inflammatories, various intravenous fluids, steroids and epidurals.[13,41] In addition systemic patient factors such as poor anaerobic threshold may be an important contributor to pancreatic perfusion.[42] A recent randomised trial has shown that epidural analgesia can improve pancreatic perfusion and reduce severity in predicted severe acute pancreatitis.[41] With the exception of somatostatin analogues[33] rarely have these factors been considered or adjusted for in studies assessing POPF following pancreaticoduodenectomy.

A real time, clinically usable and reproducible objective assessment of the microcirculatory state of the pancreatic remnant prior to reconstruction and in the early post-operative period would now seem critical if these issues are to be fully understood. Others may argue that this is only academically useful, asking how would it change intraoperative management? However, could it be possible that a critical level of perfusion exists such that below this threshold consideration should be given to immediate completion pancreatectomy or at least delaying pancreaticoenteric reconstruction? In the future, intraoperative pharmacological intervention may also be able to alter the course of POP.

Given the increasing ability to pre-operatively identify the "high risk" pancreatic remnant[34] the potential for prophylactic interventions may now exist. Prophylactic pharmacological interventions have been shown to reduce the risk of ERCP induced pancreatitis. This has included NSAID's[43] and protease inhibitors.[44] Uemura *et al.* recognised the importance of the contribution of POP to POPF and conducted a randomised trial[45] with this in mind. Forty patients undergoing PD were randomised to Ulinastatin or placebo in the peri-operative period. Ulinastatin is a trypsin inhibitor. The aim of this trial was to detect reduction in post-operative serum and drain amylase and U-TRP2. Unfortunately no power studies were provided but it was clear that it was not powered to detect a reduction in POPF. The incidence of POP (U-TRP2 >50 ug/L) was 5/40 patients. All 5 were in the placebo group, p = 0.016. There were significant reductions in post-operative hyperamylasemia POD 0–2 and drain amylase levels POD 2–3. NSAID's may need to be approached with more caution given the potential association with anastomotic breakdown.[46] Clearly it would be important to differentiate POP from true POPF when studying the impact of these medications. Alternatively direct preoperative manipulation of the remnant may be possible. Neoadjuvant radiotherapy has been shown to induce changes in the normal remnant pancreatic tissue similar to those seen in chronic pancreatitis[47] and those recently associated with a firm or hard pancreatic remnant.[31] It may be possible that only a single treatment (8 Gy) of radiotherapy is required to induce such change within the pancreas.[48] An accurate definition of what is happening at a physiological level will be critical if the true efficacy of any intervention is to be accurately determined. Recent reports of perfusion CT of the pancreas may provide this ability.[31,41]

The standardisation of definitions over the last decade has resulted in a better understanding of POPF but not an improvement in outcomes for the patients. Recent evidence suggests that the aetiology of a significant proportion of POPF may be due to POP. It is therefore proposed that the definition of POPF is changed to allow POP to stand alone as a new pancreatic specific complication. By doing so should allow the reporting of risk factors beyond anatomical and reconstructive technical factors and rethinking the approach to prevention.

Table 1 Proposed definition of post-operative pancreatitis and post-operative pancreatic fistula

	Post-operative pancreatitis (POP)	Post-operative pancreatic fistula (POPF)
Definition		
Urinary TRP-2 >50 ug/L POD 1–2	Yes	No
Elevation serum amylase/lipase > upper limit normal POD 0-1	+ (if U-TRP2 unknown)	No
Drain amylase >3x serum upper limit normal @ POD 3	+/–	Yes
Predicted severity		
CRP <180 mg/L POD 2	Grade A	Grade A
CRP ≥180 mg/L POD 2	CR-POP	CR-POPF
Actual severity[a]	**Proposed**	**Modified**
No symptoms, infectious signs or specific therapy	Grade A	Grade A
POP or POPF related symptoms or therapies including interventional	Grade B	Grade B
POP or POPF related reoperation or mortality without reoperation	Grade C	Grade C

[a] Based on modification of the grading of ISGPS definition of POPF.[40]

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Conflicts of interest

None declared.

References

1. Harnoss JC, Ulrich AB, Harnoss JM, Diener MK, Büchler MW, Welch T. (2014) Use and results of consensus definitions in pancreatic surgery: a systematic review. *Surgery* 155:47–57.
2. Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J *et al*. (2005) Postoperative pancreatic fistula: an international study group (ISGPF) definition. *Surgery* 138:8–13.
3. Denbo JW, Orr WS, Zarzaur BL, Behrman SW. (2012) Toward defining grade C pancreatic fistula following pancreaticoduodenectomy: incidence, risk factors, management and outcome. *HPB* 14:589–593.
4. Shukla PJ, Barreto SG, Fingerhut A, Bassi C, Buchler MW, Dervenis C *et al*. (2010) Toward improving uniformity and standardisation in reporting of pancreatic anastomoses: a new classification system by ISGPS. *Surgery* 147:144–153.
5. Working group IAP/APA acute pancreatitis guidelines. (2013) IAP/APA evidence based guidelines for management of acute pancreatitis. *Pancreatology* 13(4 Suppl 2):e1–e15.
6. Neoptolemos JP, Kemppainen EA, Mayer JM, Fitzpatrick JM, Raraty MGT, Slavin J *et al*. (2000) Early prediction of severity in acute pancreatitis by urinary trypsinogen activation peptide. *Lancet* 355: 1955–1960.
7. Lempinen M, Stenman UH, Finne P, Puolakkainen P, Haapiainen R, Kemppainen E. (2003) Trypsinogen-2 and trypsinogen activation peptide in urine of patients with acute pancreatitis. *J Surg Res* 111:267–273.
8. Bollen TL, Singh VK, Maurer R, Repas K, van Es HW, Banks PA *et al*. (2012) A comparative evaluation of radiologic and clinical scoring systems in the early prediction of severity in acute pancreatitis. *Am J Gastroenterol* 107:612–619.
9. Yadav AK, Sharma R, Kandasamy D, Bhalla AS, Gamanagatti S, Srivastava DN *et al*. (2015) Perfusion CT: can it predict the development of pancreatic necrosis in the early stage of severe acute pancreatitis. *Abdom Imaging* 40:488–499.
10. Koutroumpakis E, Wu BU, Bakker OJ, Dudekula A, Singh VK, Besselink MG *et al*. (2015) Admission hematocrit and rise in blood urea nitrogen at 24 hours outperform other laboratory markers in predicting persistent organ failure and pancreatic necrosis in acute pancreatitis: a post hoc analysis of three large prospective databases. *Am J Gastroenterol* 110:1707.
11. Skandalakis LJ, Rowe JS, Gray SW, Skandalakis JE. (1993) Surgical embryology and anatomy of the pancreas. *Surg Clin North Am* 73: 661–697.
12. Strasberg S, McNevin MS. (1998) Results of a technique of pancreaticojejunostomy that optimizes blood supply to the pancreas. *J Am Coll Surg* 187:591–596.
13. Cuthbertson CM, Christophi C. (2006) Disturbances of the microcirculation in acute pancreatitis. *Br J Surg* 93:518–530.
14. Valle RD, De Bellis M, Pedrrazzi G, Lamecchi L, Bianchi G, Pellegrino C *et al*. (2015) Can early serum lipase measurement be routinely implemented to rule out clinically significant pancreatic fistula after pancreaticoduodenectomy. *Int J Surg* 21:S50.
15. Palani Velu LK, Chandrabalan VV, Jabbar S, McMillan DC, McKay CJ, Carter RC *et al*. (2014) Serum amylase on the night of surgery predicts clinically significant pancreatic fistula after pancreaticoduodenectomy. *HPB* 16:610–619.
16. Winter JM, Cameron JL, Yeo CJ, Alao B, Lillemoe KD, Campbell KA *et al*. (2007) Biochemical markers predict morbidity and mortality after pancreaticoduodenectomy. *J Am Coll Surg* 204:1029–1036.
17. Okabayashi T, Maeda H, Nishimori I, Sugimoto T, Ikeno T, Hanazaki K. (2009) Pancreatic fistula formation after pancreaticoduodenectomy; for prevention of this deep surgical site infection after pancreatic surgery. *Hepatogastroenterology* 56:519–523.
18. Uemaura K, Murakami Y, Sudo T, Hashimoto Y, Nakashima A, Yamaoka E *et al*. (2012) Elevation of urine trypsinogen 2 is an independent risk factor for pancreatic fistula after pancreaticoduodenectomy. *Pancreas* 41:876–881.
19. Raty S, Sand J, Nordback I. (2007) Detection of post operative pancreatitis after pancreatic surgery by urine trypsinogen strip test. *Br J Surg* 94:64.
20. De Reuver P, Gundara J, Hugh T, Samra J, Mittal A. (2016) Intraoperative amylase in peripancreatic fluid independently predicts for pancreatic fistula post pancreaticoduodenectomy. *HPB* 18:608–614.
21. Giglio MC, Spalding DR, Giakoustidis A, Zarzavadjian Le Bian A, Jiao LR, Habib NA *et al*. (2016 Jan 21) Meta-analysis of drain amylase content on postoperative day 1 as a predictor of pancreatic fistula following pancreatic resection. *Br J Surg*. http://dx.doi.org/10.1002/bjs.10090 [Epub ahead of print].
22. Ansorge C, Regner S, Segersvardf R, Strommer L. (2012) Early intraperitoneal metabolic changes and protease activation as indicators of pancreatic fistula after pancreaticoduodenectomy. *Br J Surg* 99:104–111.
23. Kinaci E, Sevinc MM, Ozakay A, Bayrak S, Cakar E, Sari S. (2016) Intraoperative acidosis is a new predictor for POPF after pancreaticoduodenectomy. *Hepatobiliary Pancreat Dis Int* 1:1–8.
24. Hiyoshi M, Chijiiwa K, Fujii Y, Imamura N, Nagano M, Ohuchida J. (2013) Usefulness of drain amylase, serum C-reactive protein levels and body temperature to predict postoperative pancreatic fistula after pancreaticoduodenectomy. *World J Surg* 37:2436–2442.
25. Palani Velu LK, McKay CJ, Carter CR, McMillan DC, Jamieson NB, Dickson EJ. (2016) Serum amylase and C-reactive protein in risk stratification of pancreas-specific complications after pancreaticoduodenectomy. *Br J Surg*. http://dx.doi.org/10.1002/bjs.10098.
26. McMillan MT, Vollmer CM, Asbun HJ, Ball CG, Bassi C, Beane JD *et al*. (2016) The characterization and prediction of ISGPF grade C fistula following pancreaticoduodenectomy. *J Gastrointest Surg* 20: 262–276.
27. Jin S, Shi XJ, Sun XD, Zhang P, Lv GY, Du XH *et al*. (2015) The gastric/pancreatic amylase ratio predicts postoperative pancreatic fistula with high sensitivity and specificity. *Medicine* 94:1–8.
28. Strasberg SM, Drebin JA, Mokadam NA, Green DW, Jones KL, Ehlers JP *et al*. (2002) Prospective trial of a blood supply-based technique of pancreaticojejunostomy: effect on anastomotic failure in the Whipple procedure. *J Am Coll Surg* 194:746–758.

29. Subar D, Pietrasz D, Fuks D, Gayet B. (2015) A novel technique for reducing pancreatic fistula after pancreaticojejunostomy. *J Surg Case Rep* 7:1–3.
30. Sugimoto M, Takahashi S, Kobayashi T, Kojima M, Gotohda N, Satake M *et al*. (2015) Pancreatic perfusion data and post pancreaticoduodenectomy outcomes. *J Surg Res* 194:441–449.
31. Nentwich MF, El Gammal AT, Lemcke T, Ghadban T, Bellon E, Melling N *et al*. (2015) Salvage completion pancreatectomy as damage control for post pancreatic surgery complications: a single centers retrospective analysis. *World J Surg* 39:1550–1556.
32. Rudis J, Ryska M. (2014) Pancreatic leakage and acute postoperative pancreatitis after proximal pancreaticoduodenectomy. *Rozhl Chir* 93: 380–385.
33. McMillan MT, Christein JD, Callery MP, Behrman SW, Drebin JA, Kent TS *et al*. (2014) Prophylactic octreotide for pancreaticoduodenectomy: more harm than good? *HPB* 16:954–962.
34. Callery MP, Pratt WB, Kent TS, Chaikof EL, Vollmer, CM, Jr.. (2013) A prospectively validated clinical risk score accurately predicts pancreatic fistula after pancreaticoduodenectomy. *J Am Coll Surg* 216: 1–14.
35. Barthelmes D, Parvianen I, Vainio P, Vanninen R, Takala J, Ikonen A *et al*. (2009) Assessment of splanchnic blood flow using magnetic resonance imaging. *Eur J Gastroenterol Hepatol* 21:693–700.
36. Kostylev MV, Kopchak VM, Popovich OB, Egorova ON. (2006) The splanchnic blood flow indices in patients suffering external pancreatic fistula and their dynamics under the influence of sandostatin and somatulin according to the ultrasonographic duplex scanning data. *Klin Khir*, 30–35.
37. Allen PJ, Gonen M, Brennan MF, Bucknor AA, Robinson LM, Pappas MM *et al*. (2014) Pasireotide for postoperative pancreatic fistula. *NEJM* 370:2014–2022.
38. Bousquet C, Lasfargues C, Chalabi M, Billah SM, Susini C, Vezzosi D *et al*. (2012) Current scientific rationale for the use of somatostatin analogs and mTOR inhibitors in neuroendocrine tumor therapy. *J Clin Endocrinol Metab* 97:727–737.
39. McMillan MT, Christein JD, Callery MP, Behrmann SW, Drebin JA, Hollis RH *et al*. (2016) Comparing the burden of pancreatic fistulas after pancreaticoduodenectomy and distal pancreatectomy. *Surgery* 159: 1013–1022.
40. Hackert T, Hinz U, Pausch T, Fesenbeck I, Strobel O, Schnieder L *et al*. (2016) Post operative pancreatic fistula: we need to redefine grades B & C. *Surgery* 159:872–877.
41. Sakowski S, Andres A, Morel P, Buhler L. (2015) Epidural analgesia improves pancreatic perfusion and decreases the severity of acute pancreatitis. *WJG* 21:12448–12456.
42. Chandrabalan VV, McMillan DC, Carter R, Kinsella J, McKay CJ, Carter CR *et al*. (2013) Pre-operative cardiopulmonary exercise testing predicts adverse post-operative events and non-progression to adjuvant therapy after major pancreatic surgery. *HPB* 15:899–907.
43. Wong LL, Tsai HH. (2014) Prevention of post-ERCP pancreatitis. *World J Gastrointest Pathophysiol* 15:1–10.
44. Tsujino T, Komatsu Y, Isayama H, Hirano K, Sasahira N, Yamamoto N *et al*. (2005) Ulinastatin for pancreatitis after endoscopic retrograde cholangiopancreatography: a randomized, controlled trial. *Clin Gastroenterol Hepatol* 3:376–383.
45. Uemura K, Murakami Y, Hayashidani Y, Sudo T, Hashimoto Y, Ohge H *et al*. (2008) Randomised trial to assess the efficacy of Ulinastatin for post operative pancreatitis following pancreaticoduodenectomy. *J Surg Oncol* 98:309–313.
46. Behman R, Karanicolas PJ, Lemke M, Hanna SS, Coburn NG, Law CHL *et al*. (2015) The effect of early post operative NSAID on pancreatic fistula following pancreaticoduodenectomy. *J Gastrointest Surg* 19:1632–1639.
47. Guarner L, Navalpotro B, Molero X, Giralt J, Malagelada JR. (2009) Management of painful chronic pancreatitis with single-dose radiotherapy. *Am J Gastroenterol* 104:349–355.
48. Chatterjee D, Katz MH, Rashid A, Estrella JS, Wang H, Varadhachary GR *et al*. (2013) Pancreatic intraepithelial neoplasia and histological changes in non-neoplastic pancreas associated with neoadjuvant therapy in patients with pancreatic ductal adenocarcinoma. *Histopathology* 63:841–851.