PANCREATIC FLUID COLLECTIONS: TOWARDS A CLASSIFICATION TO FACILITATE TREATMENT SELECTION

By

Christos Apostolou
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By

Christos Apostolou MBChB (UCT), FCS (SA)

Department of Surgery
Surgical Gastroenterology Unit
Groote Schuur Hospital
University of Cape Town

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Faculty of Health Sciences
University of Cape Town

And

The Department of Surgery
Surgical Gastroenterology Unit
Groote Schuur Hospital

DECLARATION

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Supervisor:

Professor P C Bornman MB ChB, MMed, FRCS(Ed), FRCS(Glasg), FCS(SA)
Head Surgical Gastroenterology
Groote Schuur Hospital
University of Cape Town

Student no: APSCHR002

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Contents

Abbreviations

ERCP	Endoscopic Retrograde Cholangio Pancreatography
ERP	Endoscopic Retrograde Pancreatography
CT	Computer Tomography
US	Ultrasound
MRCP	Magnetic Resonance Cholangio Pancreatography
PD	Pancreatic duct
SD	Standard Deviation
APP	Acute pancreatitis related pseudocyst
CIP	Chronic pancreatitis intra-pancreatic pseudocyst
CEP	Chronic pancreatitis extra-pancreatic pseudocyst
PFCs	Pancreatic Fluid Collections

CHAPTER ONE

Summary

This dissertation represents the culmination of work and research on the management of pancreatic fluid collections (PFCs) undertaken at Groote Schuur hospital. The aim of the study was to review the management outcome, via different treatment modalities, of pancreatic fluid collections according to a locally derived classification.

Patients with symptomatic and unresolved PFCs treated during a nine year period were reviewed, assessing clinical features and anatomical location determined using CT scanning. The classification system applied distinguishes PFCs according to the associated pancreatitis, being acute or chronic. This was based on definitions established at the Atlanta Symposium in 1992[1]. The chronic pancreatitis related pseudocysts were further selected anatomically into intra or extra pancreatic.

Seventy three patients were analysed, the majority being male and with an aetiology of alcohol. Twenty eight patients were classified in the acute pseudocyst group, twenty in the chronic intra pancreatic and twenty five in the chronic extra pancreatic groups. ERCP was used with therapeutic intent.

Regarding primary management success, surgery was always successful, percutaneous drainage in 44%, and endoscopic drainage in 61%. Initial success of endoscopic management in chronic intra pancreatic cysts was 81%. Overall ultimate management was predominantly surgical (45%), with endoscopic drainage utilised in 32% of patients, percutaneous drainage in 12% and conservative management in 11%. Overall complication rate was 15%, with one death following surgery.

Recommendations from the study include that percutaneous drainage can be reserved for acute pseudocysts with reasonable success, while endoscopic therapy should be considered first line therapy where feasible in the treatment of pseudocysts related to chronic pancreatitis, particularly intra pancreatic cysts. Surgery is important in the management of PFCs, particularly following complications or failures of less invasive methods.

This proposed classification provides a useful guide in management of these collections, but further studies are required to assess the long term efficacy of endoscopic drainage, especially in patients with chronic pancreatitis and associated pancreatic duct abnormalities.

Background and Literature Review

INTRODUCTION

The entity defining pancreatic fluid collections (PFCs) comprises of a highly variable and heterogeneous group of collections commonly complicating pancreatitis. Attempts have been undertaken [1-5] to clarify different subgroups, in particular with reference to the associated type of pancreatitis. Associated pancreatic ductal abnormalities in chronic pancreatitis may also contribute to the development of these collections and determine the outcome of treatment.

Over the last decade, advances in pancreatic endotherapy have resulted in an increased utilisation of non operative techniques in the management of these diverse groups of PFCs. The perceived lower morbidity associated with non operative interventions, has challenged the role of open surgery in the treatment of this common complication of pancreatitis. The variable morphology of pancreatic fluid collections has bedevilled attempts at deriving a classification which can be used to dictate treatment strategy and

the validation thereof. There is therefore a need for a classification which may appropriately stratify these variable groups of pancreatic fluid collections, and allow critical audit of the different treatment modalities.

AETIOLOGY

Pseudocyst formation is directly related to that of pancreatitis and both conditions share causative factors. Alcohol-related pancreatitis appears to be the major cause in most series, accounting for 59% to 78% of pseudocysts [4]. Variation in consumption of different population groups along with varying proportions of acute and chronic pancreatitis affect the prevalence of pseudocysts secondary to alcohol (Table 1). Alcohol abuse is the principal cause of chronic pancreatitis related pseudocysts, whereas pseudocysts may complicate the clinical picture of any cause of acute pancreatitis including pancreatic cancer and endoscopic retrograde cholangio pancreatography (ERCP). Pseudocysts may develop following surgery to neighbouring organs through inadvertent pancreatic injury.

Table 1: Contributing aetiology of Pancreatic Pseudocysts.

Author (year) (patient no.)	Country	Pseudocyst Type	Alcohol	Biliary	Trauma	Other	Idiopathic
D'Egidio[5] (1991) (n=83)	South Africa	Acute & Chronic	70%	-	22%	-	8%
Walt[6] (1990) (n=357)	USA	Acute & Chronic	70%	8%	6.3%	-	16%
O'Malley[7] (1985) (n=69)	USA	Acute & Chronic	78%	7%	3%	6%	6%
Kolars[8] (1989) (n=51)	USA	Acute & Chronic	73%	6%	3%	4%	14%
Bourliere[9] (1989) (n=357)	France	Acute & Chronic	70%	13%	3%	6%	8%
Usatoff[10] (2000) (n=112)	UK	Chronic	71%	4%	-	5%	20%

Pancreatic trauma is a significant cause of pseudocysts in certain series[5] and in the paediatric population. Pseudocysts in children [11, 12] are known complications of acute pancreatitis and pancreatic trauma. The classical injury of a fall from a bicycle onto the handlebars causes compression of the

pancreas onto the vertebral column may be complicated by a subsequent pseudocyst, usually secondary to pancreatic duct disruption.

INCIDENCE

Estimated incidence of pseudocysts following acute pancreatitis has increased with the availability of ultrasound and computerised tomography (CT). Adherence to current definitions [1] is paramount for valid interpretation and comparison, as the majority of pancreatic fluid collections in acute pancreatitis will regress spontaneously [2, 13] and do not become pseudocysts. In different series [14-17] the incidence of pseudocyst formation following acute pancreatitis ranged from 5-12%. One consideration is that in the acute on chronic scenario morphological changes of chronic pancreatitis may be missed [3], particularly in managing uncomplicated cases where minimal testing is done, while in chronic pancreatitis associated pseudocyst may be incorrectly labelled as following acute pancreatitis. The incidence of pseudocysts in chronic pancreatitis is believed to be higher, series reporting 20-40% occurrence [3, 18-21]. The risk to the individual patient may be increased over their lifetime due to the unremitting nature of chronic pancreatitis.

PATHOGENESIS

Pseudocysts following Acute Pancreatitis (Post necrotic)

These collections follow an attack of necrotizing pancreatitis, with peri pancreatic necrosis in the lesser sac which may extend into the retro peritoneum and bowel mesentery [22]. The evoked inflammatory response causes the formation of a distinct cyst wall composed of well vascularised granulation tissue, which organizes with more connective tissue and fibrosis [24]. The pseudocyst cavity may contain enzymatic fluid and necrotic debris.

Pseudocyst communication with the pancreatic duct in these post acute collections is variable. Aspiration of amylase rich fluid often far exceeds serum levels and prolonged periods of drainage or pancreatic fistula formation may be expected following percutaneous intervention [4]. Communication may or may not persist because the inflammatory reaction that parallels cyst formation may occlude the fistula [25]. Different rates of pseudocyst-duct communication are presented in the literature, ranging from very low (<5%) [5, 26] up to 60% [27].

Pseudocysts Related to Chronic Pancreatitis

i) Extra pancreatic

These pseudocysts may develop as a consequence of an acute flare-up or exacerbation of underlying chronic pancreatitis, with or without an associated focal area of pancreatic necrosis. These collections are often confined to the peri-pancreatic space, but may rupture into the lesser sac and then into the peritoneal cavity resulting in pancreatic ascites [1, 22].

ii) Intra pancreatic

Here a second mechanism has been proposed: when a branch of the pancreatic duct is obstructed by fibrous scarring, protein plug, or stone, the ongoing pancreatic secretion upstream of the obstruction leads to a saccular dilation of the duct, filled with pancreatic juice. Such a cyst is truly a retention cyst [5,13]. Microcysts formed can eventually coalesce and lose their epithelial lining as they enlarge. In chronic pancreatitis, pseudocysts may be seen in those patients with minimal fibrosis as well as in those with advanced fibrosis and calculi [28]. These cysts are commonly located in the head of the gland.

Studies [10, 29] have demonstrated a high cyst duct communication (up to 60%) in this group of patients, particularly in the setting of a dilated greater than 7mm) main pancreatic duct [30].

Traumatic Pseudocysts

Pseudocysts following pancreatic trauma are usually the result of injury to the pancreatic duct or its major branches, applicable to both penetrating and blunt pancreatic trauma. The majority of pseudocysts in children are traumatic [31], whereas in most adult series [6-9] the incidence ranges from 3-6%. In countries with a higher trauma prevalence, such as South Africa, the rate increases to 10-22% [5, 32].

CLINICAL FEATURES & DIAGNOSIS

In acute pancreatitis, patients present with persistent pain, with or without upper gastrointestinal symptoms (i.e. anorexia, nausea and vomiting). Other patients only present later, after the acute attack of pancreatitis has subsided, mimicking a recurrent attack of "flare-up" of pancreatitis. A smooth mass may be palpated in the epigastrium or the left upper quadrant, depending on pseudocyst size and patient body habitus. Features of gastric outlet and/or biliary obstruction maybe present and even compression of the mediastinum has been reported when pancreatic fluid extends into the mediastinum [33]. Patients with complicated cysts will manifest features of sepsis in the setting of a pancreatic abscess, or hypovolaemic shock in the rare cases of significant bleeding within the pseudocyst.

In the setting of chronic pancreatitis the presentation may be more insidious, especially when the patient has persistent opioid dependant pain. Features included persistent pain after an acute exacerbation, gastrointestinal disturbance and jaundice [34].

A persistently elevated serum amylase may occur in up to three quarters of patients [4], but may be normal in the setting of impaired exocrine function in chronic pancreatitis. Imaging in the form of ultrasound and CT scanning is the commonest manner in which these collections are detected.

In view of potentially significant complications, ERCP is not routinely used as a diagnostic procedure [35], except as part of work up to exclude a cystic neoplasm of the pancreas [36-38]. The role of ERCP may become more important in selecting pseudocyst treatment, as suggested by certain authors [39, 40], and in particular MRCP, which may delineate duct anatomy without potential complications.

NATURAL HISTORY

Increased availability and application of accurate imaging by CT should augment our understanding of the natural history of PFCs. While there is general consensus that there is a difference in the resolution rate between PFCs following acute pancreatitis and those complicating chronic pancreatitis [3], data are variable mainly because terminology and classifications differ in published series [41].

Reported spontaneous resolution in PFCs related to acute pancreatitis varies from 20-65% of patients [42-44]. Series that have not adhered to the Atlanta criteria have reported higher resolutions rates, which presumably reflect the inclusion of predominantly post acute fluid collections. There is no hard evidence to indicate that resolution rates differ between pseudocysts which are related to the two major different causes of acute pancreatitis (alcohol vs. biliary) [44-47].

Earlier studies [42, 45] reported a low possibility of spontaneous resolution in pseudocysts which persist beyond 6 weeks after an attack of acute pancreatitis. This finding has been challenged in more recent studies [44, 46, 47]

which have demonstrated pseudocyst resolution well beyond this timeline. Most studies [42,43,48-50] on the natural history of pseudocysts in chronic pancreatitis show a resolution rate of fewer than 10%. The diameter of 6cm had previously been regarded as the upper limit beyond which resolution could not occur [47, 51], but this has subsequently been shown not be the case [52]. The great majority of pseudocysts less than 4 cm in diameter will resolve spontaneously [48, 51].

COMPLICATIONS

In the 1979 study by Bradley [53], direct correlation of complications to the age of the PFC presence (with morbidity rates up 76% after 13 weeks) and 12% related mortality was observed. This prompted the recommendation that "delay is at best fruitless and at worst hazardous". Subsequent studies [44, 46, 47] of expectant pseudocyst management have demonstrated much lower complication rates between 3-23% and mortality below 1%. The obvious disparity can partly be attributed to the fact that the patients in the later studies selected for conservative management were asymptomatic, whereas the cohort in Bradley's series included patients with symptomatic PFCs, the majority of whom were as a consequence of acute pancreatitis.

CLASSIFICATION

Terminology plays an integral part in the understanding and management of pancreatic pseudocysts and pancreatic fluid collections. Although the Atlanta symposium consensus [1] has provided clear descriptions of the various pancreatic fluid collections and their natural history, its application in assessment of treatment strategy and outcome has not as yet been clearly determined.

A *pseudocyst* is defined as a collection of pancreatic juice enclosed by a wall of fibrous or granulation tissue, which arises as a consequence of acute

pancreatitis, pancreatic trauma, or chronic pancreatitis. Formation usually requires 4 or more weeks from the occurrence of acute pancreatitis [2], or the lack of an antecedent acute episode when arising in the setting of chronic pancreatitis. An *acute fluid collection* is distinguished by occurring early in the course of acute pancreatitis, located at or near the pancreas, and not having a wall of granulation or fibrous tissue. The term *pancreatic abscess* describes a circumscribed intra-abdominal collection of pus usually in proximity with the pancreas, containing little or no pancreatic necrosis, which arises as a consequence of acute pancreatitis or pancreatic trauma. Bacteria may be present in a pseudocyst, often representing contamination and thus of little clinical significance [1]. When pus is present, the lesion is correctly termed a pancreatic abscess.

It is important to highlight that current pseudocyst classifications are based on the preceding or concurrent type of pancreatitis [1]. Thus the terms acute and chronic in this regards do not describe the known duration of the pseudocyst, but the underlying pancreatitis. Multiple classification systems have been proposed, based on pathogenesis, morphology, anatomical features or a combination thereof.

An early proposed classification [20, 21] of pancreatic pseudocysts depended on the association with acute or chronic pancreatitis. Acute pancreatitis pseudocysts were called necrotic cysts, as they resulted from pancreatic necrosis and extravasation of pancreatic secretions. The term retention cyst was used in the setting of intra pancreatic pseudocysts in chronic pancreatitis, as these were pathologically found to be true cysts caused by dilatation. Subsequent rupture into the peri-pancreatic tissues would give rise to extra pancreatic pseudocysts in chronic pancreatitis and not the sequelae of pancreatic necrosis.

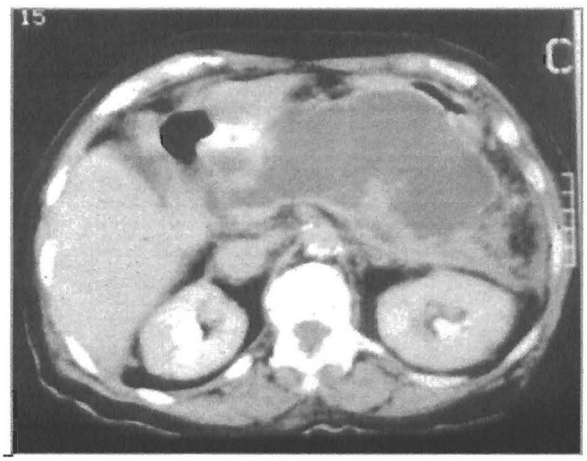
Subsequent classifications by D'Egido and Schein [5] and Bornman et al [22] identified three distinct types of pseudocysts: "Post necrotic" or acute cysts which occur following acute pancreatitis, with normal pancreatic duct

anatomy and without pancreatic duct communication, pseudocysts which follow an episode of acute-on-chronic pancreatitis (also post-necrotic), where the pancreatic duct is diseased but not strictured, and there is a significant incidence of duct-pseudocyst communication, and "retention" intra-pancreatic pseudocysts, which occur with chronic pancreatitis and are uniformly associated with duct stricture and pseudocyst-duct communication. In these classifications, distinction between acute-on-chronic and chronic type pseudocysts can be subtle, usually requiring pancreatic duct delineation. Ultimately surgery may be required to show the presence of necrotic debris, indicating a recent flare-up of acute-on-chronic pancreatitis that may have been missed clinically. Examples of the different pseudocyst types are demonstrated in Figure 1.

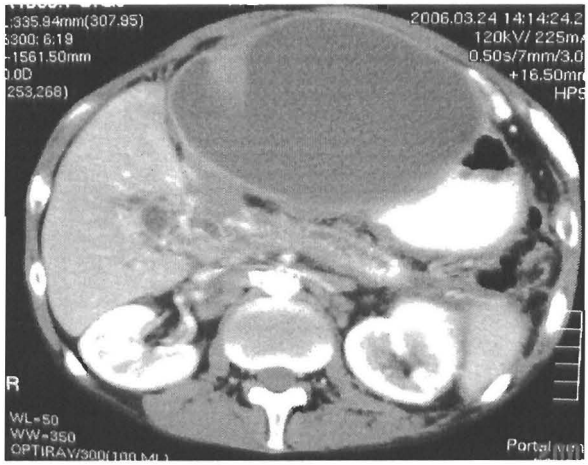
A classification system based solely on pancreatic duct anatomy has been proposed by Nealon and Walser [23], on the postulate that the main pancreatic duct determines the type and course of the pseudocysts. It has been suggested that the definition of categories seen in ductal abnormalities may direct the choice of treatment modality. However, since duct morphology and duct communication are difficult to demonstrate by imaging modalities, the value of incorporating this in formulating a classification is limited.

Figure 1: Different pseudocyst classification types

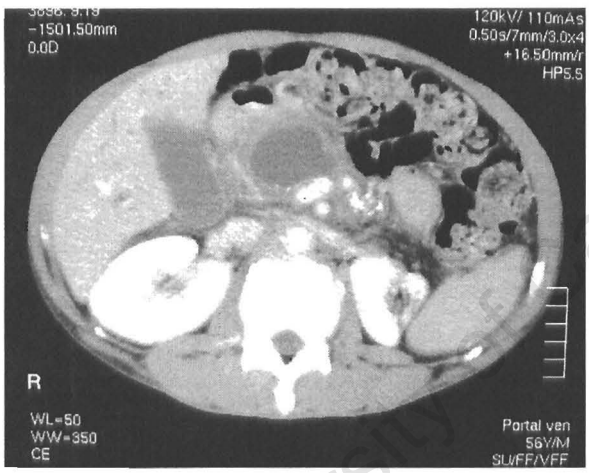
1a) Pseudocyst related to acute pancreatitis (post-necrotic)



1b) Extra pancreatic pseudocyst related to chronic pancreatitis



1c) Intra pancreatic pseudocyst in chronic pancreatitis (retention)



TREATMENT

Timing of intervention

Considering the vast literature on the natural history and complications of pseudocysts, it is reasonable to adopt an initial conservative approach in asymptomatic patients, on the basis that an appreciable proportion of pseudocysts will resolve spontaneously [42-47,54], particularly in the post acute group. A diameter of 6cm is no longer the threshold for intervention, with resolution documented in pseudocysts larger than this size [52]. Logic dictates that the larger the pseudocyst and the longer the duration, the less likely that spontaneous resolution will occur and that the risk for complications is

increased. The same may be said in underlying chronic pancreatitis [43] and pseudocysts with a thicker wall or known communication with the pancreatic duct. Provided that close clinical and radiological follow up is undertaken, action can be taken when the pseudocyst increases in size, becomes symptomatic, or complications are suspected.

Percutaneous drainage and acute/post-necrotic pseudocysts

Percutaneous methods include aspiration and catheter drainage under radiological imaging. Aspiration is mostly useful for diagnosis but ineffective for therapy, as a high incidence of re-accumulation can be expected [55], particularly in patients with pseudocyst duct communication. Gumaste and Pitchumoni [56] reported a 63% rate of recurrence and 54% failure in an analysis of five studies. Despite this it may play a selected role as primary management due to its low morbidity and ease of application. Aspiration may also contribute by sampling fluid for culture, amylase or tumour markers.

Percutaneous drainage is well established [57] in the management of infected pseudocysts [58, 59], as well as pancreatic abscesses and infected pancreatic necrosis [22]. Success rates reported range between 13-90%, and are dependant on the nature of the collection, catheter maintenance, replacement practise and duct communication. The results from major series are listed [57] in Table 2, with a cumulative success rate of 70% (235 of 334), 20% complication rate and mortality of well under 1%. In a thorough synopsis by Neff [65], potential complications elucidated were: bleeding (1-2%), visceral/pleural injury (1-2%), secondary infection (9%), and formation of pancreatico-cutaneous fistula or recurrence. Adjunctive octreotide administration may decrease duration of required drainage and even fistula formation [67].

Unfortunately overlap between different PFCs does occur in reporting, which may bias the data. Percutaneous drainage should be the initial mode of treatment for poor risk patients, for patients with infected pseudocysts, and imminent pseudocyst rupture (rapidly expanding collection with increasing symptoms). It is not the treatment of choice in established chronic pancreatitis with associated strictures and communication of the pancreatic duct, as it invariably will be complicated by pancreatico-cutaneous fistula [5, 68]. Percutaneous pancreatic cyst gastrostomy has been reported with good success [22, 56], but has not enjoyed widespread support. Figure 2 demonstrates a CT scan after percutaneous pseudocyst drainage.

Figure 2: Percutaneous pseudocyst drainage

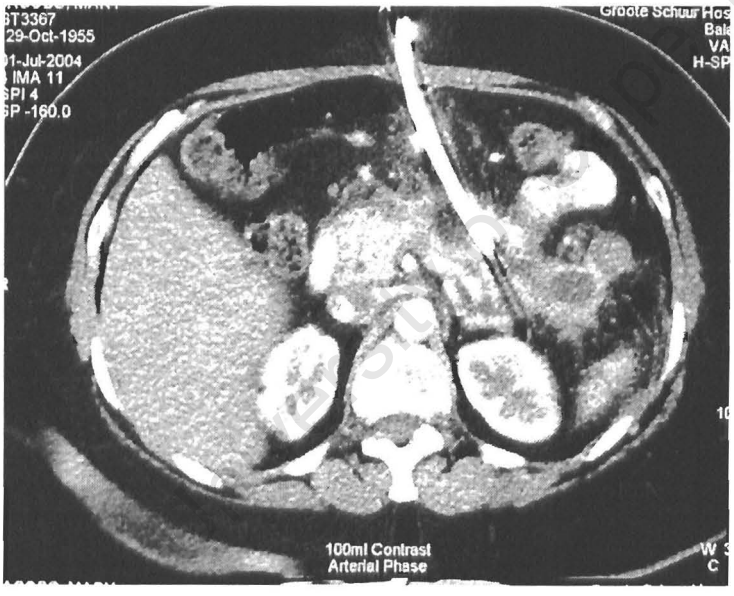


Table 2: Results of percutaneous drainage of pancreatic pseudocysts (% in parenthesis)

Author (year) (patient numbers)	Success	Failure	Mean drainage duration(days)	Mortality	Recurrence	Mean follow up	Complications	Mean hospital stay
D'Egidio et al[5] (1991) (n=23)	22(96)	na	na	0	1(4)	na	2(9)	na
van Sonnenberg et al[58] (n=101)	91(90)	6(6)	20	0	na	na	10(10)	na
Anderson et al[60] (1989) (n=22)	13(60)	3(14)	na	0	na	na	na	30
Spivak et al[61] (1998) (n=27)	17(63)	9(33)	na	1	6(22)	3yr	na	na
Adams et al[62] (1992) (n=52)	35(67)	17(33)	42	0	**na**	na	4(8) major 25(56) drain infection	na
Grosso[63](1989) (n=43)	29(67)	14(33)	na	0	9/38(24)	2-26m	2(7)	na
Heider et al[64] (1999) (n=66)	28(42)	38(58)	38	0	na	na	na	45

na = data not available

Endoscopic Therapy

The first endoscopic transgastric pseudocyst needle aspiration was reported in 1975 by Rodgers et al [69], with the first successful transmural endoscopic drainage reported in 1985 by Kozarek et al [70]. Over the last decade a plethora of published series mirror the increased popularity and application of these methods to the management of pancreatic pseudocysts.

Endoscopic options maybe transenteric through the stomach (endoscopic cystgastrostomy) or the duodenum (endoscopic cystduodenostomy) or through the pancreatic duct (transpapillary drainage). These different approaches have been evaluated in several large series, which allow assessment of their role in the management of pancreatic pseudocysts.

i) Transpapillary drainage

This is possible in pseudocysts which communicate with the pancreatic duct, ideally with a proximal duct obstruction or disruption in close proximity to the papilla [22, 71]. Technically demanding, this requires positioning of a coaxial guide wire system across the stricture and stent placement (5 or 7F) into the pseudocyst, or across the site of the disruption. No significant difference exists regarding whether the tip is placed into the pseudocyst or beyond the duct defect [72, 73]. In 1997 Beckingham et al [74] provided a detailed summary of reported series of transpapillary drainage. In 117 patients successful drainage was achieved in 84%, with a 9% recurrence rate over a 2 year mean follow up period. As can be expected drainage of pseudocysts situated in the tail of the pancreas was associated with more failures despite successful stent placement [75-77]. The commonest complication was acute pancreatitis (5%). Concern has been expressed regarding stent induced stricturing, but Huibregste et al [78] showed no clinical sequel in patients 3 years after stenting.

ii) Transmural drainage

Certain prerequisites are required before performing drainage in this manner. Only pseudocysts involving the head or body of the pancreas (which occur in 70%) [22] are suitable. Ideally the pseudocyst should be adherent to the gastrointestinal mucosa, there should be a visible bulge endoscopically, the distance between bowel lumen and pseudocyst cavity should be less than 10mm, as measured by CT or endoscopic ultrasound. Approximately half of chronic and 25% of acute pseudocysts are suitable for this approach. A needle knife is used to enter the pseudocyst cavity, followed by insertion of a guidewire/coaxial system. Most endoscopists would place one or two temporary plastic stents to maintain communication. Enlarging the opening by excising a disc of tissue, whilst promoting drainage, may increase bleeding rates.

Cumulative series of endoscopic cystgastrostomy reported success rates of 82%, recurrence of 18% and 16% major complications (8% bleeding, 8% perforation). In the cystduodenostomy group, the success rate was 89%, with a lower recurrence of 6%. Complications were less frequent at 8% (4% bleeding, 4% perforation) [74]. More recent series [79, 80] have supported these findings of high success rate with complication rates between 5-6%. Endoscopic drainage of pseudocyst with necrotic contents increase procedure related complications [81], and is generally discouraged by authors [32]. Despite initial promise to assist transmural drainage, endoscopic ultrasound has not decreased complications, including bleeding. This was demonstrated by Kahaleh et al[82] in a prospective study comparing conventional with endoscopic ultrasound guided drainage in 99 patients. Complications occurred in 19% of the endoscopic group and 18% of the conventional group.

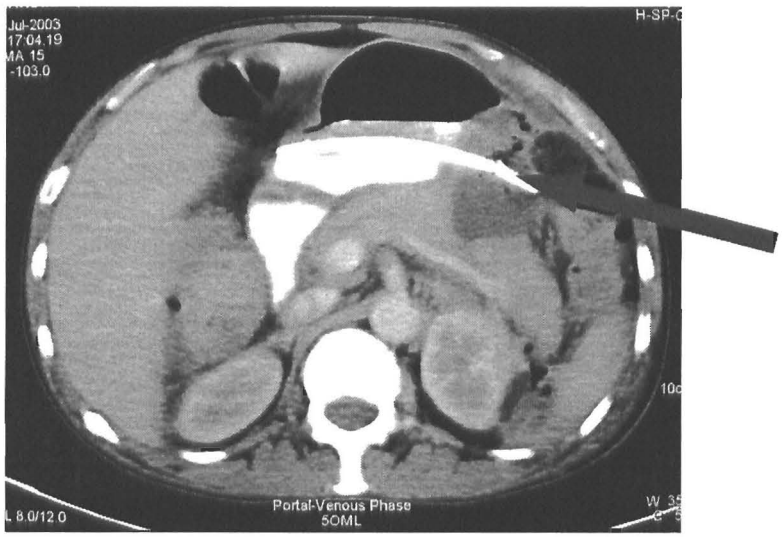
Baron et al[83] sought to determine outcome differences after endoscopic drainage of pancreatic necrosis, acute and chronic pseudocysts. The success in the chronic pseudocyst (CP) group was significantly better (92%), than that in the acute pseudocyst (AP) group (74%). Differences in complication rates (CP17% vs AP19%), and recurrence (CP12% vs AP9%), were not significant. Patients with chronic pseudocysts spend significantly less time in hospital (3 vs. 9 days). In a recent study of 170 patients from Helsinki [84] the success rate was 86%, with a 10% complication rate. 13.9% required surgery for endoscopy failures.

Current available data suggests that endoscopic management provides an acceptable substitute to surgery. It is important to note that a significant level of expertise is required in order to perform these advanced procedures with high success and low morbidity [85]. A summary of some of the series [74, 22] pertaining to endoscopic drainage is presented in table 3. Figure 3 demonstrates an example of endoscopic cystgastrostomy on CT.

Table 3: Summary of endoscopic pseudocyst drainage [74, 22]

Endoscopic Modality	Patients	Initial Success	Complications	Recurrence	Long Term Success	Follow up Months
Transpapillary	117	98 (84%)	14 (12%)	10 (9%)	88 (75%)	15-37
Cystgastrostomy	50	41 (82%)	11 (22%)	9 (18%)	32 (64%)	9-48
Cystduodenostomy	71	63 (89%)	7 (10%)	4 (6%)	59 (83%)	9-48

Figure 3: Endoscopic cystgastrostomy (Arrow: tip of endoscopic stent)



Surgical Intervention

i) Open surgery

Surgery still plays an important role in the management of pancreatic pseudocysts. It is the treatment of choice for patients with recurrent pseudocysts, when less invasive methods fail and for patients with a suspected neoplastic cyst. Open surgical procedures include internal drainage, external drainage and excision.

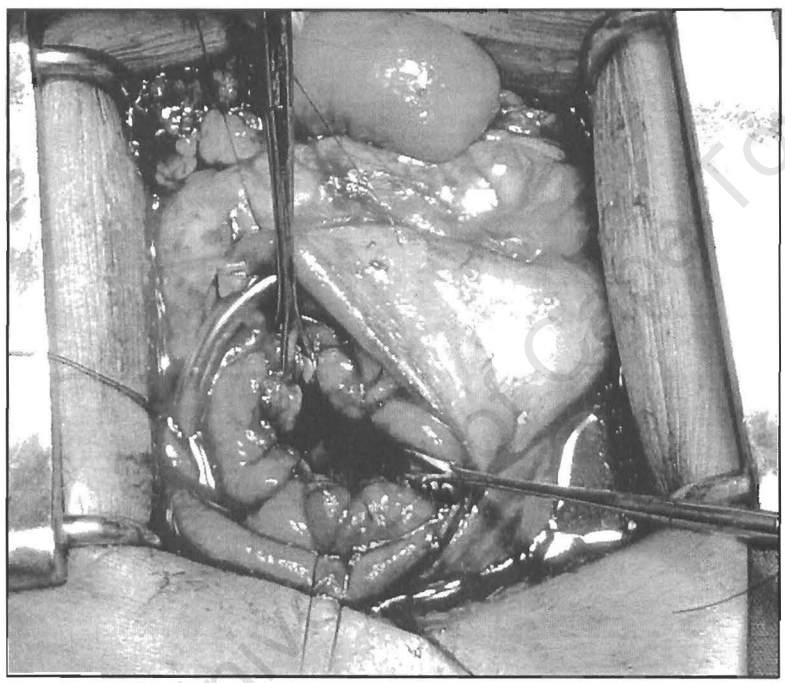
External drainage is seldom performed and reserved for infected fluid collections, usually after failure of percutaneous methods and invariably in sick patients. This accounts for high mortality, recurrence and fistula rates of over 10% [86].

Internal drainage options include cystgastrostomy (Figure 4), cystduodenostomy and cystjejunostomy. Anatomical position of the cyst determines the most appropriate procedure. Principles include aspiration of cyst fluid for localization and amylase, enterotomy and stay suture placement

into the cyst wall prior to opening. A portion of the cyst wall is removed for histology and the bowel pseudocyst communication is circumferentially sutured to maintain patency and haemostasis. Mortality rates from studies in the late 1990s [86] have decreased to 3% with an 8% recurrence.

Excision of pseudocysts in the tail or body by distal pancreatectomy (with or without splenectomy), is indicated for complicated pseudocysts, or when there is contiguous extension into the splenic hilum.

Figure 4: Surgical pseudocyst gastrostomy



ii) Laparoscopic pseudocyst drainage

The enthusiasm and perceived benefits of laparoscopic surgery have been extended to drainage of pancreatic pseudocysts. The principles of open surgery with the creation of a dependent cyst enterostomy can be achieved via this minimal access approach.

Laparoscopic cyst gastrostomy is the most commonly performed laparoscopic procedure for pseudocysts located in the lesser sac. Variations of the procedure include endogastric [87-94], transgastric [87, 95-97] and extragastric [87, 98, 99] approach. Access to the posterior gastric wall is gained through the introduction of ports including the laparoscope (endogastric), an anterior gastrotomy (transgastric), or via the lesser sac (extragastric). An endoscopically assisted laparoscopic approach has also been described [100]. More distal pseudocysts have been drained through a variety of Roux-en-Y laparoscopic cystjejunostomy [93,101,102].

Initial results indicate a success rate of 77-100%, with a complication rate of 8-17% and no mortality or recurrence [87, 89,91,94,97]. Total reported numbers are small and larger series are required for meaningful comparison with other treatment modalities and open surgery in particular.

COMPARISON OF TREATMENT OPTIONS

There are currently no prospective randomised trials comparing the various approaches in the management of pancreatic pseudocysts. High complication and mortality rates were reported in historical surgical series [45,103,104], which can bias current interpretation and comparison with other approaches. More recent complication rates [13, 23,105] have been in the region of 5-15%, with little or no mortality. This combined with the very low rate of recurrence with surgery, still holds this option as the standard to which other management approaches are measured.

Numerous retrospective studies have compared percutaneous to surgical drainage, predominantly concerning pseudocysts following acute pancreatitis. Whilst earlier studies showed a higher mortality in the surgical group [60], later comparisons [62] showed no difference. When all variables were taken into account, as reported by Lang et al [106], the results were similar. High

secondary tract infection and prolonged pancreatic drainage (mean drainage of up to 42 days) via the catheter was reported in certain studies of percutaneous drainage. Similar results in terms of success morbidity and mortality have been reported in two retrospective studies [107,108] comparing endoscopic drainage to surgery. Nealon and Walser however [109] issue a caution regarding the potential complications of non surgical methods and stress the role of surgery in managing these. They retrospectively reviewed 79 patients with complications following nonoperative measures. 66 of whom (84%) required subsequent operation. Of note is the low complication rate (6%) in the historical comparative surgical group of 100 patients in this experienced surgical unit.

The higher efficacy of surgical management of pancreatic pseudocysts compared to non-invasive methods needs to be taken into consideration when comparing different management modalities.

Improvements in imaging studies, and a better understanding of the natural history of pseudocysts have allowed clarification of pancreatic fluid collections. This enables stratification of these collections into subgroups which should help to select from the increasing current available treatment options. These include percutaneous, endoscopic and surgical drainage. Percutaneous catheter drainage is safe and effective and should be the treatment of first choice in poor-risk patients, and for infected pseudocysts related to acute pancreatitis. Endoscopic drainage should be the first management option in suitable pseudocysts related to chronic pancreatitis, with the provision that expertise is available. The high success and current low morbidity of elective open surgery still indicate that it is the standard of management in this disease.

Laparoscopic approaches are gaining favour, predominantly in drainage of collections in the lesser sac, and long term data is awaited. The precise

application of this modality will need to be critically compared to the low morbidity of mini laparotomy, which is the current standard after non operative modality failure in these patients.

It is essential to clearly stratify the different types of pancreatic pseudocysts, in particular with relation to acute or chronic pancreatitis, and perform a valid comparison of the different treatment modalities within groups. It is in this capacity that a precise and transparent classification may provide valuable answers, which forms the basis of this study.

CHAPTER TWO

Groote Schuur Hospital Study

Aim

The objective of this study was to review the outcome of different treatment modalities of pancreatic fluid collections according to a classification derived from clinical features and morphological characteristics, in order to formulate a rational and optimal treatment policy for this common complication of pancreatitis.

Patients and methods

All patients admitted to the Surgical Gastroenterology Unit (including the Hepatobiliary Firm) at Groote Schuur Hospital, with a symptomatic pseudocyst, were included in this study. Data was collected retrospectively for patients admitted between January 1997 and December 2001, and prospectively for patients admitted between January 2002 and December 2005 (total of nine years).

Inclusion was based on the presence of a symptomatic pancreatic pseudocyst. The majority of these patients were referred from secondary hospitals in the greater Cape Town metropole. Strict adherence to guidelines set out in the Atlanta symposium [1] on pancreatitis was ensured to correctly include only pseudocysts and not acute pancreatic fluid collections. Patients with pseudocysts secondary to trauma were excluded, as these form a separate entity with regards to management.

The patients underwent a thorough clinical and radiological assessment (including CT, ERCP and MRCP where appropriate). Evidence of chronic

pancreatitis was sought from a variety of clinical (significant ethanol usage, chronic pain, multiple previous attacks/admissions) and radiological data (duct morphology and/or calcification present on CT scan). Based on these factors, patients were classified into groups as indicated below, with emphasis on the underlying pancreatitis type and morphological features, based mainly on CT features:

Table 4: Groote Schuur Hospital Pseudocyst classification criteria

Type	Post-Acute Pancreatitis	Chronic Pancreatitis	
Description	Fluid collection >4weeks following acute pancreatitis	Intra Pancreatic	Extra Pancreatic

The management of these patients was according to established unit protocol; with endoscopic drainage via ERCP was the preferred first line treatment in all-suitable patients. Suitability for endoscopic drainage included a pseudocyst wall of less than one centimetre, location in the head or adjacent to the body of the gland, and a visible bulge in the gastrointestinal tract on endoscopy.

Percutaneous drainage was reserved for patients with pseudocysts related to acute pancreatitis with features of sepsis and/or residual pancreatic necrosis. Surgical drainage was reserved for cases not suitable to endoscopic drainage and following failure or complications of non-operative methods. Failure was defined by the inability to drain the collection, and or radiologically confirmed re accumulation accompanied by clinical symptom recurrence.

Endoscopic technique

Endoscopic drainage was performed using a standard operating side viewing

endoscope under conscious sedation (as per standard unit practice). After the bulge in the bowel wall was located, a needle knife diathermy incision was performed, over a co-axial catheter that was inserted into the cyst. The position within the cyst was confirmed via injection of contrast under fluoroscopy. A 10Fr plastic stent was then inserted over the guide wire co-axial system, and the stent position assessed under fluoroscopy (In the event of transpapillary drainage, the stent was positioned over a guide wire co-axial catheter system via the duodenal papilla, as part of the ERP).

ERCP was used predominantly as a management, and not a diagnostic, modality. Pancreatography was performed in patients without a visible bulge into the bowel lumen, or when considering transpapillary drainage.

Surgical technique

Surgical drainage was performed via midline laparotomy under general anaesthesia. The type of drainage procedure was influenced by cyst morphology (particularly CT scan findings). For example cyst-gastrostomy was performed via anterior gastrotomy, and anastomosis of the posterior gastric wall to the cyst wall using interrupted 3/0 absorbable sutures.

Cyst-duodenostomy was performed between the cyst wall and an appropriate part of the intra peritoneal duodenum. The bowel and pseudocyst wall are approximated via Babcock forceps and a one-layer anastomosis is performed with 3/0 absorbable monofilament sutures. Cyst-jejunostomy was fashioned using a suitable loop of small bowel onto a dependant part of the pseudocyst.

Percutaneous drainage was performed in the radiology suite, with sedation under guidance (ultrasound or CT scan). The catheter was directed into the collection, and internal external drainage was established using the Seldinger

technique. Removal of the drain was based predominantly on clinical and to a lesser extent radiological factors. Prolonged catheter placement was employed in patients with pancreatico-cutaneous fistula. Pseudocyst classification was correlated with the different treatment modalities and outcomes.

Statistical analysis

Appropriate statistical models were used to determine significant differences between the groups. These included the chi-square test, Fisher's exact test, t-test and Kruskall-Wallis ANOVA median test, as indicated.

Ethics Approval

This study was reviewed and approved by the Departmental Research Committee and approved by the Research Ethics Committee of the Faculty of Health Sciences of the University of Cape Town (appendix 1). Measures were taken to ensure patient confidentiality.

CHAPTER THREE

Results

Demographics

Seventy three patients were suitable for inclusion in the study. There were 62 males and eleven females. The mean age was 43 years (SD±11.1 years), with a range of 21-78 years. The predominant cause was alcohol in 63 patients, followed by gallstones in six, and other causes in four patients (Systemic Lupus Erythematosus, ascariasis, idiopathic, and vasculitis).

Pseudocyst formation was related to acute pancreatitis in 28 patients (APP), and was associated with chronic pancreatitis in 45 patients. In the chronic pancreatitis group, twenty patients had intra pancreatic (CIP) and 25 extra pancreatic pseudocysts (CEP). Demographic distribution according to pseudocyst type was similar between the three groups, and is demonstrated in Table 5 (Statistical significance is indicated were demonstrated). Of the ten patients who presented with jaundice, seven were in the chronic intra pancreatic pseudocyst group, two in the extra pancreatic chronic group and one in the acute group.

Radiology

CT scanning was performed on all patients. Twenty eight patients had features of acute pancreatitis. All of these pseudocysts involved the lesser sac. Features of chronic pancreatitis in the form of pancreatic calcification and PD abnormalities were evident in forty five patients, which included 20 patients with intra pancreatic pseudocysts, and 25 patients with extra-pancreatic pseudocysts. Nineteen of the twenty intra-pancreatic pseudocysts

were located in the head of the pancreas and one in the body. The majority of the extra pancreatic pseudocysts (24 of 28), involved the region adjacent to the pancreatic body and tail, with four patients exhibiting the pseudocyst in part adjacent to the pancreatic head.

Table 5: Patient demographics correlated to pseudocyst group

		Overall (% in cohort)	Post Acute Pancreatitis (% of group)	Chronic Intra Pancreatic (% in group)	Chronic Extra Pancreatic (%in group)
n		**73**	28	20	25
Sex	Men	**62(85)**	23(82)	18(90)	21(84)
	Women	**11(15)**	5(18)	2(10)	4(16)
Cause	Alcohol	**63(86)**	20(71)†	19(95)	24(96)†
	Biliary	**6(8)**	6(21)*	0	0*
Average Age ±SD [Range]		**43±11.1 [21-78]**	43±12.8 [23-78]	44±9.6 [27-63]	42±10.6 [21-62]

(Statistical significance†: APP vs. CEP p=0.04, *: APP vs. CEP p=0.046)

The average pseudocyst diameter was 8.3±3.1 cm, with a range of 3-16cm. The average size within the different classification types was as follows: a) Acute=9.8±2.4 cm b) Chronic intra-pancreatic=6.1±2.2 cm and c) Chronic extra-pancreatic=8.5±3.3 cm. Statistical comparison (t-test): APP vs. CIP $p<0.0001$, APP vs. CEP not significant (ns), CIP vs. CEP p=0.008.

Endoscopic features

Pancreatography (via ERP) was performed in 38 patients. This was performed in eleven of the 28 patients with APP, 17 of the twenty patients in the CIP group, and ten of the 25 in the CEP group. The breakdown of the

various anatomical findings is presented in Table 6. Overall pseudocyst pancreatic duct communication was present in 16 patients (42%), with the following breakdown by type: a) APP 5 of 11 patients (45%), b) CIP 8 of 17 (47%) and c) CEP 3 of 10 patients (30%). All comparisons amongst the three different groups were not statistically significant.

Table 6: Endoscopic retrograde pancreatography

Endoscopic Features		**Overall (%)**	Post Acute Pancreatitis(%)	Chronic Intra Pancreatic(%)	Chronic Extra Pancreatic(%)
Pancreatography		**38**	11	17	10
Duct	Normal calibre	**6(16)**	2(18)	3(18)	1(10)
	Cyst communication	**16(42)**	5(45)	8(47)	3(30)
	Dilated	**9(24)**	2(18)	4(24)	3(30)
	Strictured	**1(3)**	0	0	1(10)
	Cut off	**6(16)**	2(18)	2(12)	2(20)

Primary Management Outcomes

Overall success of the planned intended management modality was 44% for percutaneous drainage (7 of 16), 61% for endoscopic drainage, and 100% for surgical and conservative management (12 of 12 and 7 of 7 respectively).

Within the different pseudocyst classification groups, intended percutaneous drainage was successful in 4 of 9 (44%) of the acute group, 2 of 2 (100%) in the chronic intra pancreatic group, and 1 of 5 (20%) in chronic extra pancreatic group. Primary endoscopic management was successful in 5 of 13 of the acute group (38%), 13 of 16 in the chronic intra pancreatic group (81%), and 5 of 9 in the extra pancreatic group (56%). [CIP vs. APP p=0.02, CIP vs. CEP & APP vs. CEP = no significance]

Surgery and conservative management were successful in all patients when employed throughout the study cohort. Summary of intended management modality success is indicated in Table 7.

Table 7: Primary management success

Treatment Modality	**Overall (%)**	Post Acute Pancreatitis (%)	Chronic Intra Pancreatic (%)	Chronic Extra Pancreatic (%)
Surgical	**12 of 12 (100)**	2 of 2 (100)	1 of 1 (100)	9 of 9 (100)
Percutaneous	**7 of 16 (44)**	4 of 9 (44)	2 of 2 (100)	1 of 5 (20)
Endoscopic	**23 of 38 (61)**	5 of 13 (38)†	13 of 16 (81)†	5 of 9 (56)
Conservative	**7 of 7 (100)**	4 of 4 (100)	1 of 1 (100)	2 of 2 (100)

(†p=0.02)

Ultimate Management Outcomes

The ultimate management modality utilised was as follows: Nine patients were treated via percutaneous drainage (12%), 23 using endoscopic drainage (32%), 34 via surgical procedures (45%), and 8 patients were treated conservatively (11%), [Table 8 & Figure 5]. Conservative management was employed on patient request, or in patients with prohibitive risks for intervention.

a) Percutaneous drainage

The average duration of catheter placement was 18.1±19.4 days, with a median of 12 days and the range of 2-53 days. Six of the nine patients were from the acute group, with 2 from the intra pancreatic and one from the extra pancreatic chronic group. Four of the nine patients required more than one catheter placement. Proportions of patients treated via this modality per group were: APP 21%, CIP 10 % and CEP 4%. There was no statistical significance.

b) Endoscopic drainage

Of the 23 patients successfully treated in this manner, six underwent cyst gastrostomy, 13 cyst duodenostomy and four patients had transpapillary drainage. Of the different pseudocyst groups, endoscopic drainage was used in five patients with post acute pseudocysts (18%), in thirteen patients of the 20 in the chronic intra pancreatic group (65%), and 5 of the 25 patients in the extra pancreatic group (20%). There was a statistically higher proportion comparing CIP vs. APP (p=0.0009)

c) Surgical management

The surgical procedures used included: cyst gastrostomy in 9 patients, cyst duodenostomy in 4 patients, cyst jejunostomy in 8, open drainage in 9, and other methods (distal pancreatectomy or pseudocyst excision) in three. The distribution per group was 13 in the post acute pancreatitis group (46%), five in the chronic intra-pancreatic pseudocysts (25%), and 16 in the extra pancreatic pseudocysts with chronic pancreatitis (64%).

Of the 33 patients ultimately treated with surgery, in 22 (66.6%) this was secondary to other treatment attempts. Attempted breakdown of treatments in those patients included: combination therapy in four patients, endoscopic therapy only in 10, and percutaneous therapy alone in seven. Distribution by group was: eleven with acute pseudocyst, 3 with chronic intra pancreatic, and seven with chronic extra pancreatic.

d) Conservative management

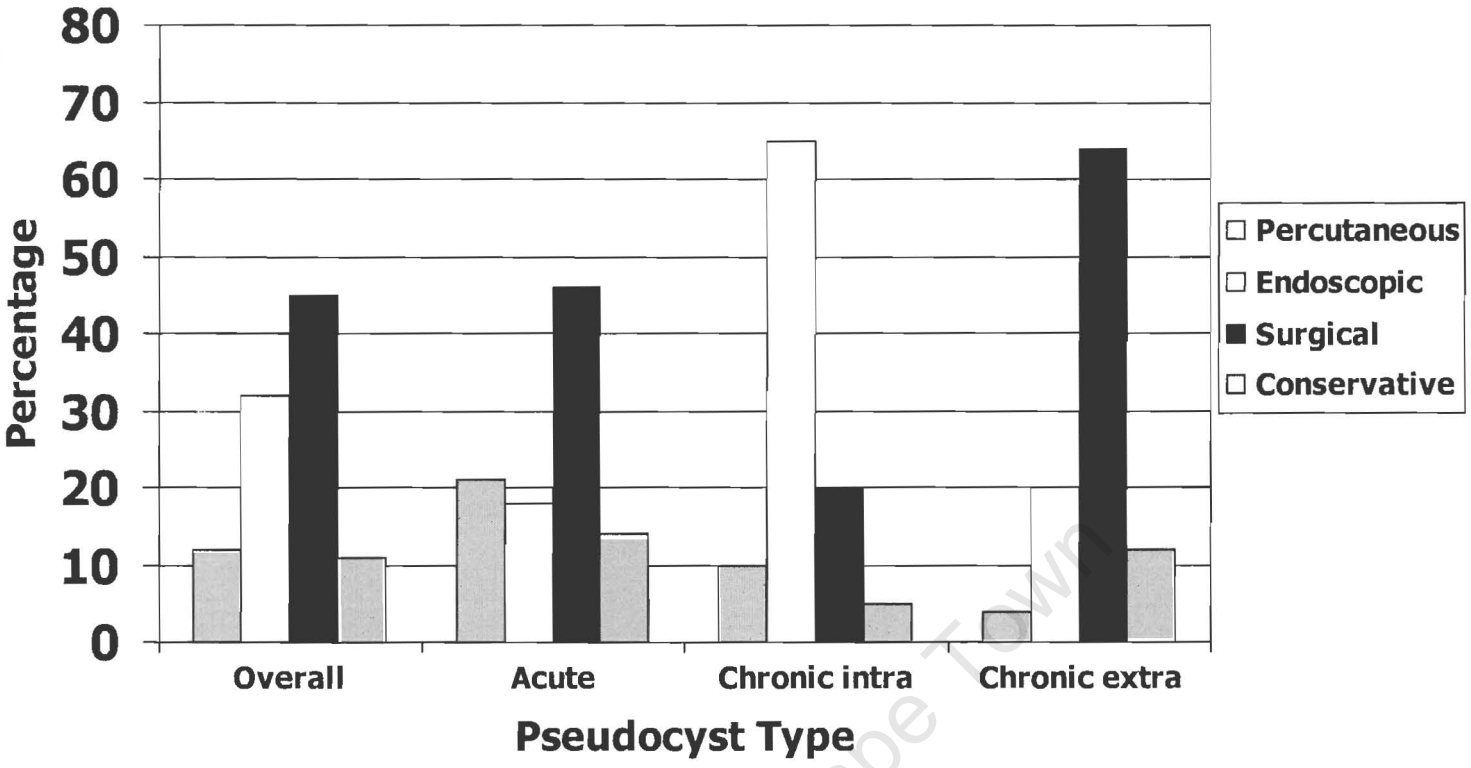
Eight patients were ultimately treated in this manner. Of the seven patients initially treated in this manner, three were severely immunocompromised (TB

and HIV), two refused therapy, and in two following improvement of symptoms whilst observation. The eighth patient improved after failed endoscopic intervention. In six of the patients the follow up was no more than 3 months. The two other patients were both asymptomatic at twenty and twenty two months, the first with a persistent cyst of 10cm diameter still declining intervention, and the second with a pseudocyst reduced in diameter from 16cm to 3cm. Group distribution was: four from the acute group, one in the chronic intra pancreatic, and three in the chronic extra pancreatic.

Table 8: Successful patient management modality

		Overall Rx(%)	Post Acute Pancreatitis(%)	Chronic Intra Pancreatic(%)	Chronic Extra Pancreatic(%)
N		**73**	28	20	25
Percutaneous		**9(12)**	**6(21)**	**2(10)**	**1(4)**
Endoscopic	Cyst Gastrostomy	**6**	4	1	1
	Cyst Duodenostomy	**13**	1	10	2
	Transpapillary	**4**	-	2	2
	Total	**23(32)**	**5(18)**	**13(65)**	**5(20)**
Surgical	Cyst Gastrostomy	**9**	3	1	5
	Cyst Duodenostomy	**4**	1	2	1
	Cyst Jejunostomy	**8**	1	1	6
	Open drainage	**9**	7	-	2
	Other	**3**	1	-	2
	Total	**33(45)**	**13(46)**	**4(20)**	**16(64)**
Conservative		**8(11)**	**4(14)**	**1(5)**	**3(12)**

Figure 5: Distribution of successful treatment by pseudocyst group



Hospital stay and follow up

Median stay for the cohort was 12 days, mean 17.6±18.4 days with a range of 1-86 days. Median stay for the different groups was 14, 8 and 12 days, for the acute, chronic intra and extra pancreatic respectively. Median stay for the chronic intra pancreatic group was statistically significantly shorter (p=0.0006) compared to the other 2 groups, and there was no difference between AIP and CEP. Overall median follow up was three months, mean of 8±13 months and a range of 1-99 months. Ten patients were lost to follow up.

Complications

Overall significant complications occurred in 11 patients (15%), of whom seven were in the acute group. The complication rate in the latter group was

25%. There were two complications in each of the other pseudocyst groups. There was no statistical significance comparing the proportion of complications between the groups. The most common complications were in the form of sepsis requiring further intervention, and bleeding requiring endoscopic or surgical control. Table 9 summarises the morbidity and mortality.

Correlating complications with treatment modalities three significant complications occurred following surgical management, all in patients with pseudocysts related to acute pancreatitis. These were: a self limiting enterocutaneous fistula, an incisional hernia, and wound sepsis requiring debridement in a patient with HIV (CD4 count 186). There were two patients with significant bleeding following endoscopic intervention, one controlled endoscopically and the other requiring surgery. Both these patients were in the acute pseudocyst group. The complication incidence per management modality was: Percutaneous 4, endoscopic 3, and surgical 4.

There was one death, with an overall mortality rate of 1.4%. The patient suffered from a fatal pulmonary embolus, ten days after cyst jejunostomy for an extra pancreatic pseudocyst associated with chronic pancreatitis, despite mechanical and pharmacological prophylaxis.

Table 9: Complications

Complications		**Overall (%)**	Post Acute Pancreatitis	Chronic Intra Pancreatic	Chronic Extra Pancreatic
Number of patients		**73**	28	20	25
Death		**1(1.4)**	-	-	1*
Complications		**11(15)**	7	2	2
Sepsis		**4(5.5)**	2	1	1
Bleeding requiring Surgery		**2**	2	-	-
Bleeding controlled endoscopically		**1**	-	1	
Enterocutaneous Fistula		**1**	1	-	-
Other	Incisional Hernia	**1**	1		-
	Wound sepsis	**1**	1		-
	Drain dislodgement	**1**			1

*Post mortem confirmed pulmonary embolus (Day 10 post surgery)

CHAPTER FOUR

Discussion

This is the first attempt of a correlation and validation of a pseudocyst classification with regards to management modalities and outcomes. The application of this classification was possible in all patients in this single center series. The current high quality of CT scanning allows for a clear distinction between the acute (post necrotic) pseudocysts and those associated with chronic pancreatitis in the majority of patients. The current role of ERCP is predominantly for therapeutic intervention, with cannulation of the papilla and pancreatography as part of attempted management.

The rate of pseudocyst duct communication in this series was significant (45%) in patients with pseudocysts following acute pancreatitis, which underwent successful pancreatography. This may have contributed to the limited success (44%) of percutaneous drainage in this group, via continued pancreatic juice drainage, sepsis and/or fistula formation. The overall of successful application of this modality in the acute group was 21%, with an overall utilisation in 9 of the 73 patients (12%). The success rate in acute PFCs compares unfavourably with reported success rates of 40-90% in other series [5, 58-64]. This may be explained in part by variability of pathology and classification in other series, which may have included post acute collections, with higher expected resolution rates.

Endoscopic management achieved a high initial success rate (81%) in the chronic intra pancreatic pseudocyst group, compared to around 56% in the chronic extra pancreatic group and 38% in the acute group. This may be explained in part by the favourable anatomy for endoscopic drainage of intra

pancreatic pseudocysts, in particular the usual location in the head of the gland, with close proximity between pseudocyst and bowel wall. Failure of drainage of chronic extra pancreatic pseudocysts was predominantly due to anatomical and technical factors such as inability to puncture into the cyst wall, and less likely due to subsequent re accumulation following stent migration or blockage.

Surgery was utilised in the management of 33 patients (45%), of which two thirds were for failures of non invasive methods, or to manage related complications. Open external drainage was used in acute pseudocysts, with a variety of internal drainage methods in the chronic groups.

The majority of the complications occurred in the acute pseudocyst group (7 of 11); with a rate of 25% in that cohort compared with a lower incidence in the other two groups (~10%). This can be explained due to the higher incidence of sepsis in these patients who were recovering from acute pancreatitis. The significantly shorter median hospital stay in the chronic intra pancreatic group (8 vs. 12 or 14 days) may be attributed to the higher proportion of patients treated endoscopically in that cohort.

The predominant retrospective nature of the study, short follow up periods and the small numbers in each of the groups are weaknesses of this trial, yet apparent trends deserve further mention:

a) Percutaneous drainage is appropriate for post acute pseudocysts as an initial and staged procedure, accepting that surgical management may frequently be required to manage failures. Endoscopic therapy is currently not first line treatment in this setting, due to the anticipated high complication rates, particularly related to sepsis, as these collections often contain much necrotic material. Recent reports have indicated success with

more aggressive endoscopic treatment and continuous irrigation, and further results are awaited [83].

b) Endoscopic drainage is ideally suited for chronic intra-pancreatic pseudocysts where feasible. The data supports this approach as first line treatment, accepting pseudocyst recurrence of around, or that a proportion of patients may require formal duct drainage for ongoing pain. The role of endoscopic therapy in chronic extra-pancreatic pseudocysts is less clearly defined. Based on this data, when comparing extra to intra chronic pancreatitis related pseudocysts, it appears that extra pancreatic pseudocysts are not as amenable to endoscopic drainage , and that success rate is lower (56% vs. 81%), yet when successful outcome is similar in both groups. It is here where endoscopic ultrasound may assist in increasing the application of endoscopic drainage in these cysts. Of interest is that extra pancreatic pseudocysts were significantly larger than intra pancreatic ones in this series (8.5cm vs. 6.1cm, p=0.008). There are however no other documented series relating pseudocyst size to success of endoscopic therapy in these patients.

There was no real correlation between management outcomes and high pseudocyst duct communication in the acute and chronic intra pancreatic groups. The accuracy of demonstrating communication via ERCP is dependant on a multitude of technical factors and this needs to be taken into consideration.

c) Surgical drainage will continue to play a significant role in pseudocyst management, but it is anticipated that its contribution will be limited to treatment failures or complications of non surgical approaches. However the high success rate of open surgical drainage, calls for prospective randomised comparison with endoscopic drainage, in particular for pseudocysts related to chronic pancreatitis.

CHAPTER FIVE

APPENDIX

UNIVERSITY OF CAPE TOWN

Health Sciences Faculty
Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Telephone (021) 406-6338 • Facsimile (021) 406-6411
e-mail: [illegible]

28 April 2006

REC REF: 055/2006

Dr C Apostolou
Hepatobiliary Unit
GSH

Dear Dr Apostolou

PROJECT TITLE: PANCREATIC PSEUDOCYST MANAGEMENT STUDY

Thank you for your letter to the Research Ethics Committee dated 11 April 2006.

It is a pleasure to inform you that the Ethics Committee has formally approved the above-mentioned study on the 26 April 2006.

Your comments to the queries raised are noted with thanks.

Please quote the REC. REF in all your correspondence.

Yours sincerely

DR. M. BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS

/mjd

CHAPTER SIX

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