CLINICOPATHOLOGICAL CHARACTERISTICS OF PANCREATITIS IN FAR NORTH QUEENSLAND

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at

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by

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ABBREVIATIONS

ABS	Australian Bureau of Statistics
AIC	Akaike Information Criterion
AP	acute pancreatitis
ATBS	2,2'-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid)
AUDIT	Alcohol Use Disorders Identification Test
Auslab	Queensland Health's electronic database of patient pathology results
BMI	body mass (kg)/[height (m)]^2
CBH	Cairns Base Hospital
CFTR	cystic fibrosis transmembrane regulator (gene)
CI	confidence interval
CP	chronic pancreatitis
CT	computed tomography
DNA	deoxyribonucleic acid
ELISA	enzyme-linked immunosorbent assay
ERCP	endoscopic retrograde cholangiopancreatography

FE-1	faecal elastase-1
[FE-1]	faecal elastase-1 assay
FNQ	Far North Queensland
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Version for 2007
IRR	interval rate ratio
MAP	mild acute pancreatitis
MAST	Michigan Alcohol Screening Test
MBH	Mackay Base Hospital
MRCP	magnetic resonance cholangiopancreatography
NA	Not available
NHPAC	National Health Priority Action Council
NPV	Negative predictive value
NQ	North Queensland
NSAID	non-steroidal anti-inflammatory drug
OR	odds ratio

PCA	Principal Components Analysis
PEI	pancreatic exocrine insufficiency
PERT	pancreatic enzyme replacement therapy
POD-Streptavidin	peroxidase-Streptavidin conjugate
PPV	Positive predictive value
PRSS1	protease, serine, 1 (gene)
PSC	pancreatic stellate cell
RCF	red cell folate
ROS	reactive oxygen species
RT	the investigator / PhD candidate
SAP	severe acute pancreatitis
SD	Statistical District
SIRS	severe inflammatory response syndrome
SPINK1	serine protease inhibitor Kazal-type 1 (gene)
TGH	Townsville General Hospital

URN	hospital unit record number
WC	waist circumference
WHO	World Health Organization
WHR	waist-hips ratio

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STRUCTURE OF THESIS

This work has been structured to reflect the process, in chronological sequence, of conceiving, acquiring, describing, and analysing a cohort of patients with a disease process (pancreatitis) in a specific geopolitical setting.

Chapter 1 is a focused review of the literature seeking to define the disease process and provide a contextual backdrop with a summary of other cohorts and case series.

Chapter 2 describes the validation of an adjunct diagnostic test for chronic pancreatitis in the clinical setting of the study. This formed the basis for a peer-reviewed publication.

Chapter 3 provides methodological details of the main cohort study, along with descriptive demographic and clinical data of the cohort thus recruited.

Chapters 4, 5, and 6 are analyses of particular aspects of the cohort's data, ostensibly with a view to translating some of these results into clinical practice or health resource planning. Chapters 4 and 5 have applied relatively novel statistical techniques to pancreatitis for the first time. These are capture-recapture and Principal Components Analysis, respectively. All three of these chapters have been the basis for peer-reviewed publications.

Chapter 7 outlines two case studies, in order to illustrate salient points emerging from the data.

Finally, Chapter 8 aims to bring together the various aspects of the cohort's analysis, and proposes considering acute pancreatitis admissions from a chronic disease perspective. This discussion chapter has also been peer-reviewed as a publication.

ABSTRACT

Pancreatitis is a common cause for unscheduled admissions in General or Gastrointestinal Surgery units throughout the world. This is particularly perceived to be the case in northern Australia, where alcohol and certain socio-demographic factors may be prominent in influencing the incidence and course of the disease. Over the years, much has been written about various aspects of pathogenesis, prognostication and management. However in the average clinical setting, many useful questions go unasked and unanswered. Because patients rarely require formal surgical intervention or even high-dependency management, there is rarely any active enquiry into the issues surrounding acute pancreatitis admissions. The chronic aspects of what is superficially considered to be an isolated acute process are also often overlooked.

This body of work evolved out of the desire to foster a better standard of care for such patients and ultimately to reduce the frequency of acute hospital admissions, particularly recurrent admissions for the same patient.

In order to effect any improvement in the management of a disease, it is first necessary to quantify and characterize it in relation to the target population. To this end, a retrospective audit was undertaken of acute pancreatitis admissions to the three major referral hospitals of Northern Queensland over the calendar year of 1997. Any inferences from this study were limited by the quality of the data recorded by a variety of clinicians. However, from what was available, it was evident that many patients admitted to hospital with a diagnosis of acute pancreatitis appeared to exhibit the characteristics of a chronic disease process. Indeed almost half of those who fulfilled the diagnostic criteria for acute

pancreatitis appeared to be harbouring underlying chronic pancreatitis, based on clinical specifications.

To better characterize the clinicopathological features of hospitalizations for pancreatitis in Northern Queensland, it was therefore necessary to acquire case data in a robust and prospective manner. A purposive and iterative literature review was undertaken to identify gaps in existing knowledge and areas that would merit further enquiry. This also assisted in informing the explanatory variables that would constitute the prospective data collection. Thus conceived was the accrual of a cohort of patients presenting acutely to Cairns Base Hospital in Far North Queensland.

Regarding outcome measures, a more objective means of diagnosing chronic pancreatitis was deemed to be desirable. The newly available faecal elastase-1 assay ([FE-1]) was proposed as a means of augmenting diagnostic certainty for chronic pancreatitis, as defined by exocrine insufficiency. The accuracy of [FE-1] in the study population was validated by a pilot study of acute hospitalizations. At the inception of the study, this assay was not available within the public health sector and was therefore performed for all cases by the researcher. The pilot study found [FE-1] to have highly acceptable positive predictive value for diagnosing underlying chronic pancreatitis in acute admissions that exhibited no evidence of developing severe acute pancreatitis.

For the eventual cohort study, the feasibility of obtaining stool specimens for all acute hopsitalizations, many of whom were admitted to hospital for less than three days, meant that [FE-1] could not be relied upon to diagnose all cases of chronic pancreatitis, if maximal patient recruitment were desired. A composite case definition that incorporated

[FE-1] and a number of validated clinical parameters were therefore utilized to define this sub-group within the study population.

For hospitalizations fulfilling diagnostic criteria for acute pancreatitis, a variety of other explanatory and outcome variables were collected. From March 2004 to July 2007, 153 cases were recruited for prospective data collection. The mean age of those admitted was 44.7 years. Males accounted for 61.4% of the cohort (n=94) and 41.2% (n=63) identified as Indigenous. In 56.9% (n=83), aetiology was deemed to be alcohol-related and in 24.7% (n=36) it was biliary or gallstone-related. Eight-three cases (54.3%) fulfilled the composite diagnostic criteria for chronic pancreatitis, and 11.2% (n=17) in the course of their admission developed severe acute pancreatitis according to the Atlanta definition.

The prospectively acquired data of the patient cohort recruited between March 2004 and July 2007 were further analysed to a number of ends:

Firstly, the incidence or admission rate of acute pancreatitis in the Far North Queensland population was estimated using a capture-recapture method, in order to account for cases missed by study recruitment or hospital separation records. This revealed that the likely admission rate for acute pancreatitis was in the order of 16.1 admissions per month, which would approximate a crude annual incidence (including recurrent admissions) of 84 per 100 000. It was therefore evident that the true incidence of the disease may be considerably underestimated by the traditional means of enumeration.

Secondly, cross-sectional associations with chronic pancreatitis were sought using a variety of available explanatory variables. Nutrient intakes were of particular interest, but none of the decomposed micro- or macronutrients showed a significant association.

When these were recast as patterns of exogenous intakes using Principal Components Analysis, it emerged that patients with underlying chronic pancreatitis, in the 24 hours prior to the onset of an acute exacerbation, were characterized by an avoidance of food-based nutrients in favour of non-nutritive substances, such as coffee and tobacco. This appeared to be independent of alcohol intake.

Thirdly, novel clinical determinants of severe acute pancreatitis were explored, exploiting the forward directionality of explanatory and outcome variables. This analysis confirmed the causal association with central adiposity inferred by a number of other studies. It also suggested an unprecedented negative association with smoking. This would merit corroboration by other observational studies, as well basic scientific research to elucidate possible mechanisms such as activation of a nicotinic anti-inflammatory pathway. Moreover, the identification of modifiable determinants of severe acute pancreatitis may contribute to future preventive and therapeutic strategies.

In conclusion, the picture that has emerged from the Far North Queensland cohort is that hospitalizations for pancreatitis, while by definition classified as acute, may in a broader sense exhibit the characteristics of a chronic disease process. Such a reconceptualization of the disease process may serve to inform more effective models of care that are tailored to both the clinicopathological characteristics of the disease and the specific population that it affects.

Publications arising from thesis.

Turner RC, McDermott R. Using faecal elastase-1 to screen for chronic pancreatitis in patients admitted with acute pancreatitis. *HPB* 2006, **8**:223 - 226.

Turner RC, D'Onise K, Wang Y. What is the 'real' admission rate of acute pancreatitis in a regional Australian population? *Australian Health Review* 2013, **37**(2):205 - 209.

Turner RC, Brazionis LB, McDermott R. Intake patterns of food nutrients and other substances associated with chronic pancreatitis. *Pancreatology* 2013, **13**:33 - 37.

Turner RC, McDermott R. Clinical predictors of severe acute pancreatitis: value-adding the view from the end of the bed. *ANZ Journal of Surgery* 2013. doi: 10.1111/ans.12390 [Epub ahead of print]

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Turner RC, McDermott R. Using fecal elastase-1 to screen for chronicity in patients admitted with acute pancreatitis. *HPB* 2005, **7**(Suppl 1):75

Turner RC, McDermott R. Fecal elastase-1 concentration as a screening tool for chronicity in acute pancreatitis admissions. *Journal of Gastrointestinal Surgery* 2005, **9**(41):603

Turner RC, Carroll A, McDermott R. Micronutrient intake and exocrine insufficiency in alcohol-related pancreatitis: Is there evidence for a protective effect in clinical practice? *HPB* 2006, **8**(Suppl 2):204

Turner RC, McDermott R. Pancreatitis in a regional Australian population: the role of faecal elastase-1 concentration in the diagnosis of chronicity. Australasian Epidemiologist 2007, **14**(3):32

Chapter 1

1. THE EPIDEMIOLOGICAL CHARACTERIZATION OF PANCREATITIS

Pancreatitis is a common cause for unscheduled admissions in General or Gastrointestinal Surgery units throughout the world. Over the years, much has been written about various aspects of pathogenesis, prognostication and management. However in the average clinical setting, many useful questions go unasked and unanswered. Because the vast majority of patients do not require formal surgical intervention or high-dependency management, there is rarely any active enquiry into the issues surrounding acute pancreatitis admissions. The chronic aspects of what is superficially considered to be an isolated acute process are also often overlooked.

This body of work evolved out of the desire to foster a better standard of care for such patients and ultimately to reduce the frequency of acute hospital admissions, particularly recurrent admissions for the same patient.

1.1 Introduction and Methods

The following overview gives a focused summary of the characterization of pancreatitis that would be necessary to inform epidemiological studies at a local or regional level. Information has been sought in a purposive manner from standard texts and the databases PubMed and Google Scholar. Boolean search phrases used were acute pancreatitis AND diagnosis, chronic pancreatitis AND diagnosis, acute pancreatitis AND epidemiology, and chronic pancreatitis AND epidemiology. Both primary and secondary sources were

examined, as were other relevant studies that were cited by these. Where possible, a synthesis of salient points arising from the body of literature is presented. In particular, it is difficult to capture all existing epidemiological studies of pancreatitis throughout the world. Those listed and discussed are thus intended to be representative rather than fully inclusive. Detailed discussion of specific management options for acute or chronic pancreatitis is considered beyond the scope of this overview.

1.2 The pancreas and pancreatitis

The pancreas is a foregut-derived gland located in the retroperitoneum, which has both exocrine and endocrine functions. The former involves the excretion of digestive enzymes by acinar cells that facilitate the rendering of nutrient macromolecules into forms that can be readily absorbed by the gastrointestinal tract. For the latter, the so-called islets of Langerhans, scattered throughout the pancreatic parenchyma, elaborate a variety of peptide hormones that control glucose homeostasis and certain other metabolic functions. (see Figure 1)

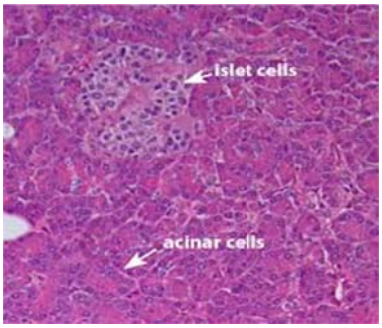


Figure 1. Histology of the normal pancreas (haematoxylin and eosin stain) http://pancreas.org/pancreas/normal-pancreas (accessed 21 February, 2014)

The term pancreatitis can be defined semantically as inflammation of the pancreas, which of itself may have a variety of pathological manifestations. Inflammation is essentially a defensive response of vascularised living tissue to local injury [2]. It may be acute, which is typically of rapid onset and short duration, and characterised by exudation of fluid and plasma proteins and the migration of leucocytes (mainly neutrophils) in response to a variety of chemical inflammatory mediators [3]. The general clinical features of acute inflammation were characterised in antiquity by Celsus as *dolor* (pain), *calor* (heat), *rubor* (redness), *tumor* (swelling) [4]. A fifth feature, *functio laesa* (loss of function) was added later by Galen [5]. This latter is particularly relevant in the case of acute pancreatitis. By contrast, chronic inflammation is a less uniform process, which is characterised by the presence of lymphocytes and macrophages, and the proliferation of blood vessels and connective tissue (fibrosis), once again effected by various inflammatory mediators [3]. It may occur as a consequence of an episode of acute inflammation where the noxious stimulus persists or of repeated episodes of acute inflammation. Alternatively, it may have a more insidious onset [6].

In the case of the pancreas, acute pancreatitis is refers to an acute inflammatory process whose initial trigger is the inappropriate intra-pancreatic activation of digestive enzymes. This is in turn associated with release of inflammatory mediators producing local and systemic side-effects of varying intensity [7]. Chronic pancreatitis refers to a slower but irreversible process characterised by parenchymal loss, fibrosis and possible calculus formation [8, 9]. Clinical consequences of this comprise abdominal pain, exocrine insufficiency (malabsorption or steatorrhoea) and eventual endocrine insufficiency (diabetes mellitus). Pain is the predominant and most characteristic symptom. In a

prospective cohort study of 207 patients with alcohol-induced chronic pancreatitis, Amman et al [10] found an average symptoms duration of 17 years. Two typical patterns of pain were identified: brief episodes over several days with long remissions, and prolonged periods of persistent pain and/or clusters of severe pain exacerbations.

1.3 Taxonomy of pancreatitis in the clinical setting

The distinction between acute and chronic pancreatitis is not always clear-cut. Historically, the clinicopathological process of pancreatitis has been classified in various ways, based on clinical observations, aetiology and the findings of medical imaging [11]. The Marseille-Rome consensus of 1988 [12] has provided simplest and most pragmatic classification of acute and chronic pancreatitis, subsuming the two additional categories if acute relapsing and chronic relapsing pancreatitis that were defined by the Marseille Symposium of 1963 [13, 14]. Within each of the two categories imposed by the Marseille-Rome consensus, various clinicopathological sub-classifications have been described to fit the particular purpose for which they are to be applied, largely relating to prognostication and management strategies.

1.4 Classification of acute pancreatitis

In the clinical setting, acute pancreatitis is generally classified in terms of severity and aetiology. Regarding severity, the Atlanta symposium of 1992 [15] dichotomised acute pancreatitis into mild or severe forms, based on certain physiological or morphological

criteria. Severe acute pancreatitis is diagnosed in the presence of organ failure (systolic blood pressure <90 mmHg, PaO_2 $\leq$60 mmHg, creatinine >2.0 mg/L after rehydration, or gastrointestinal bleeding >500 ml/24h); and/or local complications, such as necrosis, abscess, or pseudocyst, where necrosis is defined as non-enhancement of tissues on dynamic contrast-enhanced CT scan [16, 17]. The vast majority of cases that do not fulfil the criteria for severe acute pancreatitis are classified as mild acute pancreatitis.

While because of its simplicity the Atlanta classification remains the *lingua franca* for everyday clinical communication, it is left somewhat wanting when applied for research purposes. The desire for a more detailed categorisation has been expressed [18, 19]. A web-based consultative process has recently culminated in a consensus statement of a revised classification of acute pancreatitis, which recognises early and late phases of disease, and stratifies severity as mild, moderate or severe [20].

Acute pancreatitis is also commonly classified in terms of its aetiology or the clinical conditions that predispose to the particular cascade of biochemical and cellular events. As shown in Table 1, recognised aetiological categories include gallstones (biliary), alcohol, endoscopic retrograde cholangiopancreatography (ERCP), postoperative, abdominal trauma, drugs, obstruction, infection, metabolic disorders, as well idiopathic (where no specific cause can be identified) [21].

Table 1. The principle groups of aetiological factors by which acute pancreatitis can be classified.

Aetiology	Criteria for attribution
Alcohol	Moderate to excessive alcohol consumption in the absence of other attributable risk factors
Biliary	Gallstones noted on ultrasound scan or other imaging modality
ERCP	Procedure performed in preceding 24-48 hours, typically associated with endoscopic sphincterotomy
Postoperative	Recent surgery involving pancreas
Traumatic	Recent blunt or penetrating injury to epigastrium
Drugs	Idiosyncratic reaction validated by codified causal relationship algorithm
Obstruction	Obstruction of pancreatic duct demonstrated by medical imaging, due to calculus, stricture, tumour, etc.
Metabolic disorders	Hypertriglyceridaemia Hypercalcaemia
Autoimmune	Elevated serum IgG4 in the absence of other attributable factors
Idiopathic	No other aetiological factor specified [22]

This system of classification may serve as a guide to prescribing specific management to prevent further attacks or progression of disease. Indeed, successive consensus guidelines for the management of acute pancreatitis recommend that aetiological attribution be attempted based available clinicopathological data, sometime in the course of hospital admission [22-28]. As a benchmarking target, it is generally recommended that in any series of acute cases, no more than 20% should be deemed idiopathic [26]. Many of these may ultimately be attributable to less identifiable causes, such as biliary

microlithiasis [29, 30] or mutations in the cationic trypsinogen [31] or cystic fibrosis genes [32].

Consensus-based guidelines for pancreatitis are generally lacking in their prescription of criteria for aetiological attribution, which are typically based on individual clinical judgment. In most cases, these are generally straightforward, based on Hill's criteria for causation, first published in 1965 [33] and subsequently complemented by Hume's rules [34, 35]. In gallstone-related pancreatitis, a single aetiological mechanism is at work and elimination of this will prevent further attacks. In other cases of acute pancreatitis, an aetiologically based classification may over-simplify a likely multifactorial causal pathway. Arguably the second commonest cause of acute pancreatitis is alcohol, yet it is recognized that there is no pancreas-specific threshold for toxicity as there is with alcoholic liver disease, for example [36, 37]. In a meta-analysis of six studies, Irving et al [38] concluded that that is an apparent exponential relationship between alcohol dose and pancreatitis risk, although the relationship does not become significant until a threshold of four drinks daily. Clearly there are other agents or factors that sensitize the pancreas to the effects of ethanol, including smoking [39-41]. Furthermore, studies examining risk with alcohol intake do not always make a distinction between purely acute pancreatitis and acute cases with underlying chronic pancreatitis, nor between particular patterns of alcohol consumption.

Regarding idiosyncratic drug-related acute pancreatitis, Eland et al [42] in the Netherlands found that azathioprine, cimetidine, interferon-alpha, methyldopa, metronidazole, olsalazine, and oxyphenbutazone all had a definite causal relationship,

while doxycycline, enalapril, famotidine, ibuprofen, maprotiline, mesalazine, and sulindac had a probable causal relationship. These inferences were drawn based on a codified causal relationship algorithm. A case-control study from Sweden [39] was more acknowledging of multifactorial aetiology when it concluded that certain drugs could have *contributed* to acute pancreatitis based on statistically significant multi-variable adjusted odds ratios. These included H2 antagonists, non-steroidal anti-inflammatory drugs (NSAIDs), and certain antibacterials. Interestingly, this study also found that there were significant odds ratios for other gastrointestinal disorders, particularly inflammatory bowel disease, and smoking, in a dose-dependent manner. Alcohol in moderate amounts did not increase the risk, but did so for those consuming more than 420 g per week.

Despite the fact that it would appear that many cases of acute pancreatitis are multifactorial in causation, a classification system that recognizes the predominant aetiology is nevertheless pragmatic for targeted preventive strategies to attenuate the risk of recurrent episodes.

1.5 Classification of chronic pancreatitis

The Marseille-Rome consensus [12] classified chronic pancreatitis in terms of morphological and clinical characteristics: chronic calcifying pancreatitis, chronic obstructive pancreatitis and chronic inflammatory pancreatitis [11]. While of pathological interest, none of these categories had relevance for clinical management strategies. Similarly, the Cambridge classification [14] was based largely on morphological characteristics detected by medical imaging modalities (ultrasound,

computed tomography and ERCP). A system by which chronic pancreatitis could be stratified in terms of gradations of pain, and exocrine and endocrine insufficiency would be more helpful in informing management protocols. Chari and Singer thus proposed a clinical stages classification in 1994, based on knowledge of the natural history of the disease [43]. However, the currently accepted standard for clinical classification is in terms of aetiology or more precisely, risk modifiers that may interact in the multifactorial causation of this disease. The TIGAR-O classification was thus developed with a view to accommodating evolving diagnostic and therapeutic modalities [8]. (see Table 2)

Table 2. The TIGAR-O classification of chronic pancreatitis.

Toxic / metabolic	Alcohol
	Tobacco
	Hypercalcemia
	Chronic renal failure
	Toxins
Idiopathic	Early onset
	Late onset
	Tropical
Genetic	Hereditary pancreatitis (cationic trypsinogen mutation)
	CFTR mutations
	SPINK 1 mutations
	Alpha-1 antitrypsin deficiency
Autoimmune	Isolated autoimmune CP
	Syndromic autoimmune CP (PSC, Sjögren's-associated, etc.)
Recurrent and severe acute pancreatitis	Postnecrotic
	Recurrent acute pancreatitis
	Ischemic/vascular

Obstructive	Pancreas divisum
	Intrapapillary mucinous tumor
	Ductal adenocarcinoma

More recently, the so-called M-ANNHEIM multiple risk factor classification [44] has sought to categorize chronic pancreatitis in terms of risk factors (see Table 3), as well as to stratify according to the clinical stages previously proposed by Chari and Singer [43]. (see Table 4) In doing so, it represents the typical longitudinal progression of disease, as characterized by pain and exocrine insufficiency. Of note is the fact that a single episode of acute pancreatitis is defined as chronic pancreatitis (stage 0b) in the presence of a recognized risk factor such as excessive alcohol intake. This effectively acknowledges the blurred dichotomy between the acute and chronic forms of the disease. Moreover, such a unified and comprehensive system may prove useful for aetiological and therapeutic research, by facilitating comparison and pooling of inter-institutional data. However it also reflects the clinical and pathological complexity of chronic pancreatitis, in comparison to its so-called acute counterpart.

Table 3. The M-ANNHEIM multiple risk factor classification of chronic pancreatitis (adapted from Schneider et al 2007 [44])

M	Pancreatitis with Multiple risk factors
A	Alcohol consumption Excessive consumption (>80g/day) Increased consumption (20-80g/day) Moderate consumption (<20g/day)
N	Nicotine consumption (pack-years)
N	Nutritional factors Nutrition (eg. high protein and fat) Hyperlipidaemia
H	Hereditary factors Hereditary pancreatitis [45] Familial pancreatitis [45] Early-onset idiopathic pancreatitis Late-onset idiopathic pancreatitis Tropical pancreatitis Possible genetic mutations (PRSS1, CFTR, SPINK1)
E	Efferent duct factors Pancreas divisum Annular pancreas Pancreatic duct obstruction (eg. tumours) Post-traumatic ductal scarring Sphincter of Oddi dysfunction
I	Immunological factors Autoimmune pancreatitis Sjögren syndrome-associated pancreatitis Inflammatory bowel disease-associated pancreatitis Pancreatitis with other autoimmune diseases (eg. primary sclerosing cholangitis, primary biliary cirrhosis)
M	Miscellaneous and rare metabolic factors Hypercalcaemia and hyperparathyroidism Chronic renal failure Drugs Toxins

Table 4. M-ANNHEIM clinical staging of chronic pancreatitis (adapted from Schneider et al 2007 [44] and Chari and Singer 1994 [43])

Asymptomatic chronic pancreatitis	
0	Stage of subclinical chronic pancreatitis
a	Period without symptoms (determination by chance, e.g., autopsy)
b	Acute pancreatitis—single episode (possible onset of chronic pancreatitis)
c	Acute pancreatitis with severe complications
Symptomatic chronic pancreatitis	
I	Stage without pancreatic insufficiency
a	Recurrent acute pancreatitis (no pain between episodes of acute pancreatitis)
b	Recurrent or chronic abdominal pain (including pain between episodes of acute pancreatitis)
c	I a/b with severe complications
II	Stage of partial pancreatic insufficiency
a	Isolated exocrine (or endocrine) pancreatic insufficiency (without pain)
b	Isolated exocrine (or endocrine) pancreatic insufficiency (with pain)
c	II a/b with severe complications
III	Stage of painful complete pancreatic insufficiency
a	Exocrine and endocrine insufficiency (with pain, e.g., requiring pain medication)
b	III a with severe complications
IV	Stage of secondary painless disease (burnout)
a	Exocrine and endocrine insufficiency without pain and without severe complications
b	Exocrine and endocrine insufficiency without pain and with severe complications

1.6 Diagnosing pancreatitis

In order to quantify and further characterize the various clinicopathological manifestations of pancreatitis, prescribed case definition or diagnostic criteria are

required. Because of the disease's complexity, standard definitions that enable comparability between temporally or geographically disparate studies do not always exist.

1.6.1 Diagnostic criteria for acute pancreatitis

The diagnostic criteria for acute pancreatitis are an established part of clinical practice, and are generally well codified with slight variations in how these are expressed by different peak bodies. An expert working party report published in 2002 [24] stated that "the diagnosis is suspected by a typical clinical presentation and supported by raised serum amylase". The so-called typical clinical presentation is considered to be the acute onset of epigastric pain, and in a minority of cases, various degrees of associated organ failure. It is also prescribed that "atypical presentations may require confirmation by CT imaging". Of note in this consensus statement is the liberalization of the threshold for elevated serum amylase, in that any degree of elevation is acceptable to make the diagnosis.

The flexibility in diagnosis with respect to the degree of enzyme elevation is expressed slightly differently in the most recent update of practice guidelines by the American College of Gastroenterology [27]. This document states that the diagnosis of acute pancreatitis must meet two of the following three criteria: 1) abdominal pain characteristic of acute pancreatitis, 2) serum amylase and/or lipase $\geq$3 times the upper limit of normal, and 3) characteristic findings of acute pancreatitis on CT scan. In other words, lesser degrees of enzyme elevation are consistent with the diagnosis if typical clinical and imaging features are present. In an extensive review of the literature Bollen

et al [46] concurred with the majority of reported case series that an enzyme elevation of at least three times the upper limit of normal is a prerequisite for diagnosis. Once again, this was generally meant to be considered in combination with epigastric pain and/or consistent imaging findings.

From the above guidelines, it should also be noted that in many centres serum lipase is the preferred enzyme for diagnostic purposes. This is because of its greater sensitivity and specificity [47], which is attributed partly to the fact that it has a longer serum half-life than amylase, meaning that a diagnosis can be made for a longer interval following onset of symptoms [27]. There are also slightly fewer other conditions in which it may be elevated compared to serum amylase [48].

The other important aspect of acute pancreatitis for which diagnostic criteria apply is in the case definition of actual, rather than predicted, severity. Unlike acute pancreatitis *per se*, the characteristic manifestations of severe acute pancreatitis may not be evident at the onset of the disease, and are sometimes only ascertainable retrospectively after completion of the episode of care. In the Atlanta classification [15], the physiological and morphological criteria defining mild and severe acute pancreatitis have been the standard for the last two decades, although alternative diagnostic criteria have been prescribed for more detailed severity classification systems. Petrov et al [19] proposed four grades of severity based on defined clinical features. "Mild" has no (peri)pancreatic complications and no organ failure; "moderate" has sterile (peri)pancreatic complications *or* transient organ; "severe" has infected (peri)pancreatic complications *or* persistent

organ failure; and “critical” is defined by infected (peri)pancreatic complications *and* persistent organ failure. A somewhat simpler 2012 consensus-based revision of the Atlanta classification [20] defines mild, moderate and severe forms. Mild acute pancreatitis has no organ failure, local complications or systemic complications, and resolves rapidly. Moderately severe acute pancreatitis is characterized by transient organ failure, local complications or exacerbation of comorbid disease. Severe acute pancreatitis is defined by organ failure persisting more than 48 hours. As with the original Atlanta classification, local complications comprise peripancreatic fluid collections, sterile or infected (peri)pancreatic necrosis, or pseudocyst. By creating the particular intermediate severity category, this classification has effectively separated the local or structural manifestations of severity from the more serious and pathogenetically distinct systemic inflammatory response. It therefore has potential relevance for both patient management and clinical research.

The structural dimension of severity has also been separately defined since the advent of CT imaging. Balthazar et al [49] originally proposed categories A to E, in ascending order of severity, based the presence of inflammatory changes. This was further augmented by the proportion of pancreatic necrosis (non-enhancement) to give a so-called CT severity index [50]. This stratification was ostensibly devised for prognostic purposes. Recommendations have subsequently been made to standardize imaging reporting terminology so as to guide further diagnostic or therapeutic interventions [16]. Such radiological descriptors have served to enhance the diagnostic robustness of the above composite severity classification systems.

1.6.2 Diagnosing chronic pancreatitis

In contrast to acute pancreatitis, chronic pancreatitis does not have a single codified diagnostic algorithm that can be universally applied in the clinical setting. It may be defined in a number of ways, but all such characteristics are based on the premise of histological features that suggest an irreversible degenerative process. These include fibrosis, acinar cell loss, and intraductal calculi [8, 9]. If this pathological state were to be diagnosed in terms of histology, the gold standard test would therefore be a biopsy. As such an invasive procedure is not feasible in most situations due to time impost and risk, proxy measures based on structure (morphological) or function (biochemical) are typically used to infer diagnosis.

Commonly used medical imaging techniques to define pancreatic morphology are described in Table 5. For detecting various ductal or parenchymal abnormalities, they have varying degrees of sensitivity, depending on the nature and severity of specific manifestations of the disease. Not all cases of chronic pancreatitis, particularly early ones, will be captured by diagnostic imaging. Hybrid testing, where imaging is enhanced by a functional modality, may increase diagnostic sensitivity. An example of this is MRCP combined with secretin stimulation. However, this is time-consuming and expensive, and does not necessarily give any diagnostic benefits over either type of testing used alone [51, 52].

Table 5. Medical imaging tests for chronic pancreatitis

Test	Features characteristic of chronic pancreatitis
Abdominal x-ray	Calcifications or calculi
Abdominal ultrasound	Pancreatic duct dilatation
	Calcifications or calculi
Abdominal CT scan	Pancreatic main duct dilatation
	Calcifications
	Parenchymal atrophy
MRCP	Ductal abnormalities: dilatation, strictures, side branch ectasia
	Parenchymal abnormalities: atrophy, decreased arterial signal, cavity formation [51]
ERCP	Abnormal main duct or side branches
	Intraductal filling defects [14]
Endoscopic ultrasound	Ductal abnormalities: main duct dilatation, irregular contour, visible side ducts, intraductal calculi
	Parenchymal abnormalities: hyperechoic foci, strands or lobules; cysts [53]

Biochemical diagnosis is primarily based on pancreatic exocrine function. Tests, as noted in Table 6, are generally classified as direct or indirect. For direct tests, pancreatic secretions are collected via duodenal intubation while the pancreas is stimulated with exogenous hormones or ingested nutrients [54]. Indirect tests measure the products or by-products of pancreatic exocrine function at a site remote from the pancreas. In general, they are less costly and invasive than direct tests, but are also less sensitive and specific [54]. A review by Lieb and Draganov in 2008 [55] concluded that pancreatic

function tests are generally more accurate for diagnosing chronic pancreatitis than the structural tests, particularly for early disease.

Table 6. Pancreatic function tests (adapted from Boeck et al 2001 [56] and Lieb and Draganov 2008 [55])

Direct tests	Indirect tests
Secretin test	Oral tests
Secretin-pancreozymin test	Fluoroscein dilaurate (pancreolauryl) test
Secretin-caerulein test	N-benzoyl-L-tyrosyl-p-aminobenzoic acid (N-PABA) test
Cholecystokinin stimulation test	Dual label Schilling test
Combined secretin-cholecystokinin stimulation test	Triolein, mixed triglyceride and egg ^{13}C-labelled breath test
Lundh test	Faecal tests
	Faecal fat quantification
	Faecal chymotrypsin
	Faecal elastase-1
	Blood tests
	Plasma pancreatic polypeptide test
	Plasma amino acid consumption test
	Serum trypsin

The direct secretin-pancreozymin test is considered to be the most sensitive functional test [57]. Many of the other direct tests, such as the Lundh test, N-benzoyl-tryosyl para-aminobenzoic acid (NBT-PABA) test, pancreolauryl test and amino acid consumption test, are no longer used in clinical practice due to cost and invasiveness [57]. Of the indirect tests, faecal fat quantification (typically over a three-day period) is considered the gold standard for measuring malabsorption [57], although it is logistically difficult

and unpleasant to perform. Various versions of ^{13}C-substrate breath tests may provide a more acceptable alternative for assessing pancreatic enzyme deficiency [58]. In contrast to these two tests, faecal elastase-1 concentration is unaffected by pancreatic enzyme replacement therapy, and is more sensitive and specific than the comparable faecal chymotrypsin test [59-61]. The enzyme is relatively stable during gastrointestinal transit [59]. Because the test is purely observational, compliance is potentially less of an issue than with experimental function tests, although provision of a stool specimen is necessary.

It is acknowledged that in practice pancreatic exocrine insufficiency is typically diagnosed on the basis of clinical features, including self-report of bowel motions and weight loss [54]. Certain clinical features may be reasonable indicators of chronic pancreatitis in general. Recurrent acute attacks, particularly where the aetiology is alcoholic, are considered to be a characteristic feature of chronic pancreatitis [62-64]. While diabetes mellitus occurs in the advanced stages of chronic pancreatitis, its high prevalence in many populations precludes its use alone as a diagnostic marker.

Because the morphological and functional changes of chronic pancreatitis do not always develop at the same rate due to different aetiogenic pathways [65], a number of composite scoring systems have been proposed. Lankisch et al [65] initially recommended dual testing with the secretin-pancreozymin test and endoscopic retrograde cholangiopancreatography. More sophisticated probabilistic scores were also put forward by the Mayo Clinic [66] and the Lüneburg group in Germany [67]. These both drew upon a variety of morphologic examinations, exocrine function tests and imaging procedures that reflected local availability. They also award points for clinical indicators

such as steatorrhoea, prior attacks of (acute) pancreatitis and diabetes mellitus. (see Table 7) It is thus reasonable to conclude that in the clinical setting, a flexible composite of morphologic, biochemical and clinical parameters can be utilized for the diagnosis of chronic pancreatitis.

Table 7. Points awarded by diagnostic scoring systems for chronic pancreatitis.

(adapted from Lankisch, 2003 [65])

Parameter	Mayo Clinic score [66]	Lüneburg score [67]
Morphologic examinations		
Post-mortem diagnosis of chronic pancreatitis	4	4
Histology	4	4
Characteristic intra-operative findings	_	4
Pancreatic calcifications (on imaging)	4	4
Pancreatic exocrine function tests		
Abnormal secretin-pancreozymin test	2	3
Abnormal pancreolauryl test	_	2
Abnormal faecal chymotrypsin estimation	_	2
Abnormal faecal elastase-1 estimation	_	2
Imaging procedures		
Abnormal ultrasound	_	3
Abnormal endoscopic ultrasound	_	3
Abnormal computed tomography	_	3
Abnormal ERCP	3	3
Clinical features		
Steatorrhoea	2	1
More than two previous attacks of pancreatitis	2	_
Diabetes mellitus	1	_

1.7 Epidemiology of pancreatitis

Because of the relatively complex and non-standardized diagnostic criteria for pancreatitis, description of its epidemiological characteristics tends to focus on one particular disease category and reports are often location-specific.

1.7.1 Epidemiology of acute pancreatitis

Acute pancreatitis is generally easier to characterise epidemiologically because of its straightforward and readily measured diagnostic criteria, and the fact that most cases are detected by their interface with the hospital sector. Disease frequency can be conveniently expressed as incidence, which is basically the number of new cases of the disease occurring in an at-risk population over a given time period [68]. In practice, it is rarely possible to measure incidence directly at a population level because the exact time of onset is usually uncertain [69], and in the case of acute pancreatitis, milder cases may not be notified. Incidence is therefore more often indirectly measured as hospitalizations for acute pancreatitis. To provide greater utility for service planning, given that acute pancreatitis is often a recurrent condition, this may be modified as the admission rate, which differs from the definition of incidence in that recurrent episodes for the same individual may be counted [70].

Acute pancreatitis incidence varies widely across different populations, presumably as a function of prevailing aetiological and other predisposing factors. Most published figures come from High Income Countries. A representative sample of incidences since 1970 is shown in Table 8. Not all studies were explicit as to whether only first presentations

were counted, or whether cases with features of co-existing chronic pancreatitis were also considered to be acute pancreatitis. Some studies have expressly quantified admission rates rather than incidence [71, 72].

Table 8. International incidence rates of acute pancreatitis after 1970.

Authors	Location (population)	Year(s)	Crude incidence (range) per 100 000 per year
Thompson et al, 1987 [73]	North-East Scotland	1983 – 1985	24.2
Jaakkola and Nordback, 1993 [74]	Finland	1970 – 1989	46.6 – 73.4
Tran and van Schilfgaarde, 1994 [75]	Netherlands	1971 – 1990	6.5
Worning, 1994 [76]	Denmark	1981 – 1990	26.8 – 35.4
McKay et al, 1999 [77]	Scotland	1985 – 1995	25.8 – 41.9
Lankisch et al, 2002 [67]	Lüneburg County, Germany	1988 – 1995	19.7
Gislason et al 2004 [78]	Bergen, Norway	1986 – 1995	30.6
Frey et al, 2006 [79]	California	1996 – 2001	33.2 – 43.8*
Roberts et al, 2008 [80]	England	1998 – 2003	22.4 (20.9-23.9)
Sandzén et al, 2009 [81]	Sweden	1998 – 2003	27.0 – 32.0*
Shen and Lu, 2011 [82]	Taiwan	2005 – 2007	56.9
Bogdan et al, 2012 [83]	Trzebnica District, Poland	2005 – 2010	64.4
Shen et al, 2012 [84]	Taiwan	2000 – 2009	36.9
Roberts et al, 2013[85]	Wales	1999 – 2010	30 (27.6-36.4)
Stimac et al, 2013[86]	North Adriatic Region of Croatia	2000 – 2009	30 (24-35)
Vidarsdottir et al, 2013 [87]	Iceland	2010 – 2011	40

* Age-standardized

Regarding temporal trends, it would appear that both incidence and admission rates have been increasing over time in certain populations. Trapnell and Duncan [88] described an overall crude annual incidence of 5.4 per 100 000 between 1950 and 1967 in Bristol, England. This is considerably less than the more recently documented rates (see Table 8), notwithstanding possible improvements in case definition and ascertainment. Increases were also documented over shorter periods by other studies in Finland [74], the United Kingdom [77, 80, 85], Denmark [76] and Croatia [86]. By contrast, over a twenty-year period from 1987 to 2006, Lankisch et al [89] in northern Germany noted no appreciable increase in the age-standardized incidence of acute pancreatitis for either men or women. It could be surmised that such differences in change over time is due to local variations in prevailing aetiological factors. Goldacre and Roberts [72] concluded that an increase in hospital admissions in southern England between 1963 and 1998 was most likely due an increase in alcohol consumption. However, this was only based on the assumption that alcohol was the predominant aetiological factor for younger age groups, where the increase in rate was most pronounced. In Australia, Ah-Tye [71] demonstrated a 30% overall annual increase in admissions to Alice Springs Hospital from 1993 to 1999. This was largely attributed to Aboriginal patients, in whom once again alcohol was seen to be the main precipitant.

Most descriptive epidemiological studies indeed seek to quantify the proportion of cases attributable to the various aetiological factors, which may vary in prevalence across populations. Gallstones are the leading cause in most series, accounting for on average 40% of all cases [21]. The proportion is maximal in countries without a culture of mass

alcohol consumption [90]. Alcohol is generally the second commonest aetiological factor, accounting for approximately 20% of cases [21]. It may predominate in some series due to community mores, as seen in Central Australia [71] and Poland [83]. However in all series where there is stratification according to first or subsequent attack of acute pancreatitis, gallstones are the commonest aetiological factor for the former and alcohol for the latter [71, 79, 83, 91].

The other principle sub-category described by frequency is severity, which is most often defined by the Atlanta criteria [15] or case fatality. In a Polish series of hospital admissions, Bogdan et al [83] found that 22.5% of hospital admissions developed severe acute pancreatitis as judged by the usual criteria. Men appeared to be twice as likely as women. Al-Karawi et al [90] in Saudi Arabia deemed 32.1% of all cases to be severe. Shen et al [82] from Taiwan documented a case fatality of 20.4%, of which 47.4% required intensive care. Stimac et al [86] in Croatia assumed severity to be as high as 50%, although this was based on predictive scoring parameters rather than the physiological or morphological hallmarks of actual severity. In general, rigorous case definition of severe acute pancreatitis may be difficult where case data are retrospectively gathered and there is a blurred distinction between actual and predicted severity.

For the outcome of death, a prospective audit of acute pancreatitis in the North-West Thames Region of the United Kingdom found 57 attributed deaths in 631 patients (9%) over 54 months [92]. Appelros and Borgström [91] determined an annual mortality of 1.3 per 100,000 in the Swedish population. The case fatality in that series for first attacks was approximately 5.7%, but only 0.3% for recurrent attacks. In a German series of 368 first attacks, Blum et al [93] noted a 5% case fatality of which approximately half was

attributed to organ failure and septic complications. Not surprisingly, case fatality rose to 17% in the subgroup of patients with necrotizing pancreatitis. Similarly, Appelros et al [94] in Sweden noted 21 deaths in 79 cases of severe acute pancreatitis (26.6%). Regarding temporal trends, Goldacre and Roberts [72] in a series of hospital admissions in southern England, demonstrated a fall in age-standardized case fatality from 14.2% in 1963-74 to 7.6% in 1975-86, but no appreciable decline thereafter. This was presumed to be due to emergence of no new therapeutic innovations for the acute phase of the disease, following a period of improved radiological imaging and greater understanding of pathophysiology [95]. In another Swedish study, Andersson and Andrén-Sandberg [96] estimated that up to one-third of patients dying from acute pancreatitis do so before reaching hospital. Case fatality, and indeed overall incidence, may thus be underestimated by relying solely on hospitalization data.

1.7.2 Epidemiology of chronic pancreatitis

In contrast to acute pancreatitis, chronic pancreatitis has been more difficult to quantify in a given population, due to that of consensus on case definition and classification [97], and the fact that many such patients may go undetected outside the hospital system. Its slow and often insidious onset means that incidence is not a practical measure of disease burden. To instead measure prevalence demands more proactive and rigorous measurement strategies at a population level, as opposed to detection through accessing pre-existing hospital records of acute care episodes. While a considerable proportion of chronic pancreatitis patients do indeed suffer acute exacerbations [63], this may not represent the entire spectrum of prevailing disease. Overall, it is assumed that variations in incidence and prevalence in Western countries are largely due to differences in alcohol

consumption by these populations. However, relatively little detailed examination has been done on the effect of other determinants or aetiological co-factors in the pathogenesis of chronic pancreatitis [98].

Attempts at determining incidence have nonetheless been undertaken, mostly in European countries in the 1980s and 1990s [97]. In the Czech Republic, Dite et al [99] estimated the incidence of new diagnoses of chronic pancreatitis to be 7.9 per 100,000 per year. This was said to be comparable to the earlier reported incidence in Denmark (8.7 per 100,000) and Germany (7.0 per 100,000), but greater than that in Poland (4.0 per 100,000) and Switzerland (1.6 per 100,000), and less than that in Finland (23 per 100,000) [99, 100]. Levy et al [101] in France sought to determine the prevalence and incidence of chronic pancreatitis in that country by a national survey of gastroenterologists. Chronic pancreatitis was defined as being proved or suspected based on morphological criteria such as calcifications and ductal or histological abnormalities. With a response rate of 23.4%, crude annual incidence was estimated to be 7.7 per 100,000 and crude prevalence of 26.4 per 100,000. Alcohol was said to be the predominant cause in 84% of cases. In a cohort study utilizing the Danish National Registry of Patients, the standardized prevalence ratio of chronic pancreatitis was seen to increase from 11.7 per 100,000 person- years in 1980-1984 to 17.0 per 100,000 in 2000-2004 [98]. Following genetic testing, it was apparent that in 54.9% of cases, an underlying gene mutation could totally or partly explain the chronic pancreatitis [98].

1.8 The case for ongoing observational research

Despite a broad knowledge of many aspects of pancreatitis, ongoing research is desirable to deepen the understanding of certain pathological processes as well as to confirm previous findings. In addition to laboratory-based research, much remains to be achieved by observational studies of local populations with unique demographic and sociological profiles. Inferences thus drawn from descriptive and comparative data may serve to generate or enhance hypotheses that can be further tested by other research methodologies, with the ultimate goal of developing a progressively sound evidence base for management of the disease.

In general, when considering hospital admissions, it may be difficult to separate acute and chronic pancreatitis admissions for epidemiological purposes, due to the issues around robust and easily applied case definitions or diagnostic criteria for the latter [97]. Indeed, it is recognized that many cases of chronic pancreatitis have acute exacerbations of pain and conversely, a proportion of clinically defined hospitalizations for acute pancreatitis may have functional or morphological features of co-existing chronic pancreatitis [44]. Observational research that takes into account this "blurred dichotomy" is therefore warranted.

Observational data drawn from descriptive or comparative studies may be limited with respect to causal inference due to relatively small numbers. This is particularly the case were a certain outcome, such as chronic pancreatitis, is rare over a fixed period in a given population. Despite this limitation, quality data can contribute to the greater discourse by

eventual inclusion in meta-analyses. Where cases are re-identifiable, they may also serve as the basis for a subsequent longitudinal study, which would yield higher level evidence with respect to causality.

The aim of this body of work is to address gaps that remain in an already extensive field of knowledge. Data gathered from acute hospitalizations for pancreatitis will be analysed with the intent of:

- Quantifying the burden of pancreatitis in a particular Australian population for the first time;
- Contributing new insights into the determinants of outcome for acute pancreatitis; and
- Constructing a case for acknowledging the duality of acuity and chronicity that exists in many cases of pancreatitis, and thereby provide a basis for more inclusive disease management strategies.

It is anticipated that such information will serve to guide management of pancreatitis from both a health systems and individual perspective.

Chapter 2

2. USING FAECAL ELASTASE-1 TO SCREEN FOR CHRONIC PANCREATITIS IN PATIENTS ADMITTED WITH ACUTE PANCREATITIS

2.1 Abstract

Background: Patients presenting with acute pancreatitis may have co-existing chronic pancreatitis, the accurate diagnosis of which would potentially guide appropriate management. Gold standard tests are often invasive, costly or time-consuming, but the faecal elastase-1 assay has been shown to be comparatively accurate for moderate and severe exocrine deficiency. This study aimed to evaluate fecal elastase-1 concentration [FE-1] against clinical criteria for chronicity in an acute setting.

Patients and methods: [FE-1] was performed on patients admitted with acute onset of epigastric pain and a serum lipase at least three times the upper limit of normal. Clinical diagnosis of chronic pancreatitis was defined by the presence of specific clinical, pathological or radiological criteria. A [FE-1] value of <200 µg/g was similarly considered indicative of chronic exocrine insufficiency. Thus a 2×2 table comparing [FE-1] and clinical diagnosis was constructed.

Results: After exclusion of liquid stool specimens, 105 stool specimens from 87 patients were suitable for [FE-1] determination. [FE-1] was evaluated against the clinical

diagnosis of chronic pancreatitis, initially for the whole sample, and then after exclusion of cases of moderate and severe acute pancreatitis (Ranson score >2). The latter analysis, based on an exocrine insufficiency threshold of 200 µg/g, yielded a sensitivity of 79.5%, specificity of 98.0%, positive predictive value of 96.9% and negative predictive value of 86.0%.

Conclusion: [FE-1] is an accurate screening tool for underlying chronic exocrine insufficiency when taken in the course of a hospital admission for mild acute pancreatitis.

2.2 Introduction

The Marseille-Rome classification of 1988 [12] defines pancreatitis as either acute or chronic, eliminating the previous categories of acute relapsing and chronic relapsing pancreatitis. Acute pancreatitis is an acute inflammatory process of the pancreas with variable involvement of other regional tissues or remote organ systems [15]. Histological and physiological changes are potentially reversible. By contrast, chronic pancreatitis is a chronic inflammatory process characterized by irreversible or progressive fibrosis of the pancreas [102]. Clinical manifestations include chronic epigastric pain (continuous or with intermittent exacerbations) and variable degrees of exocrine insufficiency (malabsorption with steatorrhoea, weight loss) and endocrine insufficiency (diabetes). While the exact prevalence of chronic pancreatitis in various populations is difficult to determine for logistic reasons, the annual incidence of acute pancreatitis has been

reported as anywhere between 4.8 and 24.2 per 100 000 [103]. It thus represents a significant proportion of the admissions to digestive surgery units.

Despite the apparent dichotomy of disease definition, it is evident that the two processes may occur simultaneously in some patients. In any clinical population, a proportion of hospitalizations for acute pancreatitis, defined by the usual diagnostic criteria, may harbour evolving chronic disease [104]. The latter diagnosis is in practice based on clinical supposition, and then often only when symptoms of malabsorption or diabetes are overtly manifest. Early recognition of patients with underlying chronic pancreatitis is nevertheless useful so as to tailor a differential management pathway compared to those with purely acute disease.

Direct diagnostic tests of exocrine pancreatic function, such as the secretin-caerulein test [105], secretin-cholecystokinin test [106], and the Lundh meal [107], tend to be expensive, invasive or inconvenient. They are thus of limited use in all but academic practice. In the last several years, measurement of the faecal concentration of pancreatic elastase-1 ([FE-1]) has emerged as a relatively simple and non-invasive method of detecting exocrine insufficiency [59]. Additional potential advantages include specificity for pancreas [108], stability during intestinal transit, at 4–8°C for 72 hours and at −20°C for up to 12 months [108-111], concentration in faeces compared to pancreatic juice [109] and non-cross-reactivity with therapeutic enzyme supplements [60].

Measured by the ELISA method, [FE-1] has compared favourably in terms of diagnostic efficacy to other indirect tests of pancreatic exocrine function including faecal chymotrypsin estimation [59, 60, 112], the para-aminobenzoic acid test [111] and the

pancreolauryl test [60, 113]. However, Lankisch et al. concluded that [FE-1] was not distinctly superior to faecal chymotrypsin estimation, particularly in mild or moderate forms of chronic pancreatitis [114]. Similar conclusions were drawn when comparing [FE-1] to the direct Lundh test [115].

This study has thus set out to determine the diagnostic efficacy of [FE-1] in a purely clinical setting where it is applied to opportunistic detection of underlying chronic pancreatitis in patients presenting with acute pancreatitis.

2.3 Patients and methods

All patients admitted with acute pancreatitis to a single regional hospital were consecutively recruited as part of an ongoing prospective cohort study. Diagnosis was based on the generally accepted criteria of a threefold or greater increase in serum lipase and typical epigastric pain [116]. The Cairns Base Hospital, in the far north of Queensland, Australia, serves a population of approximately 250 000 from an area of >500 000 square kilometres. Indigenous Australians (Aborigines and Torres Strait Islanders) constitute about 12% of the population [117]. A previous retrospective study in this population has shown the aetiology of pancreatitis to be alcoholic in 62% of cases and biliary in 18% [118]. For the purposes of the present study, aetiology was defined as biliary if gallstones were noted on standard medical imaging, and alcoholic if there was a reported recent intake of 80 g or more of alcohol per day in the absence of other definable risk factors such as gallstones, hypertriglyceridaemia, and hypercalcaemia [119].

Severity of the acute episode was graded according to Ranson's predictive scoring system [120]. An episode was considered mild with a score of 0–2, moderate with a score of 3–4 and severe with a score of 5–11.

Where possible, the first available stool specimen was obtained from consenting patients during the course of their admission. If no stool specimen or only a subsequent specimen was obtained, these were excluded from the data analysis for this study. Frankly diarrhoeal or urine-diluted stool specimens were also excluded, as these are known to give falsely low [FE-1] measurements [59]. [FE-1] was measured by the ELISA method (Schebo® Biotech, Giessen, Germany) according to the manufacturer's instructions. (see Chapter 3) Diagnostic performance of this test was assessed with respect to a clinical 'gold standard', assuming exocrine insufficiency to be present if [FE-1] was <200 µg/g. This threshold is based on validated receiver operator characteristic calculations [59, 121]. For the clinical gold standard diagnosis, chronic pancreatitis was suspected if one or more of the following were present: a history of typical chronic epigastric pain with no other explanation, more than four admissions for acute pancreatitis in the previous 5 years (where alcohol was considered to be the aetiological factor), a history of steatorrhoea, a history of otherwise unexplained weight loss, or suggestive features seen on medical imaging (e.g. calcification, atrophy, ductal abnormalities, pseudocyst formation). Diabetes mellitus was not included as a diagnostic criterion due to the already high prevalence of type 2 disease in certain sections of the target population.

Subsequent 2×2 tables were constructed to illustrate true positives (TP), false positives (FP), false negatives (FN) and true negatives (TN). Diagnostic performance was assessed

in terms of: sensitivity = TP/(TP + FN), specificity = TN/(TN + FP), positive predictive value (PPV) = TP/(TP + FP), negative predictive value (NPV) = TN/(TN + FN) and diagnostic accuracy=(TP + TN)/(TP + FP + FN + TN).

Ethical approval for the study was obtained from the Human Research Ethics Committee of the Cairns Health Service District.

2.4 Results

Between April 2001 and May 2004, 105 suitable stool specimens, corresponding to the same number of admissions, were obtained from 87 patients at a median of 4 days (range 0–20) after the onset of symptoms. Twelve liquid stool specimens had been excluded from the analysis. Eighty-nine (84.8%) of the evaluable admissions were considered mild on the basis of a Ranson score of 2 or less. Aetiological attribution was alcoholic in 64 admissions (61.0%), biliary in 24 (22.9%) and other/unknown in 27 (25.7%). [FE-1] values ranged from 0 to 920 µg/g with a mean of 283 µg/g. In 41 (39%), [FE-1] was measured as <200 µg/g. Forty-one specimens (39%) were obtained from patients in whom there was clinical evidence of chronic pancreatitis based on the above diagnostic criteria. The frequencies of each of these are shown in Table 9. Twenty stool specimens (48.8%) were from patients with more than one positive criterion, while only 15 (36.6%) showed evidence of the later manifestations of chronic pancreatitis (chronic pain, weight loss, steatorrhoea).

Table 9. Diagnostic criteria for chronic pancreatitis.

Criterion	Number of patients	Percentage of diagnosis positive group
At least one criterion	41	100%
Recurrent admissions	26	63.4%
Positive imaging	20	48.8%
Chronic pain	9	22.0%
Weight loss	6	14.6%
Steatorrhoea	5	12.2%

Results of the initial diagnostic performance analysis are shown in Table 10. When cases of moderate or severe acute pancreatitis were excluded from the analysis, the diagnostic performance of [FE-1] improved considerably, largely due to elimination of all but one of the original false positives (see Table 11).

Table 10. [FE-1] compared to clinical diagnosis (all cases).

[FE-1]	Clinical diagnosis positive	Clinical diagnosis negative	Total
[FE-1] <200 µg/g	32	9	41
[FE-1] >200 µg/g	9	55	64
Totals	41	64	105

Sensitivity = 78.0% (95% CI: 62.0 – 88.9%)

Specificity = 85.9% (95% CI: 74.5 – 93.0%)

Positive predictive value (PPV) = 78.0% (95% CI: 62.0 – 88.9%)

Negative predictive value (NPV) = 85.9% (95% CI: 74.5 – 93.0%)

Table 11. [FE-1] compared to clinical diagnosis: mild acute pancreatitis (Ranson score <3).

[FE-1]	Clinical diagnosis positive	Clinical diagnosis negative	Total
[FE-1] <200 µg/g	31	1	32
[FE-1] >200 µg/g	8	49	57
Totals	39	50	89

Sensitivity = 79.5% (95% CI: 63.1 – 90.1%)

Specificity = 98.0% (95% CI: 88.0 – 100.0%)

Positive predictive value (PPV) = 96.9% (95% CI: 82.0 – 100.0%)

Negative predictive value (NPV) = 86.0% (95% CI: 73.7 – 93.3%)

2.5 Discussion

This study aimed to evaluate the efficacy of [FE-1] as an objective diagnostic tool in a practical clinical setting, rather than in comparison to another test of pancreatic exocrine function. It further represents a unique attempt to diagnose chronic pancreatitis in cases of acute pancreatitis at the time of, or just after, the acute attack. The criteria chosen for the clinical gold standard diagnosis are all well accepted features of chronic pancreatitis,

and are no different to what would normally be used in clinical practice to make a provisional diagnosis. This is particularly the case where the aetiological attribution is largely alcoholic, as is indeed evidenced in the current sample population and in previous epidemiological work in the region [118].

As shown in Table 10, the application of [FE-1] to all hospitalizations for acute pancreatitis yielded unspectacular results for the usual indices of diagnostic performance. These markedly improved after exclusion of cases with moderate or severe acute disease as predicted by Ranson's score. Such cases were responsible principally for false positive results, as seen in Table 11. Exocrine function may indeed be impaired by transient acinar cell dysfunction or frank parenchymal necrosis. Using [FE-1], Boreham and Ammori [122] have shown that pancreatic exocrine insufficiency occurs commonly in patients recovering from severe acute pancreatitis, and its severity correlates with the extent of necrosis documented on contrast-enhanced CT scan. Some cases of moderate or severe acute pancreatitis may nevertheless yield a normal [FE-1] given the relative stability of this enzyme in the gastrointestinal tract [110]. A stool specimen obtained early in the course of an admission may represent that which was in the colon just prior to the onset of the acute attack. However, the ileus often present in severe cases may lead to eventual degradation of the enzyme, thus also ‘falsely’ lowering the [FE-1] measurement. Indeed in this study, median time of first stool specimen from onset of symptoms was 3 days for mild cases (Ranson score <3) compared with 5.5 days for moderate or severe cases (Ranson score >2).

A number of considerations would recommend the use of [FE-1] as a cost-effective screening tool for chronic exocrine insufficiency in patients presenting with acute pancreatitis. Firstly, the assay itself is relatively inexpensive and easy to perform. Stool specimens can also be stored in a freezer at −20°C until a sufficient number has been accrued for a run. Secondly, with a specificity of 98% and positive predictive value of 96.9%, a positive result can generally be relied upon. Furthermore, PPV is optimized when the target screening population has a relatively high prevalence of the disease in question [123]. This would seem to be the case in patients presenting with attacks of acute pancreatitis, particularly where the predominant aetiological factor is alcohol, as in this sample population. Thirdly, although [FE-1] is demonstrably less reliable when dealing with moderate or severe cases of pancreatitis, the vast majority of acute admissions are typically mild [15], as is also seen in the current series. Lastly, patients with chronic pancreatitis, particularly when alcohol-related, often pose problems for compliance and follow-up. A non-invasive test such as [FE-1] measured once during the course of a hospital admission is thus more feasible than most of the other diagnostic tests currently available.

It should be noted that 39% of the sample population showed evidence of chronic exocrine insufficiency based of a [FE-1] <200 μg/g. Extrapolation of this prevalence to the overall target population must take into account the fact that an estimated 30% of incident cases were initially excluded due to unavailability of a stool specimen or delayed specimen collection (i.e. not the first one after symptom onset). It is nevertheless difficult to conceive a specific selection bias under these circumstances in favour of any particular clinicopathological subgroup.

What to do with a positive [FE-1] result remains open to the outcomes of ongoing basic and clinical research. It is conceivable that chronic pancreatitis diagnosed prior to the development of the end-stage manifestations of intractable pain, malabsorption and diabetes may be amenable to innovative secondary prevention strategies. A simple objective diagnostic test is in any case useful for defining patients suitable for inclusion in clinical trials. Positive screening results may also have specific epidemiological implications for the local target populations. Twelve (31.6%) of the 38 patients in this study with [FE-1] below 200 µg/g were indigenous Australians. This group of patients is thus over-represented for chronic pancreatitis when compared with the target population as a whole. Such a result warrants culturally orientated management strategies as well as further studies to elucidate the precise causative factors.

In conclusion, [FE-1] is a feasible and accurate screening test for chronic exocrine insufficiency in patients presenting with predicted mild acute pancreatitis. While all acute patients are amenable to screening, it is recommended that those with moderate or severe acute disease, particularly if the initial [FE-1] result is subnormal, should be re-screened after 2–3 months to assess for residual or permanent exocrine insufficiency. Similarly those with normal [FE-1] but clinical features suggestive of underlying chronic disease should undergo follow-up testing to detect deterioration in exocrine function before more severe clinical features manifest.

Chapter 3

3. PROSPECTIVE COHORT STUDY OF ACUTE PANCREATITIS ADMISSIONS IN FAR NORTH QUEENSLAND

3.1 Introduction

A previous retrospective descriptive study of acute pancreatitis admissions in Northern Queensland proved useful in suggesting those demographic groups likely to be most at risk [118]. It also revealed a high proportion of cases with presumed underlying chronic pancreatitis, and similarly those socio-demographic groups commonly affected. There were, however, a number of deficiencies related to the retrospective data acquisition that limited the clinical applicability of the results.

Causal inference was compromised by the non-directional nature of data collection. Often there was also incomplete or absent ascertainment of certain putative risk factors for which associations with clinical outcomes might be sought. For example, the quantification of alcohol intake was imprecise and did not provide any indication of temporal variation (i.e. binge drinking). The consumption of tobacco, dietary antioxidants and lipids, all of which have been implicated in the causation of chronic pancreatitis [124-128], was not included in the dataset. Smoking was generally recorded in patient notes in an inconsistent manner, either as current consumption or not at all, and rarely in terms of pack years. Dietary history was not routinely recorded as part of the

admission process. The role of a recent lipid load in precipitating an attack of acute pancreatitis in those with an underlying abnormality of lipid metabolism has previously been suggested [129]. Once again, this dietary information was rarely, if ever, noted in medical records.

Despite the apparently high prevalence of chronic pancreatitis in the study group, there was no means of externally validating a diagnosis that had been effectively based on individual clinical judgement, or at least for which a consistent diagnostic epistemology had been applied. Such diagnostic rigour was felt to be important to ensure descriptive accuracy of the disease burden, and also to provide appropriate case ascertainment when considering the role of ostensible aetiological factors. Gold standard diagnostic tests for chronic pancreatitis have been proposed, but these are typically invasive, expensive and time-consuming[14, 57]. They are not routinely done as part of standard clinical diagnostic work-up of acute pancreatitis hospitalizations.

With the above limitations in mind, a template for prospective data collection for incident acute pancreatitis admissions was devised. This was to be implemented at the Cairns Base Hospital over an approximately three-year period. The cohort of patients thus accrued would be subject to further case-comparison analysis.

3.2 Methods

The project was conceived as a mixed retrospective-prospective open cohort study.

3.2.1 Case ascertainment

Hospitalizations for acute pancreatitis were identified as soon as possible after admission by the study investigator or delegated research assistants, who had been given appropriate training. Daily sweeps of the Surgical Unit and Emergency Department were undertaken. When the diagnosis was confirmed and the patient deemed fit to be approached, they were given written and verbal information about the study. Consent was obtained for a face-to-face questionnaire, access to medical records, and follow-up contact if indicated.

The diagnosis of acute pancreatitis was defined based on the criteria prescribed by the working party formed under the auspices of the program committee of the Bangkok World Congress of Gastroenterology 2002 [24]. These were characteristic clinical features (acute onset of abdominal pain with or without vomiting) and serum lipase elevated above the upper limit of normal. For atypical presentations, diagnosis could also be made by appropriate medical imaging, such as computed tomography.

The census period was from 1 March 2004 to 31 July 2007.

3.2.2 Outcomes

3.2.2.1 Health service utilization

A number of descriptive metrics were collected to provide an indication of the impact of the disease on health service delivery.

The count of admissions for acute pancreatitis was recorded. It was also noted whether these cases were first or recurrent admissions. If the latter, the number of previous admissions for each case was recorded.

Another measure of health service utilization was length of hospital stay, measured in calendar days as noted in the patient's medical record.

3.2.2.2 Chronic pancreatitis

Chronic pancreatitis was defined based on a composite of clinical and pathological diagnostic criteria, whereby the diagnosis was considered if any one of these was fulfilled. (see Chapter 2)

Information regarding previous admissions for acute pancreatitis was obtained from the patient's medical record, corroborated by self-report where indicated. Also gleaned by self-report questionnaire were a history of intermittent or continuous abdominal pain,

steatorrhoea, and unintentional weight loss. The patient's medical records were reviewed for characteristic findings on medical imaging, such as calculi, parenchymal atrophy, ductal dilatation, and non-acute pseudocysts.

Functional testing for pancreatic exocrine insufficiency, a proxy measure for chronic pancreatitis, was performed using the [FE-1] assay. This test has previously been shown to have greater than 90% sensitivity and specificity for exocrine insufficiency given a threshold concentration in stool of 200µg/g [59, 130]. It is shows no appreciable intra-individual day-to-day variation [59] or degradation at room temperature, and thus presumably in intestinal transit, for up to one week [59, 130]. It is also similarly stable at 4^0C and -25^0C [59]. Because it is not included in commercial enzyme supplements, concurrent ingestion of these does not interfere with measurements.

For hospitalised patients with an episode of acute pancreatitis, a specimen was obtained of the first stool following admission, provided this was within 72 hours. This was typically done by a nurse using a bedpan, the patient having been advised to avoid simultaneously urinating and defaecating. The specimen was collected in a standard stool sample container (Sarstedt Australia), on which the time and date of collection was noted. Stool specimens were stored in a freezer at -20ºC for a maximum period of six months, or until a sufficient number of specimens for an assay kit had been obtained.

Faecal elastase-1 assays were performed by the study investigator according to a standardized protocol provided of a commercially available assay kit (Schebo Biotech

AG, Giessen). Stored frozen specimens were thawed overnight at 4°C. (If the stool specimen was purely liquid, either due to diarrhoea or significant mixing with urine, this was documented, but the specimen still subjected to the assay process.) After thawing, between 50 and 100 mg of each stool specimen was weighed into a test-tube to which was added extraction buffer in such volume as to give a final concentration of 10mg stool/ml buffer. Homogenisation was facilitated using a vortex mixer. The resulting stool suspensions were left overnight at 4°C for the extraction process to take place.

The following day, extracted stool samples were diluted in a ratio of 1:250 i.e. 10 µl extracted stool sample with 2.5 ml washing buffer (phosphate buffered saline, pH 7.2, with detergent). They were then subject to an ELISA using a plate of micro-titre wells impregnated with monoclonal antibody against pancreatic elastase-1. Each assay kit also includes reference solutions of four standard enzyme concentrations (15, 50, 150 and 500 µg/g) and a blank (no enzyme). Fifty microlitre duplicates of reference solution or extracted diluted stool specimen were pipetted into the wells and incubated for 30 minutes at room temperature. The wells were then emptied and washed three times with washing buffer, by an automated process. Fifty microlitres of a ready-to-use complex of anti-E1-biotin and POD-Streptavidin were added to each well and incubated for 15 minutes in the dark at room temperature. The wells were once again emptied and washed three times with washing buffer. The colour reaction was then effected by adding 100 µl of ready-to-use substrate solution (ABTS in aqueous solution) to each of the wells, and incubating for 15 minutes in the dark at room temperature. The substrate reaction was stopped by the addition of a further 100 µl of alkaline aqueous “stop” solution. After 30

minutes, the optical density in each of the wells was measured using a spectrophotometer set at a wavelength of 405 nm with a reference wavelength of 492 nm.

For the final quantification of elastase-1 concentrations, the mean optical densities of duplicate wells were calculated after the subtraction of the mean blank value. The values of the four standards versus their corresponding elastase-1 concentrations were plotted on log-log paper, and a line-of-best-fit drawn through these. The elastase-1 concentrations of each of the stool specimens were then read from this standard curve. Pancreatic exocrine insufficiency was defined as [FE-1] of <200 µg/g.

3.2.2.3 Severe acute pancreatitis

Severe acute pancreatitis was diagnosed as per the Atlanta criteria [15] if in the course of the acute episode the patient developed organ failure (systolic blood pressure <90 mmHg, PaO_2 ≤60 mmHg, creatinine >2.0 mg/L after rehydration, or gastrointestinal bleeding >500 ml/24h); and/or local complications, such as necrosis, abscess, or pseudocyst, where necrosis is defined as non-enhancement of tissues on dynamic contrast-enhanced CT scan [16, 17]. This information was obtained by iterative reviews of the patient's medical records whilst in hospital. If a particular test was not performed, it was assumed that the parameter was normal based on clinical impression.

Death or case fatality was also recorded, this being also one of the defining criteria for severe acute pancreatitis as per the Atlanta consensus [15].

In addition to actual severity, variables enabling computation of predicted severity scores were noted. These were the previously validated Ranson [120] and Glasgow [116] scores, as shown in Tables 12 and 13. Collection of contributory variables for these was dependent on the judgement of the attending clinicians. If a specified variable was missing from the patient's medical record, it was assumed that this would most likely be within the normal range and therefore not contribute to the severity score. An example would be arterial blood gases not being performed in a patient who appears clinically stable. This assumption should be borne in mind when interpreting the relevant descriptive data.

Table 12. Ranson's criteria for prediction of severity of acute pancreatitis* (adapted from Lankisch et al 1997[131])

Parameter	Alcohol-induced	Biliary-induced
Value at admission or diagnosis		
Age	>55 years	>70 years
White blood cell count	>16 x 10^9/l	>18 x 10^9/l
Blood glucose	>10 mmol/l	>12.2 mmol/l
Serum lactate dehydrogenase	>350 IU/l	>400 IU/l
Serum aspartate transaminase	>250 IU/l	>250 IU/l
Worst value during initial 48 hours		
Haematocrit decrease	>10%	>10%
Blood urea nitrogen increase	>1.8 mmol/l	>1.8 mmol/l
Serum calcium	<2.0 mmol/l	<2.0 mmol/l
Arterial pO_2	<60 mm Hg	<60 mm Hg
Base deficit	>4 mEq/l	>5 mEq/l
Estimated fluid sequestration	>6 l	>4 l

* Score categories

0 – 2: mild pancreatitis

3 – 5: moderate pancreatitis

6 – 11: severe pancreatitis

Table 13. Glasgow criteria for prediction of severity of acute pancreatitis* (adapted from Lankisch et al 1997[131])

Worst value during initial 48 hours	
Age	>55 years
White blood cell count	15 x 10^9/l
Arterial pO_2	<60 mm Hg
Blood glucose	>10 mmol/l (if no diabetic history)
Serum calcium	<2.0 mmol/l
Serum albumin	<32 g/l
Serum lactate dehydrogenase	>600 IU/l
Serum aspartate transaminase	>200 IU/l

* A score of >2 predicts severe acute pancreatitis

C-reactive protein (CRP) was measured in the majority of incident cases, albeit at the discretion of the attending clinician. This acute-phase response protein increases in response to most forms of tissue injury, inflammation or infection [132, 133]. It basically serves to defend against bacterial pathogens and clear apoptotic and necrotic cell debris [134]. Following an acute phase stimulus, serum CRP concentration may increase up to 10,000-fold by *de novo* hepatic synthesis regulated by proinflammatory cytokines such as interleukin-6 [135]. Thus CRP has come to reflect the degree of inflammation and tissue injury associated with an attack of acute pancreatitis, and thereby predict the advent of severe local or systemic complications. In a review of the literature by [136], CRP is deemed to be the single most effective parameter in predicting severe disease and pancreatic necrosis. According to an earlier study by [137], a value of $\geq$210 mg/l in the

first few days of an admission yielded the best discrimination for severe acute pancreatitis.

3.2.3 Covariates

Factors that would potentially contribute to the nominated outcomes were measured by appropriate means. These were chosen on the basis of prior or novel hypotheses of association or causation. The complete set of the collected covariates is shown in Appendix 2.

3.2.3.1 Alcohol consumption

For the purposes of analysis, alcohol consumption was considered in terms of three primary self-reported variables: beverage-specific 7-day recall, usual weekly intake, and recent binge, which was a binary variable defined as a 7-day recall in excess of the self-reported usual weekly intake. The first two of these were initially expressed in standard drinks or the equivalent of 10 g of pure ethanol. Patients were shown pictorial representations for various drinks to ensure accuracy of reporting [138]. (see Appendix 3)

Rationale for use of these variables was based on evidence suggesting that different dimensions of alcohol consumption affect particular disease processes or health-related problems. Meta-analyses conducted by Rehm et al [139] show that chronic diseases such as oropharyngeal cancer, hepatocellular carcinoma and cirrhosis were associated with

average alcohol consumption, whereas both pattern of drinking and average consumption contributed to coronary heart disease and intentional and unintentional injury.

A review of the literature by Feunekes et al [140] indicates that retrospective diary methods such the 7-day recall, tend to systematically underestimate alcohol intake. This may be further accentuated where alcohol is seen to be a principal aetiological factor of the disease outcome being studied, and the questionnaire is administered face-to-face. It was nevertheless felt that a 7-day recall was the most feasible solution for this particular means of opportunistic data collection. It was also partly offset by enquiring about the specific types of alcoholic drinks [140].

No attempt was made to use composite scores, such as the Alcohol Use Disorders Identification Test (AUDIT) [141] or the Michigan Alcohol Screening Test (MAST) [142], that evaluate aspects of alcohol intake other than the amount of alcohol *per se*. In addition to the unproven validity of such these tools in the study population, particularly its Indigenous component, it was felt that they had no additional utility in elucidating the biological mechanisms of disease.

3.2.3.2 Nutritional data

Nutrient intake was investigated using two validated measurement tools, 24-hour dietary recall and red cell folate concentration [143].

24-hour dietary recall was obtained for the calendar day prior to the onset of acute symptoms. This involved asking the patient to recount all food and beverage intake for the 24-hour period. As much detail as possible was recorded regarding food preparation method, commercial brand names, and portions sizes. No visual aids were utilised to assist the estimation of food portion sizes, although in all interviews maximum detail was requested from the patient, and quantities only recorded when mutual understanding had been reached. There is therefore reasonable assurance of the reliability of the data obtained in terms of absolute quantities of nutrient equivalents. Despite this, it is possible that the variability in retrospective representations of portion sizes is so large that these may not be accurately estimated from memory [144]. Quantification of specific macro- and micro-nutrient intakes was performed using the dietary analysis software, Foodworks 2007© version 5 (Xyris Software Pty. Ltd., Highgate Hill, Queensland, Australia).

Red cell folate concentration at the time of admission was determined by an immunoassay performed by the Queensland Health Pathology Service. The stated reference range was 360-1400 nmol/l.

While serum levels of antioxidant vitamins are ostensibly representative of dietary intake, they were not measured in the incident cases of this study. Oxidative stress of the acute episode would be a likely confounder, potentially causing transient depletion of circulating antioxidants.

For follow-up data collection, a 24-hour dietary recall was requested for the day preceding the interview or questionnaire. The subject was then invited to present for a red cell folate blood test to the public hospital or a private pathology laboratory close to their residence.

3.2.3.3 Smoking history

Smoking is considered to make an aetiological contribution to both acute and chronic pancreatitis [41, 145, 146].

Smoking was measured both in terms of currency of smoking and cumulative dose, former being putatively associated with acute pancreatitis and the latter with chronic pancreatitis. Information on tobacco consumption was thus obtained as number of cigarettes smoked per day, duration of smoking, and time since cessation of smoking, if applicable. For the purposes of subsequent statistical modelling, two different ordinal categorical variables were created. Cases were classified as current heavy smokers ($\geq$ 20 cigarettes per day), current light smokers (< 20 cigarettes per day), former heavy smokers (having ceased smoking $\geq$ 20 cigarettes per day more than three months prior to interview), current light smokers (having ceased smoking < 20 cigarettes per day more than three months prior to interview), and non-smokers (having never smoked). The categorisation was further reduced to the variables of current smoker (having been a regular smoker to within 3 months of interview) and current non-smoker (having never smoked or not smoking since at least three months prior to interview).

Cohort studies elsewhere have suggested that self-reporting of smoking habits is a reliable tool for measuring tobacco intake. Janzon et al [147] demonstrated that subjects' self-reporting of whether or not they are currently smoking showed good agreement with plasma carboxyhaemoglobin levels. In the current study, the self-reporting process did not take into account the smoking of other substances such as cannabis.

3.2.3.4 Indigenous status

The indigenous status of patients of patients was self-reported. If clarifications were sought, the definition was based on the 1983 judgement of the High Court of Australia [148], subsequently modified by further legal judgements [149, 150]. People were defined as Aboriginal or Torres Strait Islander if they identify as such and are accepted as such by the community in which they live. Because this is essentially a social definition, no valid causal inferences could be drawn regarding genetic predisposition.

3.2.3.5 Adiposity

Certain metrics of adiposity may be considered as either risk factors or consequences with respect to pancreatitis. As part of routine care, patients were weighed on admission to hospital. In addition to this, for the purposes of the study, recruited patients were also measured for height, waist circumference and hip circumference. This enabled the calculation of body mass index (BMI) and waist-to-hips ratio (WHR).

BMI was calculated according to the formula: BMI = mass (kg)/[height (m)]^2 [151] For WHR, waist circumference was measured with a tape measure midway between the lower margin of the last palpable rib and the top of the iliac crest; hip circumference was taken at the widest portion of the buttocks with the subject standing and the tape measure parallel to the floor [152]. These measurements were taken at the end of a normal expiration.

BMI is seen as a general proxy measure for percentage body fat. While not seen as an optimal tool for individual diagnosis or prognostication, it is generally deemed appropriate for population-based studies due to its relative simplicity [153]. The World Health Organization considers a BMI of less than 18.5 as underweight, and possibly indicative of malnutrition, while a BMI greater than 25 is considered overweight and above 30 is obese [154]. In contrast to BMI, WHR, or even waist circumference alone, is a better indicator of individual health outcomes due to obesity, largely due to the metabolic or endocrine role of visceral fat [155]. The WHO has broadly defined abdominal obesity as a WHR of over 0.9 for males and over 0.85 for females [155].

It should be noted that reference ranges for both measures of adiposity are also susceptible to ethnicity. For example, when estimating risk for cardiovascular disease, the upper limit of normal for measures of central and overall adiposity is generally lower in Asian populations [156]. An Australian study has also shown that Aboriginal and European Australians have a significantly different body fat distribution and fat mass for

a given body weight or BMI, and that the WHO recommendations may be inappropriate [157]. This would need to be borne in mind when interpreting results from the current study.

3.2.3.6 Aetiological attribution

For descriptive epidemiological purposes and to adjust for possible confounding in multivariable analyses, an aetiological attribution was sought for all incident cases. In the absence of ratified guidelines, this was achieved by commonly accepted reasoning used in clinical practice. An attack of acute pancreatitis was considered to be due to alcohol if there was a history of moderate or excessive alcohol consumption in the absence of any other possible risk factors. Biliary aetiology was assumed if gallstones were seen on recent imaging. ERCP-induced pancreatitis was defined if this procedure had been performed in the 24-48 hours before the onset of symptoms. Neoplasia-related pancreatitis was considered when a tumour was diagnosed by imaging, tumour markers, or histology. A codified causal relationship algorithm was used to confirm cases of suspected drug-induced pancreatitis. If at admission serum levels of triglycerides or calcium were significantly elevated, in the absence of other factors, aetiology was classified as hypertriglyceridaemic or hypercalcaemic respectively. If no other nominated aetiological factor could be identified, the episode was deemed to be idiopathic.

3.2.4 Data management

For each admission, parameters informing outcomes and covariates were recorded on a hard copy case report form. (see Appendix 2) These were then manually and entered as discrete case-event units into EpiData™ (version 2.0, Odense, Denmark) for storage purposes. Quality was further assured by double data entry with comparison of summary statistics and referral to the original data collection forms where indicated. Data were subsequently exported to Stata™ (StataCorp, Texas, USA, 1984-2007) for statistical analysis.

For descriptive purposes, count variables were expressed as a percentage of evaluable cases. Continuous variables were summarized as mean and standard deviation if parametrically distributed, and as median and 95% confidence interval if non-parametrically distributed.

3.2.5 Ethical considerations

The observational nature of this study meant that no specific interventions or treatments were applied to patients beyond what would otherwise be considered standard practice by the clinicians responsible for their care. The only two exceptions to this were two investigations that imposed no additional invasive procedure on the patient's episode of care: red cell folate concentration (obtained with other routine blood specimens) and faecal elastase-1 concentration (from an available stool specimen).

Patients with a provisional diagnosis of pancreatitis were identified by daily perusal of the Surgical Unit's nominal roll. Case notes were reviewed to confirm eligibility criteria (i.e. a diagnosis of acute pancreatitis), and patients were then approached using third-person intermediary, usually a member of the nursing or medical staff involved in their care. No approach was made if a patient refused contact or if deemed too ill to be interviewed. In these cases, a repeat approach was negotiated for a later time or date, if suitable.

Informed consent was obtained specifically for an interview of approximately 30 minutes' duration, simple anthropometric measurements, a red cell folate blood test and a stool specimen for faecal elastase-1 estimation. Consent was also sought for follow-up consisting of an interview or questionnaire, a red cell folate blood test and a further stool specimen. Appropriate contact details were recorded at the time of the initial interview. (see Appendix 1)

Data collection and analysis was approved by the Human Research Ethics Committees of the Cairns Health Service District (approval number 319) and James Cook University (approval number H1753). Hard copies of case report forms were stored in a locked filing cabinet in the Cairns Clinical School (Cairns Base Hospital). Electronic data were stored in a password protected computer.

3.3 Results

During the study period, a total of 153 incident cases were recruited for prospective data collection. The median length of hospital stay was 5 days (95% CI: 4-5). Case fatality during admission was 2.6% (n = 4). Seventeen cases (11.2%) developed severe acute pancreatitis according to the Atlanta definition. Regarding predictors of severe acute pancreatitis, four of 109 evaluable cases (3.7%) had a Ranson or Glasgow score of >2. Of 87 cases in which C-reactive protein was measured, twelve (13.8%) had a value of >210 mg/l.

Regarding chronic pancreatitis, 38 of 68 evaluable stool specimens (55.9%) showed [FE-1] less than 200 µg/g. When the composite definition of chronic pancreatitis was applied to the whole cohort, 54.3% (n = 83) of cases fitted these diagnostic criteria. Also of note was that 47.4% of admissions (n = 73) had had one or more previous acute episodes, with nine cases (5.9%) having had 20 or more. (see Figure 2) Table 14 summarises the clinical or pathological characteristics present in the cohort that would contribute to the composite case definition.

Table 14. Clinical or pathological features suggestive of chronic pancreatitis.

Feature	Percentage	Number of evaluable cases
[FE-1] <200 µg/g	55.9%	68
Previous admission(s) for acute pancreatitis	47.7%	153
Chronic or interval episodes of abdominal pain	31.8%	151
Steatorrhoea	14.5%	152
Weight loss	22.4%	152
Chronic pancreatitis on medical imaging	22.2%	95

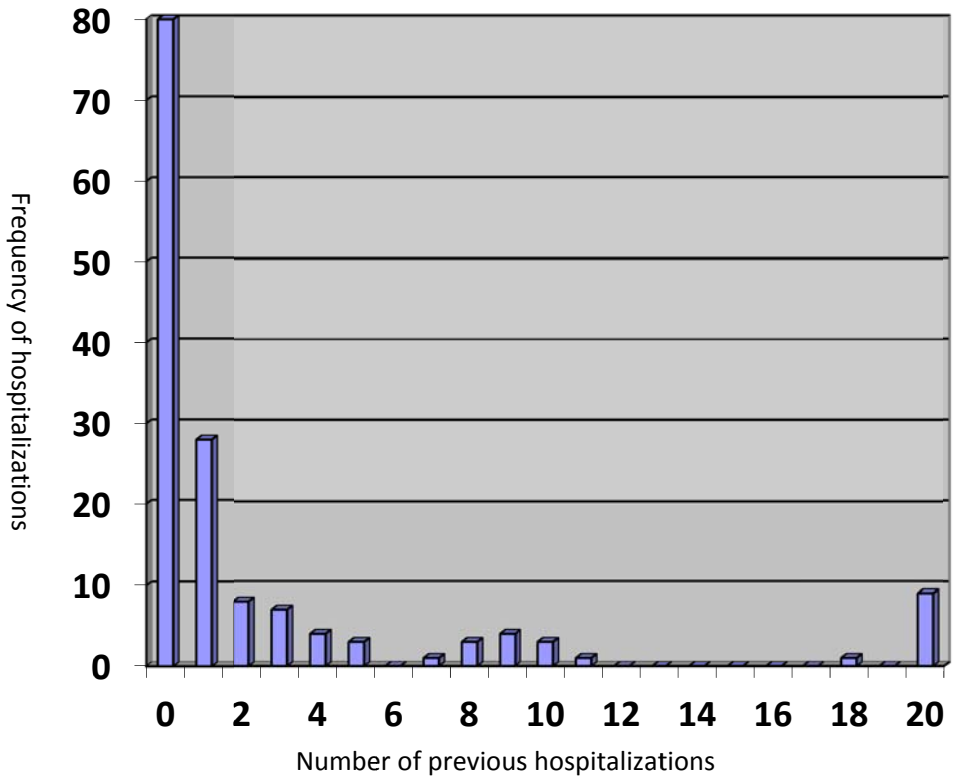


Figure 2. Number of previous documented episodes of acute pancreatitis in FNQ admissions, March 2004 – July 2007

A summary of socio-demographic characteristics is shown in Table 15. Figure 3 shows aetiological attribution of the hospitalized cases. Of the three cases with "other" aetiology, two were due to carcinoma and one to hypercalcaemia. Principal examples of other clinicopathological explanatory variables are seen in Table 16.

Table 15. Socio-demographic characteristics of the FNQ pancreatitis cohort.

Variable	**Value / frequency**	**Number of evaluable cases**
Age	44.7 (± 15.6)* years	153
Male sex	61.4%	153
Length of residence at current address	6 months (4 – 11)†	153
Born in Australia	86.3%	153
Aboriginal or Torres Strait Islander	41.2%	153
Lives alone	26.8%	153
Unemployed or disability pension	38.6%	153
Did not complete Year 12 education	58.6%	152

* Mean ± standard deviation

† Median (95% CI)

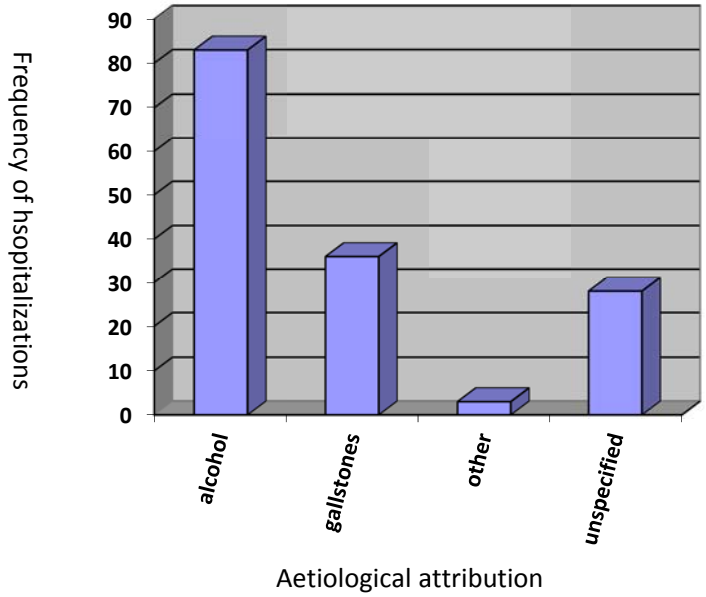


Figure 3. Aetiological attribution of admission numbers of acute pancreatitis in FNQ, March 2004 – July, 2007

Table 16. Other clinicopathological explanatory variables pertaining to the FNQ pancreatitis cohort.

Variable	Value / frequency	Number of evaluable cases
Duration of symptoms prior to admission	8 hours (6 – 12)*	151
Documented comorbidities	54.6%	152
Diabetic	17.1%	152
Previous abdominal surgery	37.5%	152
First degree relatives with pancreatitis	8.0%	151
Adiposity		
Body mass index	25.3 (± 5.7)†	142
Waist circumference	93.7 cm (± 13.9)†	142
Waist-to-hips ratio	0.94 (± 0.09)†	142
Alcohol intake		
7-day alcohol	4.5 standard drinks (0.2 – 13.6)*	150
Average weekly alcohol	5.0 standard drinks (1.5 – 10)*	150
Recent binge	18.7%	150
Tobacco intake		
Cigarettes per day	10 (8 – 15)*	150
Duration of smoking	18.4 (± 13.9) years†	149
Current smoker	62.3%	151
Nutritional intake		
24-hour energy	4795 kJ (± 3462)†	137
24-hour fat	33 g (25 – 39)*	137
24-hour protein	52.5 (± 38.2) g†	137
24-hour folate	129.5 µg (106.2 – 148.4)*	137
24-hour vitamin A	317.4 µg (277.0 – 448.3)*	137
24-hour vitamin C	28.4 mg (20.6 – 45.0)*	137
24-hour coffee	0.7 cups (± 1.5)†	143
Red cell folate	927.3 (± 266.6)†	79

* Median (95% CI)
† Mean ± standard deviation

3.4 Discussion

This cohort of incident acute cases provided descriptive data that enabled comparison with those recruited elsewhere in the world. There was a not unexpected preponderance of males [24]. Actual severity was relatively low compared to certain other series [83, 90]. This may have been due to the fact that severity was defined by the Atlanta criteria [15], with the proviso that organ failure occurring in the first week and resolving within 48 hours was not considered an indicator of a severe attack of acute pancreatitis [26]. Case fatality was also lower than in some series [82]. However, when considering only first attacks, it was indeed comparable to that reported from a number of European populations [91, 92, 158]. At 56.6% (n = 83), the proportion of cases attributable to alcohol was considerably higher than generally described [21], although it should be noted that many of these cases were not first admissions, as is usually specified in the epidemiological literature. If only first attacks were considered, 39.2% (n = 29) of cases were deemed alcohol-related. Aetiology was unattributed in 18.7% (n = 27), which was within the quality recommendations of successive international consensus-based guidelines [26, 159].

There are also certain features described by the FNQ cohort that make it relatively unique at a global level. Firstly, it describes the proportion of acute cases that actually display functional or morphological features of co-existing chronic pancreatitis. The prevalence in this series is over 50%. Secondly, it documents the over-representation of Indigenous

Australians presenting with acute pancreatitis. Over 40% of cases identified as Aboriginal or Torres Strait Islander, in comparison to the 15.5% in the region [160]. Such a finding is in accordance with the only other documented Australian series dedicated to pancreatitis in recent years [71]. It would also appear that the group of patients represented by the cohort is less educated and less engaged in the workforce than the population at large.

Regarding incident acute cases harbouring structural or functional manifestations of chronic pancreatitis, despite the relatively high proportion with subnormal [FE-1], only 14.5% (n = 22) of those interviewed described symptoms of stearrhoroea. It is generally accepted that steatorrhoea occurs in chronic pancreatitis when exocrine function is below 10% of normal, due to the large reserve capacity of the pancreas [161, 162]. However, steatorrhoea was not a prominent symptom even in the 85.7% (n = 24) of cases with [FE-1] in the severely low range, where it would be expected that pancreatic exocrine capacity was below the critical threshold. This apparent paradox may be partly explained by a compensatory increase in gastric lipase output, as noted by Carrière et al [163]. In this situation, malabsorption of other nutrient macromolecules such as proteins (azotorrhoea), is less clinically evident. In addition, such patients may also naturally tend to limit dietary fat intake. Moreover, the clinical significance of asymptomatic malabsoprtion is subject to discussion. Although not overtly debilitating, there may be a degree of subclinical malnutrition due to malabsorption of fat-soluble and other micronutrients. In a study of 29 patients with sub-clinical steatorrhoea, Domínguez-Muñoz et al found that consistently low circulating levels of fat-soluble vitamins, pre-

albumin and ferritin were normalized when enzyme substitution was instituted [164]. This would imply that the patients in the series with [FE-1] <200mcg/g (with a mild attack of acute pancreatitis) and/or a history consistent with chronic pancreatitis may potentially benefit from enzyme replacement therapy.

Population-based studies have revealed that admissions for acute pancreatitis, despite the non-communicable nature of this disease, may demonstrate seasonal variation. Poikolainen showed that admissions to Finnish hospitals for alcohol-related pancreatitis in men exhibited a sinusoidal relationship with respect to seasons, peaking in summer and autumn [165]. Statistically significant seasonality was also seen in a larger study from Ontario [166]. Such observations may be of relevance both in terms of aetiological speculation as well as health resource planning. An attempt to demonstrate statistically significant temporal variation in the Far North Queensland cohort was not possible due relatively small numbers spread across more than one aetiological grouping.

The principal strength of the cohort was the prospective nature of data collection, which enabled quantification of exposure variables that would otherwise be inconsistently available in medical records, or measured using non-standardized and unreliable tools.

Data were also collected for hospitalized cases in a consecutive manner over the study period. While it was aimed for this to be as comprehensive as possible, there were invariably gaps in data collection due to workforce capacity and periods of leave. As a result, the number of cases recruited may not be a complete representation of the local

admission rate or incidence of acute pancreatitis. There may also have been some bias with respect to the proportional representation of certain epidemiological descriptors such as chronicity, severity and ethnicity. Despite this, and the relatively small numbers from the one regional centre, the sample nevertheless appeared to contain sufficient variation to enable meaningful case-comparison analysis.

Collection of covariate data was as rigorous as possible, although in some cases clinical circumstances precluded obtaining a complete data set. Fields most likely to have missing variables for this reason notably included [FE-1], which may not have been obtained due to a patient's inability to produce a stool specimen during the 3-day post-admission interval. Patients may have also been unwilling to provide a stool specimen; further qualitative enquiry would be necessary to ascertain the reasons for this. Because of the number of missing cases for [FE-1], it was deemed pragmatic to use a composite case definition for chronic pancreatitis, based on clinical, morphological and biochemical criteria. As with [FE-1], red cell folate measurements were often not done because it was specified that blood be drawn for this only if indicated for other clinical reasons. Consent for study participation typically occurred following initial diagnostic blood tests, and often none further were clinically indicated during a brief admission for mild acute pancreatitis.

A further limitation of the study was the limited capacity for longitudinal follow-up. For the purposes of analysis, this was essentially restricted to the duration of the hospital admission. Attempts to gather out-of-hospital data post-admission were largely

compromised by patient compliance, contactability and geographical distance. Any analyses would have been inadequately powered for statistical significance, and also biased by over-representation of certain demographic or pathologic sub-groups. Furthermore, because of the long latent phase of disease outcomes such as chronic pancreatitis, a study of a few years' duration would be unable to generate sufficient *de novo* events in order to draw any causal inferences. In summary, considerable time and resources would be required for rigorous long-term follow-up. Cases studies based on a mixture of prospectively and retrospectively acquired data may nevertheless provide insight into the course of the disease. (see Chapter 7)

Finally, regarding representativeness of the FNQ population, it should be noted that the cohort was sourced from a single public hospital. However this is the sole secondary referral centre for the region. Most acute cases from outlying areas would be transferred there, although a few well-known cases of recurrent (mild) acute pancreatitis may have been cared for solely in the district hospitals. There is only one substantive private hospital serving the FNQ region, which during the study period did not have an active Emergency Department. Therefore, almost all acute cases would have been initially received by the public hospital.

3.5 Conclusions

Prospective *pro forma* data collection from acute pancreatitis hospitalizations appears to yield high quality detailed information, although the representativeness of the recruited

cases for descriptive epidemiological purposes should be formally assessed by appropriate statistical methods.

"Novel" variables that are not generated as part of routine clinical practice can be prescribed, but acquisition of these may be limited by available human and financial resources, patient compliance, and ethical considerations. Where there are sufficient numbers in the covariate categories, the data set can be used for case-comparison studies to elucidate determinants of outcomes such as chronic pancreatitis and severe acute pancreatitis.

Chapter 4

4. ADMISSION RATES FOR ACUTE PANCREATITIS IN FAR NORTH QUEENSLAND

4.1 Abstract

Objective: Capture-recapture analysis was used to more accurately quantify the admission rate for acute pancreatitis in a regional hospital setting, in comparison to the usual method of case ascertainment. Reasons for differences in capture for the various methods were also sought.

Methods: Admissions for acute pancreatitis were enumerated over a 40-month period using three data sources: hospital classification of admission diagnoses, prospective case identification, and receipt of diagnosis-specific pathology specimens. Capture-recapture analysis was applied with log-linear modelling to account for likely dependency between data sources. Covariates were noted to explain capture probability by the various data sources and for eventual stratification in the analysis process.

Results: For the census period, there were 304 admissions after merging of data sources, giving a crude admission rate of 7.6 per month. Crude ascertainment rates for discharge records and prospective identification were 44% and 52% respectively. Following log-linear modelling, total admissions more than doubled to 644 (adjusted admission rate

16.1 per month). Of the covariates considered, admissions of less than three days' duration and those occurring in December and January were significantly associated with increased capture by the hospital discharge records data source.

Conclusions: In this clinical setting, admissions for acute pancreatitis are grossly underestimated by the standard case ascertainment method. The reasons for this are not clear. Hospital discharge records are nevertheless more effective than prospective case ascertainment for certain cases, such as brief admissions and those in holiday periods.

4.2 Introduction

Acute pancreatitis is recognised as a common cause for hospital admission to General Surgery units, largely as a function of the local prevalence of gallstone disease and alcohol abuse [91]. A retrospective audit from Alice Springs, Australia showed an average admission rate of 2.75 cases per month over a 6-year period. A 30% annual increase in admissions was largely attributable to Indigenous patients [71]. Accurate recording of hospitalized cases is necessary to inform health policy and resource allocation, and also to evaluate the impact of aetiological factors and interventions over time and across sites [167]. In the Australian setting, estimations of incidence or admission rates are typically based on retrospective hospital coding systems, where trained non-clinicians enter ICD-10 diagnoses derived from admission documentation recorded by mostly junior clinical staff. Although generally accepted as best practice,

case ascertainment by this means may be subject to inaccuracies due to misclassification or incomplete documentation, even for acute events [168, 169].

Collection of data by more than one method may compensate, although simply merging data lists with elimination of duplicate cases tends to bias estimates of admissions downwards [170]. The concept of capture-recapture was initially applied to the estimation of wild animal populations as a way of estimating population numbers [171]. Since then, it has been used to calculate epidemiological indicators such as mortality [172] and to enumerate case numbers for a variety of disease processes including diabetes [173-175], cancer [176-179], HIV [180, 181], stroke [182], trauma [183] and alcoholism [184]. It basically involves counting the number of cases in a defined population using more than one source of information, and assuming that each source alone may underestimate the true number [183]. The "true count" can then be estimated using a range of modelling techniques.

This study aimed to provide a more accurate estimation of admission rates for acute pancreatitis in a hospital population by the application of capture-recapture methods on three sources of data. Secondarily, case characteristics explaining differential catchability by data sources were also sought.

4.3 Methods

The number of admissions for acute pancreatitis to Cairns Base Hospital in Far North

Queensland was estimated. As the sole tertiary referral hospital for a population of approximately 250 000, it was assumed that most cases in the region would have been admitted to this institution.

Acute pancreatitis was defined by prescribed diagnostic criteria as an acute onset of typical epigastric pain in conjunction with elevated serum lipase or consistent appearances on medical imaging [24].

Admissions were ascertained over the period from 1 March 2004 to 31 July 2007.

Three data sources were utilised:

1. Hospital classification of admission diagnosis (hereafter referred to as “coding”)
2. Prospectively recruited interviewees (hereafter referred to as “interview”)
3. Prospectively recruited stool specimen providers (hereafter referred to as “specimen”)

The coding data consisted of patient admission episodes routinely collected retrospectively and coded by the hospital’s Medical Records Department, based on the diagnosis indicated in the documentation relating to a particular episode of care. ICD-10 codes requested were K85.0, K85.1, K85.2, K85.3, K85.8 and K85.9. The interview data source was patient admission episodes where hospitalized cases with acute pancreatitis consented to be interviewed as part of a prospective observational study, and have the information recorded as written documentation. These cases were identified by the project’s research team as part of an intended daily surveillance of relevant hospital

wards. The specimen data source was cases of acute pancreatitis identified by the receipt of an appropriately labelled stool specimen for the measurement of faecal elastase-1 concentration. These were obtained independently by nursing staff as part of the aforementioned observational study. Patients had agreed to provide a stool specimen as part of their clinical management prior to an interview with one of the researchers.

In addition, variables of potential interest were analysed to give information on characteristics for catchability by each of the data sources, and also for eventual stratification to provide maximally accurate estimates when performing capture-recapture analysis. These covariates, considered as dichotomous variables, were age <40 years, male sex, alcohol-related aetiology, admission in December-January, admission on Friday-Sunday, indigeneity, length of hospital stay <3 days, and death. Information on indigeneity was only available for the coding and specimen data sources. Only complete datasets were analysed (i.e. missing values were not imputed).

4.3.1 Statistical analysis

Admission episodes were matched between data sources by their name (first and surname), unique hospital unit record number (URN) and admission dates, using STATA™ version 10 (StataCorp, Texas, USA, 1984-2007). For the specimen data source, cases were considered matchable to the other data sources if the date of the stool specimen fell within the recorded admission period of the corresponding URN. Following

the data merging process, the names of admitted individuals were removed and the data was analysed de-identified.

A descriptive analysis of admissions was undertaken by data source. Bivariate analyses were undertaken using a multinomial logistic regression to estimate the relative risk ratio of each of the covariates by the different data sources.

Log-linear modelling was used to estimate the number of admissions not ascertained by any of the data sources, using CARE software (http://www.stat.nthu.edu.tw/~chao/) [170]. Data source dependency and individual heterogeneity were managed by the inclusion of interaction terms in the models, starting first with a model that assumed data source independence (no interaction terms included). Data source interaction terms were then added to the model until saturation [170]. The Akaike Information Criterion (AIC) was used to determine the model of best fit [185]. The number of unobserved admissions was then estimated from the chosen model. Confidence intervals were calculated using the profile likelihood approach, which allows for asymmetry on the log scale [186].

The completeness of case identification was measured by the ascertainment rate, which was calculated by dividing the number of admissions identified by each of the data sources by the aggregated number of admissions identified by all three sources. The crude admission rate was determined by dividing the aggregate number of admissions by the time period of the study. For the adjusted admission rate, the numerator in this

calculation was replaced by the number of admissions estimated by capture-recapture modelling.

The study was approved by the Human Research Ethics Committees of the Cairns Health Service District and James Cook University.

4.4 Results

The cases ascertained by each data source are shown in Figure 4. In the 40-month period, the total number of cases observed by all three sources merged, with elimination of duplicates, was 304. Crude ascertainment rates were 44%, 52% and 38% for the coding, interview and specimen data sources, respectively. Only 8 cases were common to the coding and interview data sources, in contrast to 90 between the interview and specimen collection data sources. The crude admission rate was 7.6 per month.

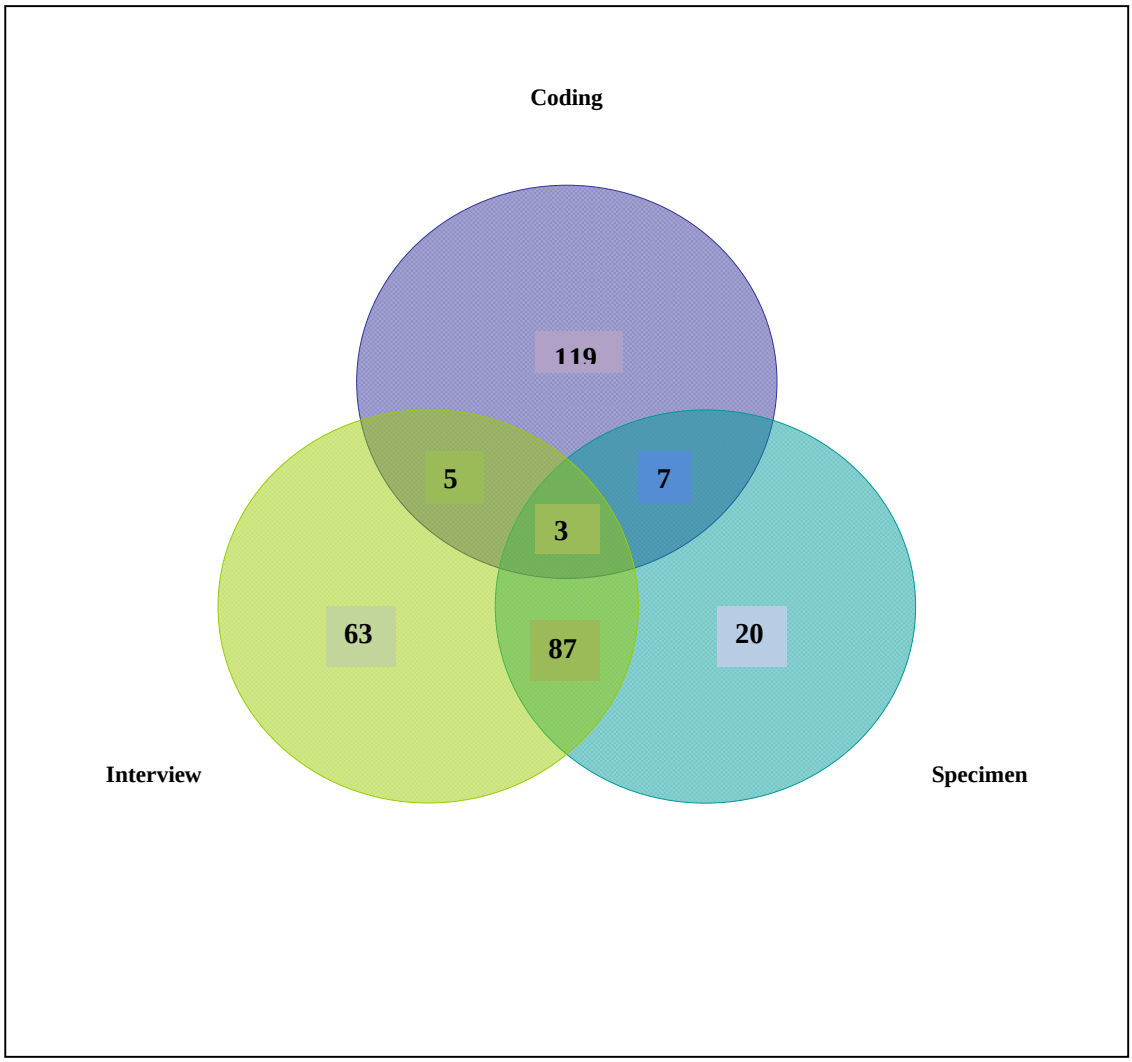


Figure 4. Capture-recapture of 304 acute pancreatitis admissions from March 2004 to July 2007 by discharge records (coding), researcher (interview), and faecal elastase-1 assay request (specimen).

For capture-recapture analysis, the log-linear model of best fit based on AIC included interaction between the coding and interview, and interview and specimen data sources. The estimated number of unobserved cases was 340, giving a total number of cases in the study period of 644 (95% CI: 449-1100). Adjusted ascertainment rates were 21% (95% CI: 12%-30%), 25% (95% CI: 14%-35%) and 18% (95% CI: 11%-26%) for the coding,

interview and specimen data sources, respectively. In addition, 53% (95% CI: 30%-77%) were captured by none of the data sources. The ascertainment (or capture-recapture)-adjusted admission rate for the study period was 16.1 cases per month (95% CI: 11.1-28.1)

For each data source, capture probabilities of the nominated covariates configured as dichotomous variables are shown in Table 17. When considering case characteristics that may have explained preferential capture by either of the two principal data sources (coding and interview), bivariate analyses for the nominated covariates using multinomial logistic regression showed two significant associations. (see Table 18) Hospital classification of admission diagnosis was more likely to capture cases than prospective identification by researchers for admissions of less than three days (RRR 2.35; 95% CI 1.14-4.97) and during the principal holiday months of December and January (RRR 2.98; 95% CI 1.58-5.64). None of the covariates examined were shown to be less catchable by hospital classification of admission diagnosis compared to the other data sources.

Table 17. Capture probabilities of nominated covariates by data source.

	Data source		
Covariate	Coding	Interview	Specimen
	n = 134	*n* = 158	*n* = 117
Age <40 years	48 (35.8%)	63 (39.9%)	38 (32.5%)
Male sex	81 (60.5%)	97 (61.4%)	68 (58.1%)
Alcoholic aetiology	32 (23.9%)	85 (53.8%)	53 (45.3%)
Admission in December-January	24 (17.9%)	15 (9.5%)	16 (13.7%)
Admission on Friday-Sunday	58 (43.3%)	70 (44.3%)	46 (39.3%)
Indigenous	NA	66 (41.8%)	34 (29.1%)
Length of stay <3 days	38 (28.4%)	18 (*n* = 147) (12.2%)	9 (*n* = 94) (9.6%)
Death	9 (6.7%)	4 (2.6%)	5 (4.4%)

Table 18. Multinomial logistic regression for catchability of covariates by data source, relative to interview-only data source.

Covariates : relative risk ratio (95% confidence interval)	Data source	
	Coding	Coding and interview
Age <40 years	0.83(0.51–1.36)	0.90(0.21–3.91)
December–January admission	2.35(1.14–4.87)*	3.51(0.64–19.20)
Friday-Sunday admission	0.94(0.58–1.51)	0.17(0.02–1.40)
Admission <3 days	2.98(1.58–5.64)**	1.03(0.12–8.85)
Indigenous	_ †	0.83(0.19–3.60)
Male	0.95(0.59–1.54)	4.67(0.56–38.90)
Death	2.70(0.81–9.00)	_ †

* $P = 0.021$; ** $P = 0.001$; † not able to be estimated due to a zero cell.

Because of the relatively small numbers of cases for each of the covariates, as well as the missing data for some of these, further multivariable regression was considered not feasible. Similarly, log-linear modelling with stratification for covariates would not have achieved stable estimates.

4.5 Discussion

This is the first study to apply capture-recapture methods to quantify acute pancreatitis cases, and to evaluate the efficacy of ascertainment by the traditionally accepted means of

data collection. With the advent in Australia of hospital case-mix funding based on diagnostic-related groups [187], the efficacy of case ascertainment for specific disease events has significant implications for local health budgets and service delivery. Using capture-recapture analysis, it has been shown that hospital admissions for acute pancreatitis may be considerably underestimated by the conventional means of case identification. Based on the 2007 ERP of 229 996 for FNQ, the annual admission rate for the catchment population could be estimated as 84.0 per 100 000. This number is considerably more than those reported by comparable admissions-based studies [71, 72].

There are various means by which disease episodes can be ascertained and enumerated for epidemiological and administrative purposes. The use of these data sources is often a function of the disease process itself (eg. acute or chronic), clinical setting (eg. hospital or community), and cost. Hospital discharge records, which represent a type of secondary database [188], are a well-established and convenient means of ascertaining hospitalizations. However, even with the assurance of expert clinical diagnosis and data entry, they are not without limitations. In an audit comparing case ascertainment by cancer registry and hospital discharge files, Penberthy et al found the latter to capture only 62% of the unique cases captured by both sources combined [189]. The positive predictive value of hospital discharge files was nevertheless high (94%).

Alternative methods of incident case ascertainment include so-called primary databases. These typically record events prospectively as they occur, or just after completion. Examples include active censuses for a specific disease process (as illustrated by

interview data source in this study) or disease registries with “mandatory” reporting. Compared to secondary databases, the efficacy and quality of primary ones are more susceptible to behavioural factors and interactions between the data collectors and the types of cases to be ascertained. They are also relatively costly to implement and maintain.

In this study, it is intuitively clear that the two prospectively acquired data sources would be likely to miss cases due to variable availability of research personnel to identify, consent and recruit patients during their acute admission episode. This was indeed borne out by the relative underperformance of the interview data source in capturing cases admitted for only short periods or during the summer holiday period. It is more difficult to speculate as to why a retrospective method of case ascertainment, based on clinically validated diagnoses, should fall short of expectation. Diagnostic coding in Australian hospitals is a rigorous process with strict quality assurance measures. However coders are only authorised to classify what is recorded in case records by clinical staff. A random audit of medical records identified by the coding data source confirmed excellent specificity (data not shown), in accordance with the above findings of Penberthy et al [189]. The apparent lack of sensitivity may have been due to inadequate or inaccurate documentation. For example, misclassification may have occurred where the primary diagnosis of pancreatitis was overridden by an aetiological factor such as alcoholism or gallstones. A wider audit of medical records would be needed to evaluate this hypothesis. Furthermore, no conclusions based on the representations of pancreatitis-specific

aetiological factors as covariates in the three data sources could be drawn, due to much of this information not being recorded in the Medical Records list.

Capture-recapture methods using multiple record lists are subject to a number of implicit and explicit assumptions [190]. The former include: accurate case diagnosis; identifiable matching of common cases between data sources; and each data source incorporating the same time-space unit under study. The latter include: equal case ascertainment probability within each data source; independence of case ascertainment between at least two of the sources; and no entries or losses for the population during the study period.

For this study, it is reasonable to expect that all the implicit assumptions hold. Cases identified prospectively were included on the basis of set diagnostic criteria. As mentioned above, those ascertained retrospectively by the Medical Records department may have been subject to misclassification, although as mentioned above case record examination of a random selection of approximately 20% of these suggested that diagnostic classification was indeed accurate. With regard to accurate matching, cases in each data source had a set of unique identifiers, and each data source recruited cases that presented to one hospital over the same time period.

Some of the explicit assumptions may have been violated however. The data sources were not independent. This can nevertheless be statistically accommodated by log-linear modelling techniques, which were originally suggested by Fienberg [191] and subsequently recommended by the International Working Group for Disease Monitoring

and Forecasting [192], and undertaken in this study. Selection of the most appropriate log-linear model may be informed by prior knowledge and belief of likely behaviour patterns, as well as by statistical testing for goodness of fit. Our preferred model was selected on the basis of the lowest AIC. It incorporated interaction between the coding and interview, and interview and specimen data sources, which would seem intuitively plausible given the nature of case ascertainment in the hospital setting. Another means of dealing with the interdependence of the interview and specimen data sources would be to simply pool the cases into a single list that could be then considered in a two-list model with the interview data source. This method has previously been used effectively in studies on the prevalence of diabetes mellitus [193-195].

Within each data source, there was heterogeneity of case ascertainment probability for certain subgroups. For example, brief admissions for mild acute pancreatitis are more likely to have evaded documentation compared to those requiring longer hospital stay and greater medical attention, in a variable manner across all data sources. More accurate case number estimates could be obtained by stratifying the data lists according to covariates that have been selected on the basis of substantive knowledge or behavioural assumptions [193]. Such estimations were not possible in this study due to the relatively small number of cases under the available covariates and also because of missing data. Any future studies should thus aim for case ascertainment over a longer timeframe and across more than one comparable centre.

Whether the population under consideration could strictly be assumed closed is doubtful.

Although likely to be stable overall during the three-and-a-half-year study period, it is likely that migration and deaths had occurred. However log-linear modelling is thought to be able to accommodate situations where there are possible gains and losses within the timeframe of the study, in addition to dealing with interdependence of data sources [196].

4.6 Conclusion

The use of retrospective case record data alone greatly underestimates admission rates for acute pancreatitis in this regional Australian setting. To obtain maximally accurate estimates of specific diagnoses for research purposes, reliance on more than one data source is advisable. For each of these, there should be detailed recording of key covariates to enable stratification. In practice, it may suffice to conduct intermittent prospective censuses to supplement ongoing retrospective data collection from discharge records. When the priority is general health resource planning, it would be more cost-effective to better train clinical staff to provide maximally accurate and comprehensive diagnostic information in the case documentation. Such training should commence at undergraduate level in order to effect culture change with the ongoing promulgation of case-mix funding.

Chapter 5

5. INTAKE ASSOCIATIONS WITH CHRONIC PANCREATITIS

5.1 Abstract

Background: While alcohol is considered the most common aetiological factor for chronic pancreatitis, the intake of various nutrient and other substances are thought to act as cofactors in the pathogenesis of the disease due to modulation of oxidative stress. This study examined admissions for acute pancreatitis to determine the dietary and other intakes that characterize those harbouring underlying chronic pancreatitis.

Methods: Cases of acute pancreatitis presenting to a single institution were prospectively recruited (n=153). The presence of chronic pancreatitis was defined by a composite of clinical, biochemical and radiological criteria. Information was obtained on the intake of dietary macro-and micronutrients, coffee, tobacco and alcohol in the period just prior to the acute exacerbation. Univariate and multivariate analyses of association were undertaken. Principal components analysis (PCA) was employed to elicit patterns of intake.

Results: After adjustment for key demographic variables, no individual nutrient or other substance showed a significant association with chronic pancreatitis. However, following PCA there emerged a significant positive association with a so-called “stimulant” intake pattern and a negative association with a so-called “nutritive” pattern.

Conclusions: Preceding an acute exacerbation, patients with underlying chronic pancreatitis are more likely to substitute food-based intake for combinations of other substances, such as tobacco and coffee. This finding may have application in the clinical setting as part of a chronic disease management protocol.

5.2 Introduction

Chronic pancreatitis is an irreversible degenerative condition of the pancreas characterised by varying degrees and combinations of fibrosis, acinar atrophy and intraductal calculus formation [8, 9]. In most cases, fibrosis is the predominant and driving lesion for the disease process. It is largely thought to be the result of activation of pancreatic stellate cells (PSCs) [197] in response to successive episodes of tissue injury [198]. At a cellular level, this process is partly driven by oxidative stress or the release of reactive oxygen species (ROS) [199, 200]. It is therefore plausible that the presence of anti-oxidant substances may moderate such oxidative stress, attenuating the impact of the initiating noxious stimulus.

While alcohol is the most prevalent aetiological factor in Western countries, it is clear that not all heavy drinkers succumb to chronic pancreatitis. It is also accepted that, unlike liver cirrhosis, there is no apparent threshold for toxicity of alcohol on the human pancreas, but rather a continuum of risk [201]. This would once again suggest moderation by a variety of possible co-factors including smoking, genetic mutations, and nutrient intake. Over the years, numerous studies have been undertaken to seek evidence

for the impact of ingested substances other than alcohol on the pathogenesis of chronic pancreatitis.

In the 1970s, a case-control nutritional survey conducted across a number of Caucasian-populated centres demonstrated a log-linear relationship for relative risk of chronic pancreatitis with alcohol and protein intake, and an apparent quadratic relationship with daily fat intake [202]. Balakrishnan et al further suggested the role of a low fat diet for those with chronic tropical pancreatitis [128]. With regard to antioxidants, a small case-control study involving subjects with pancreatic calculi in South Africa revealed significantly lower serum levels of anti-oxidants such as vitamin C, carotene and tocopherol [126]. Similarly, Morris-Stiff et al [203] demonstrated in chronic pancreatitics significantly lower plasma levels of selenium, vitamin A, vitamin E, ß-carotene, xanthine, ß-cryptoxanthine, and lycopene, when compared to controls. This reinforced inferences drawn from contemporaneous ecological studies showing an inverse relationship between the bio-availability of certain antioxidants in subjects from various populations and the prevalence of chronic pancreatitis [126, 204]. These studies, however, are limited with respect to causal inference; it could reasonably be argued that low antioxidant levels are due to a state of persistent oxidative stress leading to circulatory depletion.

A number of animal studies have demonstrated the protective effect of antioxidant preparations on chemically induced pancreatic fibrosis [205-207]. These findings reinforce the so-called Manchester Model [208] whereby relatively unopposed oxidative stress in acinar cells leads to an inflammatory response with consequent structural and functional changes [127]. The presence of enhanced oxidative stress (in terms of elevated ROS and reduced antioxidant capacity) has been further validated by clinical

studies both systemically [199, 209] and within the pancreas itself [210, 211]. Similarly, combined antioxidant supplementation has been shown to relieve pain and ameliorate antioxidant profiles. Uden et al [212] performed a double-blind placebo controlled trial utilizing organic selenium, carotene, vitamin C, vitamin E, and methionine. In this small group of patients with chronic pain and recurrent acute pancreatitis, they found that fewer patients on antioxidant therapy had recurrent attacks compared to placebo ($p=0.032$). The authors concluded that clinical improvement was noted in patients on therapy above and beyond placebo effect. Another small study by Heaney and colleagues looked at the role of antioxidant therapy in patients with recurrent acute pancreatitis from familial hypertriglyceridemia [213]. They showed that in a very small group of patients, antioxidants prevented recurrent episodes, despite unchanged triglyceride levels. A more recent randomized study from India evaluated the antioxidant curcumin (from turmeric) and its effect on patients with tropical pancreatitis [214]. Patients on therapy had decreased markers of oxidative stress compared to placebo, although no improvement of pain was seen. Another randomized, placebo-controlled cross-over study by Kirk and colleagues evaluated the efficacy of combined antioxidants (selenium, β-carotene, L-methionine, and vitamins C and E) in patients with CP [215]. Only 19 of 36 patients completed the trial. Nevertheless, the investigators found that treatment with combination antioxidants led to significant improvements in quality of life with regards to pain, physical and social functioning, and general health perception.

Limitations of the aforementioned trials include small sample sizes, lack of evaluation of confounding variables, and short duration of antioxidant supplementation. The largest randomized study to date for relieving pain in CP with antioxidant therapy was published

by Bhardwaj and colleagues [216]. In this trial the investigators studied patients with both alcoholic and idiopathic CP. One hundred twenty-seven patients were randomized to receive either antioxidant therapy (n=71) or placebo (n=56) for a 6-month period. The antioxidant supplementation was a combination of 600 μg selenium, 0.54 g ascorbic acid, 9000 IU β carotene, 270 IU α-tocopherol and 2 g methionine daily in divided doses. The primary outcome was pain relief assessed by reduction in painful days per month as measured by a pain diary. The primary outcome was evaluated by a blinded clinician. Secondary outcomes evaluated were decrease in requirement for oral and parenteral analgesics, decrease in attacks leading to hospitalization, percentage of patients becoming pain free during therapy, days missed from work, and change in serum markers of oxidative stress and antioxidant levels. The results showed that reduction in painful days per month was 3.21 days in the placebo group compared to 7.37 days in the antioxidant group ($p < 0.001$). Additionally, the antioxidant group had statistically significant reductions in the number of monthly analgesics required, need for hospitalization, and number of days lost from work. Interestingly, one-third of the patients in the antioxidant group became pain free compared to 12.5% of the placebo group ($p = 0.009$). Patients with CP had higher levels of markers of oxidative stress and lower antioxidant levels. No adverse events were noted.

It should also be noted that data from most observational and interventional studies thus far are non-directional with respect to causal inference, given that they involve cases where chronic pancreatitis is already well established and give no indication of antioxidant bio-availability leading up to the genesis of the chronic inflammatory state. In humans, there is an apparent paucity of work on intentional dietary intake of antioxidants

either prior to or after the onset of chronic pancreatitis. This may be due to logistic difficulties in obtaining long-term prospective data from such patients.

Whilst it is accepted that acute pancreatitis and chronic pancreatitis are two distinct disease processes [12], it is also evident that they often co-exist in the same person [217-219], and repeated attacks of acute pancreatitis may evolve into chronic pancreatitis [220]. Indeed for many with chronic pancreatitis, the only interface with the healthcare system is by virtue of hospital admissions due to acute exacerbations. This would therefore seem to be a convenient and clinically relevant means of accruing a study sample.

The aims of this study were thus to quantify recent nutrient and other substance intakes in a sample of incident acute pancreatitis cases, and to determine any significant associations with underlying chronic pancreatitis that may contribute to causal inference.

5,3 Methods

As part of a prospective cohort study, hospitalizations for acute pancreatitis were consecutively recruited over a three-year period at Cairns Base Hospital in Far North Queensland, Australia. This tertiary referral hospital drains a population of approximately 250 000, approximately 12% of which is indigenous Australian (Aboriginal and Torres Strait Islanders). Acute pancreatitis was defined as acute onset of typical epigastric pain

in conjunction with elevated serum lipase or consistent appearances on medical imaging [24].

Chronic pancreatitis was defined by a composite of clinical, morphological and biochemical criteria. An incident acute case was considered to have underlying chronic pancreatitis if at least one of the following was fulfilled: four or more previous admissions for acute pancreatitis, a history of continuous or recurrent consistent epigastric pain, malabsorption (steatorrhoea), radiological abnormalities (calculi, parenchymal atrophy, ductal dilatation, non-acute pseudocysts), and faecal elastase-1 concentration ([FE-1]) less than 200μg/g where the acute attack was not severe [59, 219].

Data on a variety of explanatory variables were collected. These included age, sex, indigenous status, severity of the acute episode, alcohol and tobacco history, and nutrient intake. Severe acute pancreatitis was defined by the so-called Atlanta criteria [15] as organ failure (with specified physiological thresholds) and/or local complications (such as necrosis, abscess or pseudocyst). Alcohol intake was measured by a self-reported beverage-specific 7-day recall. Aetiology was considered to be attributed to alcohol if in the absence of other known aetiological factors intake exceeded 80g per day for men and 60g per day for women, for a 24-hour period. Smoking or tobacco consumption was described in terms of current smoking behaviour (a dichotomous variable or cigarettes/day) or cumulative dose (cigarette-years).

Nutrient intake was represented by a 24-hour dietary recall obtained for the calendar day prior to the onset of acute symptoms. This involved asking the patient to recount all food and beverage intake for the 24-hour period. As much detail as possible was recorded

regarding food preparation methods, commercial brand names, and portions sizes. The macro- and micronutrient composition of food intake was calculated using FoodWorks 2007© version 5 (Xyris Software Pty. Ltd., Highgate Hill, Queensland, Australia). The former comprised carbohydrates, fat, protein and total energy intake. The latter were vitamin A, vitamin C and folate. In addition, coffee was itemized separately as a "non-nutritive" substance.

All data were checked and entered into EpiData (www.epidata.dk), then exported to STATA™ version 9.2 (StataCorp, Texas, USA, 1984-2007) for statistical analysis. Univariate comparisons were conducted using Pearson's chi-squared for categorical variables, Student's t-test for parametric continuous variables, and the Mann-Whitney test for non-parametric continuous variables. Multiple logistic regression was performed on selected variables, based on *a priori* knowledge, identified univariate associations and extracted PCA intake patterns. This was based on a Poisson distribution of the outcome variable with robust estimates to control for potential overestimation of errors in binomial data [221]. Effect measures were expressed as incidence rate ratios (IRR). Only cases with a complete set of variables were included in the analysis.

Correlations between intake items were analysed by Principal Components Analysis (PCA), utilizing methods applied in previous nutritional studies [222-224]. This multivariate technique is essentially a form of exploratory factor analysis that has been outlined in detail by recent review articles [225-227]. It is based on the fact that within a large data set there are clusters of data points defined by the covariates that vary with each other in multiple dimensions. As with simple linear regression in two dimensions, a component of significance is conceived as an elongated cluster of points around an axis.

The more strongly a particular covariate constrains the data points to the axis of the component (ie. its association with the component), the greater its so-called loading. The contribution of a component to the total variability in the data set is computed as an eigenvalue. A commonly used criterion to determine the number of components to extract is the Kaiser criterion [228], whereby an extracted component is considered worthy of consideration if it has an eigenvalue greater than one. A derived component is generally described in terms covariates that have a significant loading score within it (often set above 0.5). When extracting components and computing loading scores, an orthogonal transformation is the default starting point in most software packages, but should only be performed if the components are not likely to be correlated with each other. However, in most instances this cannot be assumed, and an oblique transformation should be applied.

In this study, the orthogonal (varimax) rotation was initially performed, but because a correlation matrix of the components suggested some degree of correlation, the data were rotated by the oblique (oblimin) method. Components were retained for subsequent logistic regression analysis if their calculated eigenvalues were greater than one and were described in terms of constituent intake variables with which there was the most correlation (loading scores >0.5). These components were then included in the final multiple logistic regression model. The suitability of the dataset for PCA was assessed by the Kaiser-Meyer-Olkin Measure of Sampling Adequacy [229] and Bartlett's Test of Sphericity [230].

Ethical approval for the study was obtained from the Human Research Ethics Committees of James Cook University and the Cairns Health Service District.

5.4 Results

Over the study period, 153 acute admissions were recruited, whose key demographic and clinical specifications are outlined in Table 19. Of these, 137 cases had complete data for all of the covariates considered. Univariate comparisons with respect to the presence or absence of underlying chronic pancreatitis are shown in Table 20. From this it can be seen that patients with chronic pancreatitis, prior to their acute attack, were generally characterised by increased intake of so-called non-nutritive substances and decreased intake of macro- and micronutrients. Most of these differences were statistically significant.

Table 19. Characteristics of acute admissions for pancreatitis, Cairns Base Hospital, 2004 - 2007.

Total cases (n)	*153*
Mean age (years)	44.7
Males (*n*)	94 (61.4%)
Indigenous Australians (*n*)	63 (41.2%)
Alcohol aetiology (*n*)	83 (54.3%)
Severe acute pancreatitis (*n*)	17 (11.2%)
Chronic pancreatitis (*n*)	83 (54.3%)

Table 20. Characteristics of study sample by chronic pancreatitis status (n = 137).

	CP absent	CP present	*p* value
Sociodemographics			
Age, years	46.0	43.4	0.2887
Male sex, %	47.9	72.9	0.0014
Indigenous, %	33.8	45.9	0.1257
Body Mass Index, kg/m^2	27.3	23.8	0.0002
Non-nutrient intakes			
Current smoker, %	48.4	73.9	0.0016
Cigarettes/day	8.9	15.6	0.0005
Cigarette-years	10.5	500	0.0000
7-day alcohol intake, g/week*	30	80	0.5725
Average alcohol intake, g/week*	25	80	0.2858
Coffee intake, cups/day	0.45	0.94	0.0411
Macronutrient intakes			
Energy intake, kJ	5713	4211	0.0095
Fat intake, g/day*	48.0	24.5	0.0021
Carbohydrate intake, g/day	115.8	89.1	0.0379
Protein intake, g/day	59.6	45.9	0.0323
Micronutrient intakes			
Folate, µg/day*	145.7	98.7	0.0174
Vitamin A, µg/day*	445.6	278.0	0.0699
Vitamin C, mg/day*	35.4	25.3	0.1367

When the intake behaviours of individual nutrients or substances were adjusted for covariates deemed to be of significance or interest by univariate analysis (Table 21), none showed significant associations with chronic pancreatitis, or with any appreciable effect size.

Table 21. Association of intake items with chronic pancreatitis, adjusted for sex, indigenous status, and BMI.

Variable	IRR	95% CI
Male sex	1.42	0.997 – 2.036
Indigenous	1.25	0.923 – 1.716
Body Mass Index	0.96	0.933 – 0.995
7-day alcohol	0.99	0.998 – 1.000
Cigarettes/day	1.01	0.999 – 1.000
kJ/24h	0.99	0.999 – 1.028
Fat/24h	0.99	0.978 – 0.998
Protein/24h	1.01	0.999 – 1.011
Carbohydrate/24h	0.99	0.997 – 1.003
Folate/24h	0.99	0.998 – 1.000
Vitamin A/24h	0.99	0.999 – 1.000
Vitamin C/24h	1.00	0.998 – 1.003
Coffee/24h	1.08	0.999 – 1.176

For the variables selected for PCA, the calculated Kaiser-Meyer-Olkin statistic was 0.73, indicating reasonable sampling adequacy of the data. Bartlett's test of sphericity also yielded a p-value of less than 0.0001, confirming appropriateness of the model. Three factors were isolated with an eigenvalue greater than one. These accounted for 68.9% of the total variance in the data. Following oblique rotation (Table 22), the three factors could be functionally interpreted as "nutritive" (strong positive loadings on all macro-and micronutrient groups), "stimulant" (strong positive loadings on daily tobacco and coffee intake; also a moderate negative loading on 7-day alcohol intake), and "abusive" (strong positive loadings on daily tobacco and 7-day alcohol intake).

Table 22. Loading scores derived from principal component analysis of non-nutritive, macro- and micronutrient intake behaviours.

	Component 1 "Nutritive"	Component 2 "Stimulant"	Component 3 "Abusive"
Total energy	**0.8369***	-0.0413	0.1068
Carbohydrates	**0.7844**	0.1300	-0.1200
Fat	**0.8523**	-0.1341	0.0944
Protein	**0.8026**	-0.1661	0.1658
Folate	**0.7014**	0.1674	-0.1036
Vitamin A	**0.6995**	0.0461	0.0187
Vitamin C	**0.6918**	-0.0455	-0.0265
Alcohol	-0.1482	-0.3896	**0.7520**
Cigarettes	-0.0330	**0.5893**	**0.6046**
Coffee	0.0292	**0.8136**	0.0150

* Bold type denotes significant factor loading scores within the listed components.

When the three chosen intake patterns were re-inserted into an adjusted multiple logistic regression model (Table 23), the "nutritive" pattern showed a significant inverse association with chronic pancreatitis and the "stimulant" pattern a significant positive one.

Table 23. Associations of selected principal components with chronic pancreatitis, adjusted for sex, Indigenous status, and BMI.

Variable	**IRR**	**95% CI**
Male sex	1.38	0.95 – 2.00
Indigenous	1.43	1.04 – 1.98
BMI	0.96	0.93 – 0.99
"Nutritive" pattern	0.83	0.71 – 0.97
"Stimulant" pattern	1.16	1.05 – 1.29
"Abusive" pattern	0.97	0.82 – 1.14

5.5 Discussion

Because of the temporality of the key covariates measured, this study specifically aimed to demonstrate associations with acute exacerbations occurring on a background of chronic pancreatitis, rather than the evolution of chronic pancreatitis *per se*. Based on the multiple logistic regression analysis with principal components, it would thus appear that

in the period preceding an attack of acute pancreatitis, patients with underlying chronic pancreatitis are more likely to forego nutrient-based intake in favour of non-nutritive substances (coffee and tobacco). Although suggestive of typical “binge” behaviour, these associations seem to be independent of alcohol intake. Moreover, it is counterintuitive that there should be no significant difference between the median recent alcohol intakes of those with underlying chronic pancreatitis and those with a purely acute episode. This may be due to those with chronic pancreatitis decreasing their alcohol consumption over time, as a result of medical advice and conditioning by symptoms. It is likely that those with alcohol-related chronic pancreatitis had higher alcohol consumption in the past, and also over a longer period of time, when compared to those with purely acute pancreatitis.

It is well recognized that acute exacerbations of chronic pancreatitis attributed to alcohol can occur in periods of abstinence or low intake. If considered from a broader perspective over a longer timeframe, it could be hypothesised that a behavioural pattern of intermittent nutrient deprivation and substance excess that leads to acute exacerbations of pancreatitis are in keeping with the repeated insults that constitute the pathogenesis of chronic pancreatitis, or the so-called necrosis-fibrosis sequence [198]. Thus while alcohol may have been the initial noxious stimulus, various other substances through their excess or deficiency may sustain ongoing oxidative stress. Indeed smoking has previously been implicated as an independent co-factor in the pathogenesis of chronic pancreatitis [125, 145, 231-234].

This study is the first attempt to apply pattern analysis techniques to elicit associations of nutrient and other substance intakes with chronic pancreatitis. Since it was first described by Karl Pearson in 1901 [235], principal components analysis has been applied in

disciplines as diverse as engineering [236], chemistry [237] and psychology [238], as a means of identifying underlying constructs that explain the correlations among a set of items. It basically aims to reduce a larger set of difficult-to-interpret variables to a smaller set, known as factors or components. The use of pattern analysis in nutritional epidemiology has been in the literature since the 1980s [239]. Traditional regression models applied to complex data like self-reported nutrient intake have been inadequate to reveal underlying patterns of consumption for individuals and groups. Dietary intake is complex and isolated foods, nutrients and behaviours may not capture the interactions between foods, nutrients, and non-nutrient components of diet, as well as patterns of behaviour such as dietary habits. Rather than examining individual nutrients or foods, PCA considers the effects of overall diet. Dietary patterns represent a broader and more realistic picture of food and nutrient consumption, and may thus be more predictive of disease risk than individual foods or nutrients [240]. Studies have been published on the application of PCA to dietary intakes in studies where the outcome variable was cardiovascular disease [223, 241], metabolic syndrome [224][33] and cancer [222].[34] For the current study, additional meaning has been conferred by including so-called non-nutritive intake behaviours in the pattern analysis.

Although the main aim of the analysis was to determine the effect of intake behaviours, the sociodemographic and anthropometric co-factors for which there was adjustment are also worthy of mention. Not surprisingly, BMI had a slight but significant negative association with chronic pancreatitis. Due to malabsorption and possibly other lifestyle factors, chronic pancreatitis patients are likely to have a lower BMI than those without chronic pancreatitis. Similarly, malabsorption and steatorrhoea in such cases might also

lead to an aversion to dietary fat intake, thereby in part explaining the association, in univariate analyses, between a lower BMI and fat intake with an increased risk of chronic pancreatitis. While sex revealed no particular association with chronic pancreatitis, indigenous status had a significantly positive association after adjustment for the various intake patterns. Intrinsic predisposition could be inferred, but the Australian Aboriginal people are a genetically diverse group. Other unmeasured confounders may need to be sought.

If accepting that no direct inferences can be drawn regarding the pathogenesis of chronic pancreatitis *per se*, certain other limitations of the study should also be acknowledged. Firstly, the case definition of the outcome variable is not the accepted gold standard. The hallmark of chronic pancreatitis is fibrosis and acinar atrophy, which can only be diagnosed by biopsy [161]. Given the impracticality of this in a clinical setting, a number of other functional or morphological tests can be used a proxy measures, although their universal application is once again unfeasible in the context of opportunistic case recruitment. Chronic pancreatitis is a disease process with a variety of clinical manifestations and pathogenetic pathways. The use of a novel composite case definition based on sound clinical, functional and morphological criteria was felt to be a suitable compromise in order to optimize statistical power. It has precedents in the case definition of acute pancreatitis [24] and other chronic conditions [242], and is readily applicable in the clinical setting. Application to other clinical research on chronic pancreatitis would provide further validation.

Secondly, the explanatory intake behaviours were all measured by retrospective self-reporting. This may be a source of bias, particularly with respect to alcohol intake, which

could be construed as under-reported by those with an abusive behaviour pattern or with pancreatitis attributed to alcohol. The literature nevertheless suggests that that self-report questionnaires of alcohol intake are often accurate [243], particularly when details are obtained regarding amount, frequency and type of beverages [140]. This is countered by the fact that those with clinically deemed alcohol-related pancreatitis reported significantly higher median 7-day and average weekly alcohol intakes compared to those whose pancreatitis was attributed to other aetiologies. Although dietary recall was specified as being prior to the onset of acute symptoms, the possibility of intake modifications as a pre-conditioned response to more subtle prodromal symptoms cannot be discounted. This may be particularly the case for those with a prior history of acute attacks – approximately 24.5% of the whole cohort or 45.2% of those with a diagnosis of chronic pancreatitis.

Furthermore, in an attempt to optimize reporting accuracy, most of the intake variables were measured immediately prior to the acute episode. They therefore only represent a snapshot in time, rather than being representative of a long-term behaviour pattern. Results must be interpreted with this in mind.

A third limitation of the study was the somewhat artificial decomposition of food intakes into macro- and micronutrients, in order to achieve comparability with previous nutritional research into pancreatitis. This is somewhat counter to the more inclusive philosophy of the subsequently utilized statistical technique of PCA. Future work may be better served, and more clinically relevant, if diet is considered in terms of more naturalistic food categories, rather than by molecular composition.

Finally, the study's relatively small sample size may limit its generalizability. Despite the logistic difficulties of prospective data collection in hospitalized cases of acute pancreatitis, it would nevertheless be worth aspiring to a larger, possibly multi-centre, study over a longer timeframe.

Despite the above limitations, this study has contributed new insights into a condition that does not readily lend itself to observational clinical research. As mentioned above, the diagnosis and management of chronic pancreatitis is often compromised in the acute setting. Thus any additional knowledge that better characterizes this group of patients will also serve to inform improved chronic disease management protocols. At the very least, this may involve actively advising against periods of nutrient withdrawal and minimization of tobacco and coffee intake, in order to reduce the risk of recurrent acute attacks and possible progression to the more end-stage manifestations of chronic pancreatitis.

Chapter 6

6. CLINICAL PREDICTORS OF SEVERE ACUTE PANCREATITIS

6.1 Abstract

Background: Research into clinical determinants of severe acute pancreatitis remains important for therapeutic and preventive purposes. To contribute to practical prognostication, this study aimed to define clinical risk factors for the development of severe acute pancreatitis.

Methods: As part of a prospective cohort study, using multiple logistic regression.153 cases of acute pancreatitis were recruited in a regional Australian hospital from March 2004 to July 2007. Data were collected regarding demographic and clinical characteristics. The main outcome measure was severe acute pancreatitis, as defined by composite consensus criteria. Multiple logistic regression was used to identify significant associations.

Results: After adjustment for potential confounders, there was a significant positive association with waist circumference and a negative association with current smoking status.

Conclusions: The study confirms other work suggesting central adiposity as a risk factor for severe acute pancreatitis. The finding of a possible protective effect for smoking merits further confirmatory research.

6.2 Introduction

Severe acute pancreatitis (SAP) accounts for up to 20 to 30% of admissions for acute pancreatitis.[7, 25] It has been defined by the Atlanta consensus statement of 1992 as the presence of organ failure (systolic blood pressure <90 mmHg, PaO_2 $\leq$60 mmHg, creatinine >2.0 mg/L after rehydration, or gastrointestinal bleeding >500 ml/24h) and/or local complications (necrosis, abscess, or pseudocyst).[15] The actual severity must however be distinguished from the predicted severity of acute pancreatitis. Such prognostication has long been an important clinical objective, as failure to pre-emptively manage severe acute pancreatitis has been shown to result in increased case fatality.[23, 244] Not only does it serve the purpose of determining which patients require more intensive support, but in some instances may also provide insight into the pathophysiology of the severe inflammatory response syndrome (SIRS), which may in turn lead to the development of targeted therapies.

Various sets of evidence-based practice guidelines recommend that all acute pancreatitis admissions should undergo severity prognostication,[23, 25, 245] although they are less prescriptive about the means by which this should be done. In the clinical setting, composites of physiological parameters such as the Ranson [120, 246] and Glasgow [116,

247] scores are the traditionally accepted means of predicting severity in cases of acute pancreatitis. However, in practice, compliance is hampered by the fact that often not all parameters are routinely measured, and a complete score may take up to 48 hours to be calculated. In addition, a meta-analysis of 110 studies showed that the Ranson score had relatively poor predictive power.[248] In many cases, clinicians tend to rely on a single observation. This may involve a biological marker such as C-reactive protein (CRP),[136] procalcitonin,[136] haemoconcentration,[249] blood glucose,[158] serum creatinine,[158] and even serum lipase.[158]

Despite this, a considerable proportion of experienced physicians admit to simply relying on their intuitive clinical impression.[250] Certain isolated clinical findings may nevertheless assist prognostication by augmenting the so-called "view from the end of the bed". Of these, obesity as a predictor of progression to severe manifestations has been validated by animal and human studies in recent years.[251-254] As well as its use in composite scoring systems, older age (eg. >55 years) has also been demonstrated to be independently predictive of severe complications.[116, 255] While this may be a function of confounding co-morbid disease, little work has actually been done on the impact of specific underlying chronic conditions. Failure in various single organ systems on admission may be defining criteria for severe acute pancreatitis as well as predictors of subsequent multiple organ failure and case fatality.[256-262] By contrast, certain morphological hallmarks of actual severity such as necrosis and pseudocyst formation are not necessarily associated with organ failure or subsequent mortality,[255, 256] implying

that these two categories of severity manifestation should be considered separately in any observational or interventional studies.

To contribute to ongoing discourse around practical prognostication, this study has aimed to define clinical risk factors for the development of severe acute pancreatitis in a regional Australian hospital population.

6.3 Methods

Hospitalizations for acute pancreatitis were consecutively recruited between March 2004 and July 2007 at Cairns Base Hospital in Far North Queensland, Australia. This tertiary referral institution drains a population of over 200,000 people, approximately 15.5% of whom identify as Aboriginal or Torres Strait Islander.[160]

Acute pancreatitis was defined as acute onset of typical epigastric pain in conjunction with elevated serum lipase or characteristic appearances on medical imaging.[24] Severe acute pancreatitis was defined by the so-called Atlanta criteria[15] as organ failure (with specified physiological thresholds) and/or local complications (such as necrosis, abscess or pseudocyst).

A variety of possible explanatory variables were collected on initial presentation and during the subsequent episode of care. These included demographic characteristics, aetiology of pancreatitis, co-morbidities, and recent dietary intakes. The latter were

obtained by asking patients what food and beverages they had consumed in the 24 hours prior to symptom onset. The macro- and micronutrient composition was calculated using FoodWorks 2007© version 5 (Xyris Software Pty. Ltd., Highgate Hill, Queensland, Australia). Alcohol intake was measured by a self-reported beverage-specific 7-day recall. Smoking was described in terms of both currency (ie. current smoker or non-smoker, or cigarettes per day) and cumulative dose (duration of smoking). Adiposity was measured as body mass index (BMI), waist circumference (WC) and waist-to-hips ratio (WHR). A patient was considered to have co-existing chronic pancreatitis if at least one of the following criteria were fulfilled: four or more previous admissions for acute pancreatitis, a history of continuous or recurrent consistent epigastric pain, malabsorption (steatorrhoea), radiological abnormalities (calculi, parenchymal atrophy, ductal dilatation, non-acute pseudocysts), and faecal elastase-1 concentration ([FE-1]) less than 200µg/g where the acute attack was not severe.[64, 218]

Data were checked and entered into EpiData (www.epidata.dk), then exported to STATA™ version 12.1 (StataCorp, Texas, USA, 1985-2011) for statistical analysis. Univariate comparisons were conducted using Pearson's chi-squared for categorical variables, Student's t-test for parametric continuous variables, and the Mann-Whitney test for non-parametric continuous variables. Multiple logistic regression was performed on variables that were selected purposively on the basis of statistical significance, physiological plausibility and clinical interpretability. Where statistically significant variables described the same characteristic, only one was selected in order to achieve a suitably parsimonious model. A Poisson distribution of the outcome variable was

assumed, with robust estimates to control for potential overestimation of errors in binomial data.[221] Effect size was expressed as incidence rate ratios (IRR) with 95% confidence interval (CI). Only cases with a complete set of variables were included in the analysis.

The proportion of variability in the dependent variable accounted for by the covariates was expressed in terms of the pseudo-R^2, which is a modification of the coefficient of variation for the purposes of logistic regression.[263] In terms of predicting outcome, the efficacy of the model was assessed by the Hosmer-Lemeshow test for goodness of fit.[264]

The study was approved by the Human Research Ethics Committees of the Cairns Health Service District and James Cook University. Written informed consent was obtained from recruited patients or their delegates.

6.4 Results

During the study period, there were 153 admissions for acute pancreatitis, of which 17 (11.2%) developed severe acute pancreatitis by the Atlanta criteria.[15] Of these, 4 cases (23.5%) died during the course of their hospital stay. Indigenous patients comprised 41.2% (n = 63) of the whole cohort. Eighty-three cases (54.3%) were deemed to have underlying chronic pancreatitis based on a composite of morphological, functional and

clinical criteria. The aetiology of acute pancreatitis was attributed to alcohol in 54.4% of admissions (n = 80).

Univariate comparisons of the various potential determinants of severe acute pancreatitis for cases with complete data sets are shown in Table 24. Statistically significant positive associations with SAP were age, waist circumference and waist-to-hip ratio. Significant negative associations were alcoholic aetiology and measures of current tobacco intake. Of note were non-significant associations with duration of smoking and BMI.

Table 24. Characteristics of cohort according to severity of acute pancreatitis. (n = 137)

Variable	Mild acute pancreatitis	Severe acute pancreatitis	P-value
Age (years)	43.5	55.7	0.002*
Sex (male)	60.0%	70.6%	0.399**
Indigenous	43.0%	29.4%	0.285**
Alcoholic aetiology	57.6%	26.7%	0.023**
7-day alcohol	4.3	6.0	0.650†
Diabetic	17.2%	17.6%	0.960**
BMI	25.1	26.9	0.253*
Waist circumference (cm)	92.6	103.3	0.003*
Waist:hip ratio	0.9	1.0	0.007†
Cigarettes / day	15	0	0.001†
Smoking duration (years)	18.7	16.6	0.564*
Current smokers	68.5%	20.0%	0.0002**
Chronic pancreatitis	53.0%	40.0%	0.339**
Red cell folate (n = 79)	928.0	919.3	0.940*
24-hr folate	129.5	126.2	0.955†
24-hr vit. A	316.8	341.3	0.909†
24-hr vit. C	28.4	28.1	0.584†
24-hr kJ	4831.1	4434.2	0.682*
24-hr fat	30.0	35.5	0.504†
24-hr protein	47.0	46.0	0.851†

* 2-sample t-test with equal variances

** 2-sample test of proportion

† 2-sample Wilcoxon rank-sum (Mann-Whitney) test

Following multivariate adjustment for age, indigenous status, alcohol aetiology and the presence of underlying chronic pancreatitis, a statistically significant positive association was demonstrated with SAP for waist circumference (IRR 1.04, 95% CI 1.01 – 1.07) and a negative association with smoking status (IRR 0.14, 95% CI 0.03 – 0.80) (Table 25). The pseudo-R^2 of the model was 0.21, suggesting that the selected variables accounted reasonably well for the outcome (ie. 21% of the variance). Similarly, goodness-of-fit testing yielded a p-value of 1.000.

Table 25. Multiple logistic regression for clinical characteristics associated with severe acute pancreatitis, adjusted for age, Indigenous status, aetiology and chronic pancreatitis.

Variable	**IRR**	**95% CI**
Waist Circumference (cm)	1.04	1.01 – 1.07
Current smoking	0.14	0.03 – 0.80
Age (years)	1.01	0.98 – 1.04
Indigenous	1.17	0.33 – 4.19
Alcoholic aetiology	0.76	0.28 – 2.04
Underlying chronic pancreatitis	1.36	0.56 – 3.32

6.5 Discussion

Prediction of severity in acute pancreatitis remains an ongoing focus of enquiry. The holy grail of a single accurate prognosticator remains elusive, and it is generally assumed that “a combination of relevant markers, rather than a single predictor, will be needed to confirm the diagnosis, predict severity, monitor progress, and guide therapy of pancreatitis”.[265] Of the various prognostic systems and biological markers currently in use, none is ideal in the evaluation of individual patients.[18] While it is recognized that “bedside” impression is a poor predictor,[18, 266-268] and that nonetheless many clinicians admit to relying on this,[250] it is unclear how this process is actually defined, and indeed if any single definition can be applied to what would be otherwise considered “clinical judgement”. It may simply mean that a clinician is basing opinion on a set of objective observations other than those obtained from laboratory or medical imaging data. This being the case, it is reasonable to assume that any additional information in the form of anthropometric measurements or recent substance history may be useful adjuncts to a clinically based predictive algorithm. Information on a patient’s obesity indices and smoking status could therefore be incorporated, along with other clinically acquired variables, into a stepwise logistic regression model [269] or an artificial neural network, [270] in order to predict an individual’s progression to severe disease.[18]

Because of the directionality of data collection, it could be assumed that the associations between central adiposity and smoking status, and severe acute pancreatitis, may be

causal. Causal inference should nevertheless be reinforced by additional observational evidence as well as pathophysiological plausibility.

For some time, obesity has been known to be a risk factor or predictor for severe acute pancreatitis. This association was originally expressed in terms of body mass index (BMI).[251] Similar to the subsequent 2002 study by Mery et al,[253] the current study found that it is specifically an android fat distribution that favours the evolution of a more severe inflammatory response. It is thought to do this by two possible mechanisms. Firstly, increased intra-abdominal or peri-visceral fat provides greater substrate for locally activated digestive enzymes,[253] leading to a higher likelihood of severe local complications, such as necrosis, haemorrhage and pseudocyst formation. Secondly, central adiposity is of itself a pro-inflammatory state, which may exert a pre-conditioning effect on the systemic inflammatory response triggered by acute pancreatitis.[253] In a case-comparison study, Sempere et al[271] demonstrated raised levels of inflammatory mediators in obese patients with acute pancreatitis, who also had an increased incidence of severe manifestations. Moreover, severe acute pancreatitis has been shown to be related to an efflux of specifically fat-associated cytokines or adipokines.[272]

In the case of smoking, the inverse relationship with severe acute pancreatitis has no apparent precedent in the literature, but there is a recognized body of evidence implicating smoking in a dose-dependent manner with the pathogenesis of pancreatitis *ab initio*.[41] Retrospective or case-control studies have traditionally associated cumulative tobacco smoking with chronic pancreatitis,[125, 145, 232, 234] although not all studies

have shown a positive association.[231, 273] More recently, smoking has been implicated as an independent aetiological factor in acute pancreatitis. Lindkvist et al[40] demonstrated a statistically significant dose-dependent relationship between baseline cigarette consumption and the subsequent occurrence of a first attack of acute pancreatitis. Causal inference was slightly compromised in that study by the lack of information on changes in tobacco intake in the interval between initial data collection and disease outcome.[146] In an extensive prospective cohort study, Morton et al[233] had previously shown a positive association between smoking and attacks of acute pancreatitis, but only in cases that were deemed to be alcohol-associated or idiopathic.

No other observational studies have described the moderating effect of smoking on the acute inflammatory response in acute pancreatitis. Evidence does exist however for other inflammatory or degenerative conditions. Using total joint replacement as a proxy for major osteoarthritis, Mnatzaganian et al[274] have demonstrated a dose-response inverse relationship with duration of smoking, in keeping with earlier studies.[275-278] An *in vitro* study has suggested that these observations may be explained by nicotine-mediated stimulation of chondrocyte anabolic activity.[279] Similarly, smoking cessation has been shown to worsen the clinical course of ulcerative colitis[280] and controlled trials suggest that nicotine therapy is effective in the attenuation of acute exacerbations.[281] Based on initial clinical observations, there has also been some evidence that oral or topical nicotine therapy is effective in the treatment of aphthous ulcers of the mouth.[282, 283]

Regarding biological plausibility in the case of acute pancreatitis, Wang et al[284] have described a nicotinic acetylcholine receptor alpha7 subunit that is essential for inhibiting cytokine synthesis by the vagally mediated so-called cholinergic anti-inflammatory pathway. The implication is that stimulation of specific nicotinic receptors on macrophages (by nicotine) may lead to reduced output of tumour necrosis factor and other inflammatory mediators in response to the noxious stimulus of acute pancreatitis. Furthermore, while cigarette smoke contains hundreds of chemical compounds with various mechanisms of toxicity,[285, 286] the significant association for variables reflecting currency of smoking rather than duration of exposure, would suggest the effect of a relatively short-acting or non-cumulative attenuating agent, such as nicotine.

This observational study had certain strengths, particularly pertaining to its prospective data collection and forward directionality. The former assured detailed and standardised recording of independent and dependent variables. The latter meant that by measuring exposure variables prior to the onset of the outcome of interest, some degree of causality can be inferred for covariates showing significant association. Furthermore, the multivariable analysis enabled adjustment for a number of potential confounders. For example, underlying chronic pancreatitis, which was quite prevalent within the cohort (54.3% or 83 cases), may have exerted a confounding effect due to it being a possible consequence of some of the other explanatory variables (such as smoking), and because the associated fibrosis and acinar cell loss may ostensibly lead to there being less

parenchymal substrate available to produce a severe inflammatory response. Despite this, both central adiposity and smoking yielded independently significant associations.

The study also had a number of weaknesses. The outcome variable was measured according to the composite Atlanta definition[15] in order to maximize numbers and thus increase the likelihood of significant statistical inference. However, the specific defining criteria for SAP represent a number of distinct pathological processes. Ignoring these sacrifices information regarding the pathogenetic mechanisms of the proposed clinical predictors. Indeed to simply define acute pancreatitis as “mild” and “severe” may be somewhat limiting. In a meta-analysis of 1478 cases, Petrov et al[287] showed that two of the principle SAP-defining criteria, organ failure and infected pancreatic necrosis, were independently predictive of severe disease and potentiated each other when both present. In addition, organ failure persisting for more than 48 hours has been shown to be associated with increased mortality.[258, 261] This further led to the proposal that four categories of severity (mild, moderate, severe and critical) may be more clinically meaningful.[19] It would therefore be worthwhile to evaluate the suggested clinical predictors against such a classification, but greater case numbers would be required.

Also regarding the outcome variable, the proportion of hospitalized cases that developed SAP was relatively low compared to similar series.[253, 255, 270, 288] This may have been because, unlike those studies, this study did not exclude recurrent cases or those with suspected underlying chronic pancreatitis. The case definition was still that of acute pancreatitis based on the accepted biochemical, morphological and clinical parameters. It

was considered reasonable to include cases with recurrent or chronic disease, as such patients in the clinical setting can nevertheless develop manifestations of SAP requiring the same management as those with *de novo* disease. Indeed, four of the patients with evidence of co-existing chronic pancreatitis (6%) developed SAP during their admission. Case ascertainment for SAP may have also been selective or skewed. For example, a certain number of fatal cases may have been admitted directly to the Intensive Care Unit and missed by the standard recruitment methods. The impact of this, however, is likely to be minimal as such cases would have been nominally under the care of a surgical unit. Those cases that died prior to presentation to hospital, which may account for up to one-third of deaths in some series,[96] were considered beyond the scope of this study.

Limitations may have also existed in the ascertainment of covariates. The self-reporting of some of these may have led to information bias, although methodological studies have suggested that self-reporting is usually a valid measure of alcohol intake, even for alcoholics.[243] In the case of smoking, the assumption of under-reporting may only serve to increase the likelihood and magnitude of an inverse association with SAP. Evidence suggests that Indigenous and European Australians differ significantly with respect to body fat distribution and fat mass for a given body weight or BMI.[157] Because of this, it was deemed necessary to adjust for Indigenous status in the multivariable model. However, to assume Indigenous status to be a dichotomous variable for statistical economy may not represent the anthropometric and genetic heterogeneity within both populations. A greater sample size may have afforded more detailed stratification.

6.6 Conclusion

This prospective cohort study has revealed two clinical associations that potentially contribute to the ongoing discourse on the prognostication, pathogenesis and treatment of SAP. Ongoing and more detailed observational data collection may be required to consolidate these inferences, particularly in the case of the negative association with smoking. Nevertheless, some degree of practical application may already be feasible in terms of encouraging more focused ascertainment of proposed determinants, as well as augmenting the predictive value of initial clinical impression.

In addition, a number of specific potential applications to clinical practice can be drawn from the study:

- While most patients are routinely weighed on admission to hospital, other anthropometric measurements are rarely obtained. This study suggests that useful prognostic information can be derived from the simple measurement of waist and hip circumference. Such collected information may also provide a valuable resource for other studies looking at outcome determinants for diseases other than acute pancreatitis.
- Although information on a patient's smoking history is usually obtained on admission to hospital, this is often not standardised. When done, it often takes the form of "pack-years" or cumulative dosage, which is certainly relevant as a determinant of malignant or degenerative conditions. This study also indicates

that simply asking about current smoking behaviour may give insight into the outcome of certain acute disease processes.

- Based on the hypothesis that the apparent attenuating effect of smoking on severe acute pancreatitis is due to circulating nicotine levels, the possibility arises of a randomised controlled trial of nicotine therapy administered at the time of admission. Multiple centres would be required to achieve statistical power and to allow for various stratifications.

Chapter 7

7. CASE STUDIES IN PANCREATITIS

The following case studies, accrued as part of the prospective cohort, represent extreme ends of a pathological continuum. They are presented as individual examples of how admissions for acute pancreatitis can evolve into a chronic disease process. Lesser degrees of such pathology may be evidenced elsewhere within the Far North Queensland cohort.

7.1 Case 1

This Aboriginal man presented in 1996, then aged 37 years, with a three-day history of epigastric pain and nausea. He had recently consumed two casks of wine and a half carton of beer over a two-day period. He had experienced no previous similar episodes, and had no other medical or surgical history of note. On examination, he was afebrile and vital signs were within normal limits. There was tenderness to palpation across the upper abdomen. Blood tests revealed a serum amylase level of 1543 IU/L (reference range: 44-128). A diagnosis of acute alcohol-related pancreatitis was made. Symptoms resolved after two days of conservative management, consisting of nil-by-mouth, intravenous fluids and analgesia.

In 1999, the patient was admitted with another episode of epigastric pain following an alcohol binge. Since the initial presentation in 1996, he had had eight recorded hospital admissions for acute pancreatitis, and reported episodes of lesser pain between admissions. On this occasion, serum amylase on admission was 523 IU/L (reference range: 44-128), once again confirming an attack of acute pancreatitis. Symptoms once again resolved with conservative management, and the patient self-discharged after 24 hours.

By January 2005, the patient was experiencing continuous epigastric pain and was narcotic-dependent. He had ceased alcohol intake in 2003. On this occasion, he was admitted for pain management. A previous attempt to endoscopically stent a stricture in the main pancreatic duct, thought to be contributing to his pain, was unsuccessful. A stricture in the distal common bile duct had however been stented using endoscopy, resulting in a normalization of his liver function tests, but no improvement in the pain. He had been an insulin-dependent diabetic since 2004, and had also been commenced on pancreatic enzyme supplementation for symptomatic malabsorption. The latter was confirmed by a faecal elastase-1 concentration of 50μg/g, which is indicative of severe pancreatic exocrine insufficiency. A computed tomography scan of the abdomen revealed foci of calcification within the pancreas, as well as a tortuous dilated main pancreatic duct and atrophic parenchyma. (see Figure 5)

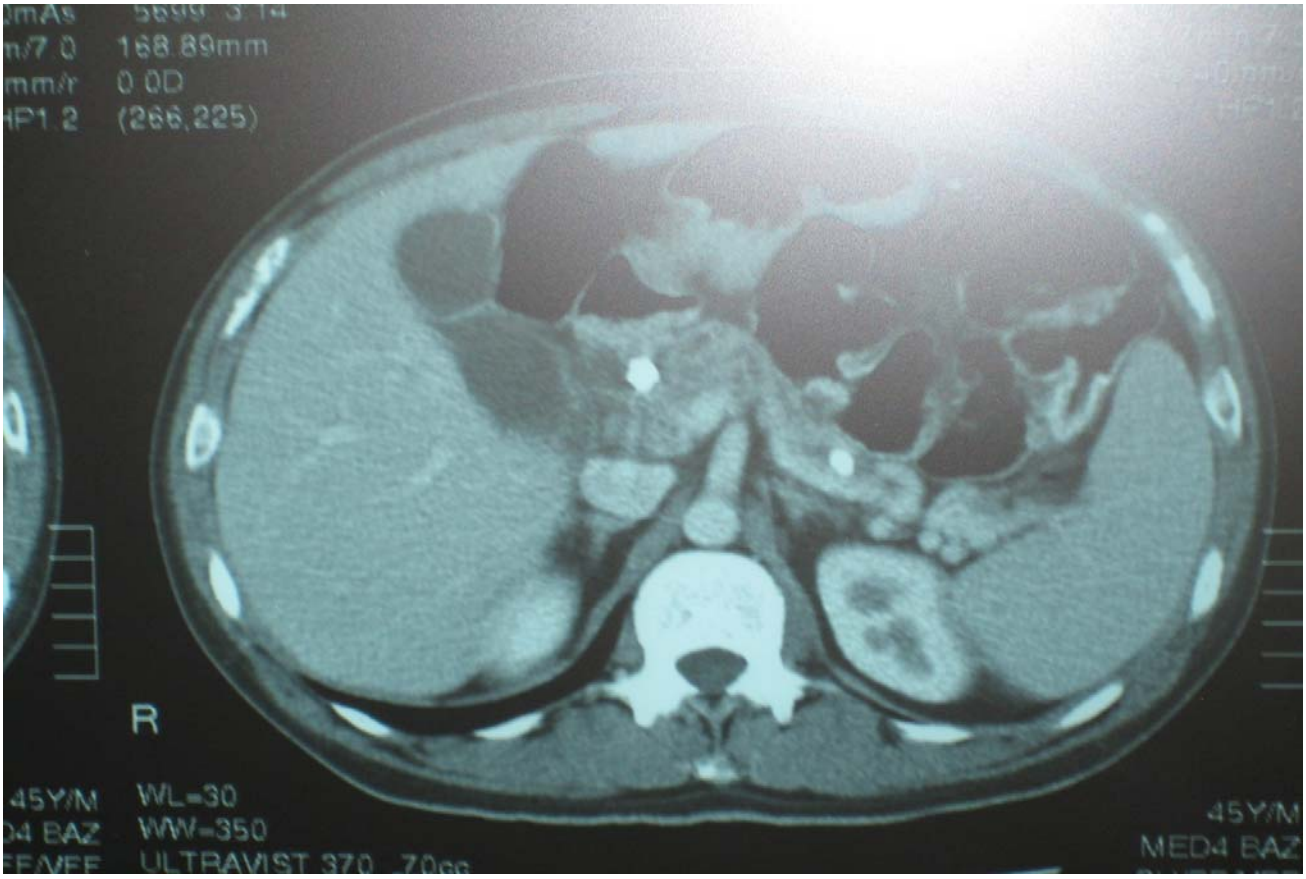


Figure 5. CT scan illustrating chronic pancreatitis with parenchymal atrophy, intraductal calculi, and main duct dilatation.

Given that all lesser therapeutic options had been exhausted, the patient underwent a pancreaticoduodenectomy (Whipple's operation) in February 2005. Due to the fact that there was minimal pancreatic exocrine function, no attempt was made to perform a pancreatico-jejunal anastomosis, rather choosing to definitively oversew the distal stump of pancreatic tail. The postoperative course necessitated gradual withdrawal of narcotic medications, but was otherwise uneventful.

When seen for follow-up in August 2005, the patient stated that he only experienced occasional epigastric pains and had a minimal analgesic requirement. He remained on

insulin and pancreatic enzyme supplements. Predictably, a measurement of faecal elastase-1 concentration was 0μg/g. His weight was stable and there was no evidence of steatorrhoea.

This patient's history is a typical example of alcohol-induced chronic pancreatitis. The trajectory is one of recurrent acute attacks that gradually decrease in frequency as chronic continuous pain supervenes. Malabsorption, as evidenced by steatorrhoea and weight loss, then manifests, followed by eventual pancreatic endocrine failure necessitating insulin replacement therapy. Although typically the pain of chronic pancreatitis has often abated by the time malabsorption and diabetes occur, this was not the case here. Although still incompletely understood, pain in chronic pancreatitis may be due to ductal obstruction or neural inflammation [289], with both of these mechanisms informing the nature of surgical interventions on the relatively infrequent occasions that these become necessary. The Puestow operation involves drainage of the main pancreatic duct by a lateral pancreaticojejunostomy [290]. Beger's duodenum-preserving pancreatic head resection [291] and Frey's local resection of pancreatic head with longitudinal pancreaticojejunostomy [292] combine drainage with resection or debulking of the pancreatic head, while preserving the duodenum. However, for this patient, a full pancreaticoduodenectomy was considered necessary due to the presence of a distal common bile duct stricture [293]. From the unsuccessful stenting, it was also clear that relief of obstruction alone was insufficient to relieve pain.

Following surgery for chronic pancreatitis, the desired outcome of pain relief and cessation of narcotic dependence was achieved. As expected, exocrine and endocrine pancreatic insufficiency persisted, requiring ongoing chronic disease management.

7.2 Case 2

This 24-year-old woman of Torres Strait Islander origin was admitted to hospital in March 2005 with a two-day history of worsening upper abdominal pain radiating to the back and associated with nausea and vomiting. There was no significant past medical or surgical history. She was a non-smoker and drank alcohol only very occasionally. On admission, she was afebrile. Other vital signs were within normal limits. Abdominal palpation revealed tenderness and guarding in the epigastrium. A diagnosis of acute pancreatitis was confirmed by a serum lipase of 13 600 IU/L (8-78 IU/L). The serum total bilirubin was 60μmol/L (<25μmol/L), and the serum levels of all liver enzymes were slightly elevated. In order to establish the aetiology of the attack, an ultrasound scan of the upper abdomen was performed. This demonstrated multiple small gallstones in the gallbladder, but the biliary tree was not dilated.

The patient was treated with gut rest (nil-by-mouth), intravenous fluids and analgesia. Oral intake was reintroduced as the pain settled, and the episode of acute biliary pancreatitis resolved after three days, at which time the patient was discharged. To prevent further attacks of acute pancreatitis, it was planned to readmit her for a

laparoscopic cholecystectomy in the near future. The date for this was however postponed due to more urgent cases on the elective operation waiting list.

On the eve of her operation, the patient developed further abdominal pain. Serum lipase was measured at 8000 IU/L (8-78 IU/L), thus diagnosing acute pancreatitis once again. On this occasion, despite initial conservative management, she progressed to develop severe acute pancreatitis, as evidenced by respiratory failure and extensive peripheral oedema (due to falling serum albumin levels). This required admission to the Intensive Care Unit with endotracheal intubation and positive pressure ventilation. A computed tomography scan of the abdomen with intravenous contrast was taken to ascertain the state of the pancreas. This showed extensive necrosis. (see Figure 6) Because of the possible complication of infected necrosis, CT-guided fine needle aspiration of the non-enhancing pancreas was performed for microscopy and culture. However this proved to be sterile. Additional management included nasojejunal alimentation. Haemodialysis was not required. This total time of hospital admission on this occasion was seven weeks.

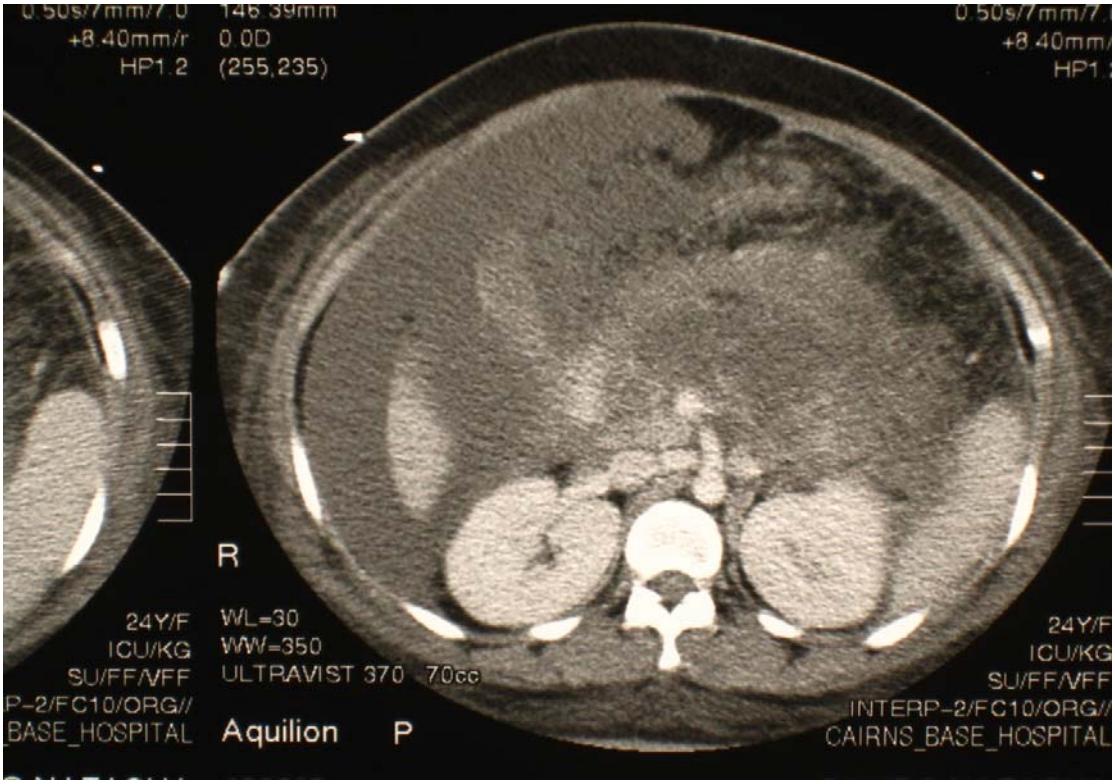


Figure 6. CT scan illustrating extensive pancreatic oedema and necrosis (non-enhancement with intravenous contrast) with peri-hepatic fluid collection.

In July 2005, the patient was seen as an outpatient, having had a follow-up abdominal CT scan. This revealed a moderately sized pancreatic pseudocyst in the lesser sac of the peritoneal cavity. (see Figure 7) At this time, the patient was complaining of a mild upper abdominal bloating sensation and early satiety. On abdominal palpation, there was minimal epigastric tenderness and the impression of a firm non-pulsatile mass. An open cholecystectomy and cystogastrostomy were performed in September 2005. The postoperative course was unremarkable.

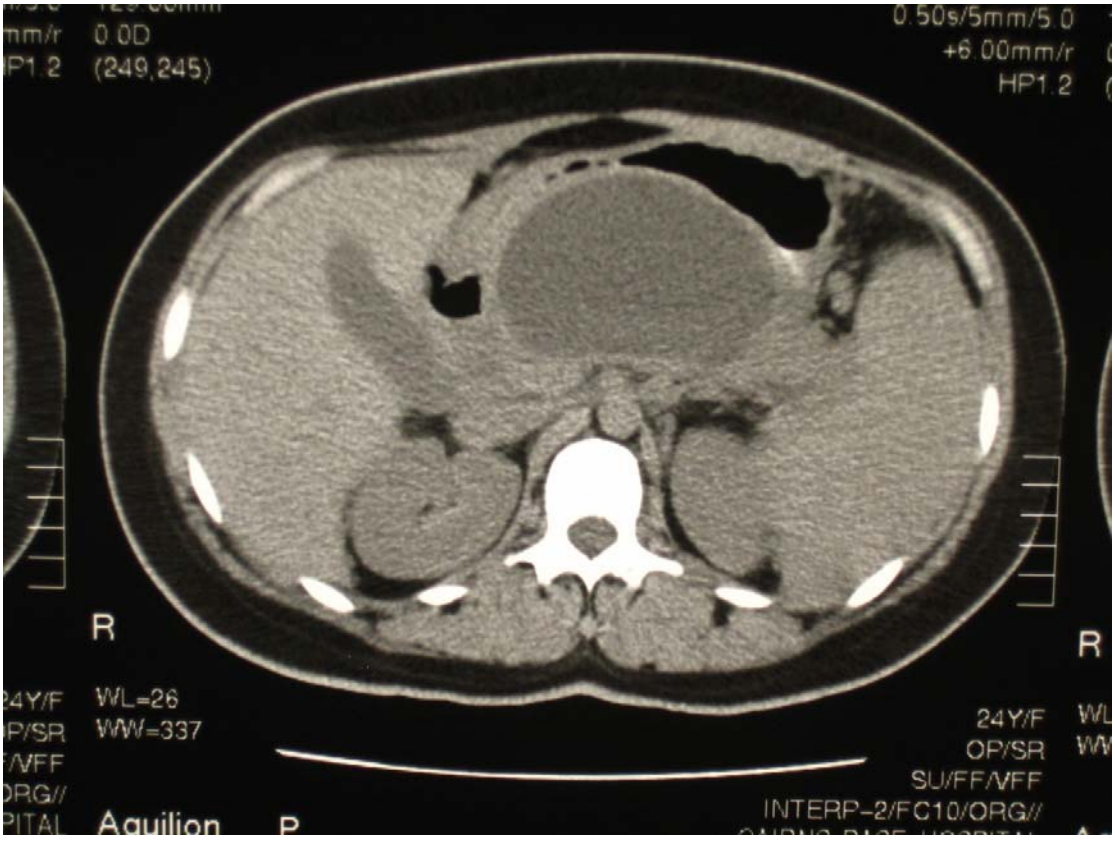


Figure 7. CT scan illustrating a pseudocyst in the lesser sac with overlying attenuated stomach.

When seen for follow-up in December 2005, the patient stated that she was feeling well. Periodic random blood glucose levels had been within normal limits. A recently measured faecal elastase-1 concentration was 210μg/g (<200 μg/g). Although this borders on the definition of exocrine insufficiency, she reported no symptoms of malabsorption.

This patient's story illustrates a typical course of severe acute pancreatitis with long-term sequelae. At least two salient points relevant to clinical management emerge. Firstly,

delaying cholecystectomy following acute biliary pancreatitis risks a further attack with more serious consequences. Various international consensus-based guidelines [24-26, 159] have recommended that after mild gallstone-associated acute pancreatitis, cholecystectomy should be performed as soon as the patient has recovered, and within the same hospital admission. It would appear that a number of human and systemic errors may have led to delayed operation in this case. Such an adverse outcome would be a worthy of a formal investigation process such as Root Cause Analysis [294].

Secondly, a severe attack of acute pancreatitis has ongoing consequences that merit follow-up, as would be indicated for a chronic disease process. In this case, it would be expected that there would be at least one return to a specialist clinic following discharge, given that pseudocyst is a well-recognised complication of necrotising pancreatitis warranting surgical treatment. However, less attention tends to be paid to longer term consequences for pancreatic function, in both the specialist and primary care settings. Although this patient would appear to be left with adequate endocrine and exocrine reserves, these are likely to be borderline at best, and may deteriorate more rapidly over time than would otherwise be the case. Regular monitoring would therefore be advisable. A retrospective cohort study from Sweden [94] showed that of those patients who survived severe acute pancreatitis (n=35), over half at long-term follow-up had either frank diabetes or impaired glucose tolerance, and one quarter had signs of severe exocrine dysfunction. In a smaller case-comparison study from the same institution [295], diabetes or impaired glucose tolerance were significantly more prevalent following a single episode of severe acute pancreatitis compared to mild acute pancreatitis.

However, there were no apparent differences in long-term exocrine function or overall quality of life. Such studies tend to be limited by cases numbers available for follow-up in single centres, and by the logistics of the follow-up itself. Ongoing studies in multiple sites and pooling of comparable data are desirable in order to provide generalizable evidence on which management guidelines can be based.

Chapter 8

8. TOWARDS A CHRONIC DISEASE MANAGEMENT PARADIGM FOR ACUTE PANCREATITIS

8.1 Abstract

Based on the example of a cohort of patients treated at a regional Australian hospital, it is evident that many incident acute pancreatitis cases merit consideration as a chronic disease process, for a number of reasons:

- A considerable proportion of acute cases harbour underlying pancreatitis.
- An attack of severe acute pancreatitis may lead to long-term structural or functional impairment.
- Following an attack of acute pancreatitis, risk factors or precursors of chronic pancreatitis or recurrent acute pancreatitis may persist.

As such, it is argued that cases of acute pancreatitis should by default be managed from the perspective of a chronic disease paradigm. A management strategy based on a prevention hierarchy is proposed.

8.2 Introduction: *Is acute pancreatitis necessarily an acute disease?*

Chronic disease has various possible definitions in the literature, mostly relating to duration of symptoms [296]. In the clinical setting a number of characteristics clearly distinguish it from the acute disease event. The Dictionary of Health Services Management [297] states that chronic diseases have one or more of the following characteristics: they are permanent, leave residual disability, are caused by non-reversible pathological alteration, require special training of the patient for rehabilitation, or may be expected to require a long period of supervision, observation, or care. According to the Australian National Health Priority Action Council (NHPAC) [298], a chronic disease is one that:

- has complex and multiple causes;
- usually has a gradual onset, although acute phases may also occur;
- occurs across the life cycle, but prevalence typically increases with age;
- may compromise quality of life through physical limitations and disability;
- is long-term and persistent, resulting in gradual deterioration of health; and
- is not immediately life-threatening but often a cause of premature mortality.

Cardiovascular disease, diabetes, arthritis and cancer are examples of chronic diseases that have gained particular public health priority in developed countries [1].

The Marseille-Rome consensus of 1988 classified pancreatitis as either acute or chronic, thereby eliminating the previously used, but somewhat confusing categories of acute relapsing and chronic relapsing [12]. Acute pancreatitis (AP) is due to acute

inflammation of the exocrine pancreas due to the inappropriate intraparenchymal activation of digestive enzymes [21]. The principal aetiological factors in most demographic settings are gallstones and alcohol [100]. In clinical terms, it is characterised by a rapid onset of typical epigastric pain in conjunction with elevated serum lipase and/or consistent appearances on medical imaging [24]. Chronic pancreatitis (CP), by contrast, involves a chronic inflammatory process with a variable but progressive course of fibrosis and loss of parenchyma [21]. The basic pathogenetic mechanism is considered to be the cumulative effect of successive acute insults, or the so-called necrosis-fibrosis sequence, on a background of oxidative stress [198]. In the Western world, the principal causative factor is alcohol [21], although various other effect modifiers such as smoking [40, 41], diet [119, 128] and genetic predisposition [299-301] are thought to play a part in its multifactorial aetiology. Clinical manifestations of chronic pancreatitis, which are variable in extent and time-course, are pain, malabsorption and diabetes. Chronic pancreatitis is also associated with an increased risk of pancreatic cancer [302, 303]. Diagnosis is a typically composite one, based on clinical history, morphologic abnormalities and functional impairment of exocrine and endocrine function [304]. From the preceding description, chronic pancreatitis *per se* would have most if not all of the characteristics of chronic disease as outlined by the NHPAC [298]. In addition, by virtue of the proposed necrosis-fibrosis hypothesis, acute pancreatitis can also be seen as at least a pathogenetic pathway to chronic pancreatitis in many cases. Indeed some authors consider even a first documented attack of alcohol-related acute pancreatitis to be a manifestation of a chronically diseased pancreas [305].

While Marseille-Rome's dichotomous classification of pancreatitis represents a biologically cogent argument, when taken within the everyday clinical context it is often left wanting. Dissatisfaction can be evidenced in the use of the term "acute-on-chronic pancreatitis", which is often accepted in colloquial clinical parlance and occasionally in published literature [306, 307]. According to the International Classification of Diseases Version 10 (ICD-10) [308], the frequently observed phenomenon of an episode of acute pancreatitis occurring in a patient with underlying chronic pancreatitis could be classified as K85 ("acute pancreatitis") but without a specific sub-classification to privilege the underlying chronic disease process; alternatively, it could be included under K86.1 ("other chronic pancreatitis"), which has provision for "recurrent" or "relapsing" chronic pancreatitis, although it is typically not the manifestations of chronic pancreatitis *per se* that are occurring at periodic intervals.

In essence, a considerable proportion of acute pancreatitis cases could also be considered in a broader therapeutic context as part of a chronic disease process, and thus amenable to more appropriate management strategies.

This chapter aims to further this argument with supporting data from a representative patient cohort, as well as other examples from the literature. Three discrete clinical scenarios will be presented whereby acute pancreatitis can be conceived as a chronic disease. Finally, a rationale will be given for the placement of pancreatitis, both acute and chronic, within a chronic disease therapeutic paradigm.

8.3 Methods and patients: *The clinicopathological characteristics of pancreatitis in Far North Queensland*

A prospective cohort study of hospitalizations in Cairns Base Hospital, the principal referral hospital for the region of Far North Queensland (FNQ), Australia was undertaken from March 2004 to July 2007. Cases were recruited if they fulfilled the diagnostic criteria for acute pancreatitis, namely acute onset of epigastric pain with an associated elevation in serum lipase [24].

At admission, data were collected from medical records and by facilitated questionnaire on a variety of potential explanatory variables including age, sex, indigenous status, aetiological attribution, alcohol, smoking, and diet. Outcome variables were length of hospital stay, actual severity as per the Atlanta criteria [15], and clinical, functional or morphological features consistent with chronic pancreatitis. For the latter, a diagnosis of underlying chronic pancreatitis was considered if one or more of the following were present: more than two previous (or subsequent) admissions for acute pancreatitis, chronic otherwise unexplained epigastric pain, steatorrhoea, otherwise unexplained weight loss. In addition, elastase-1 concentration ([FE-1]) was measured on the first available stool specimen following admission. Based on a previous efficacy study [218], a patient was considered to have pre-existing exocrine insufficiency if [FE-1] was less

than 200 µg/g and they were predicted not to have severe acute pancreatitis with a Ranson score of less than 3.

Data analysis was performed using STATA™ version 9.0 (StataCorp, Texas, USA). Descriptive data were presented as absolute counts, means or medians, and proportions. Where applicable, standard univariate tests of comparison and multiple logistic regression were employed. Additional inferences were drawn from the data using capture-recapture [176] and principal components analysis (PCA) [222]. Only complete datasets were considered for analysis.

Supporting literature was sought using PubMed, entering terms such as “chronic pancreatitis”, “severe acute pancreatitis”, “endocrine insufficiency”, and “exocrine insufficiency”. Representative articles were reviewed, and included for discussion if relevant.

Ethical approval for the study as a whole was granted by the Human Research Ethics Committees of the Cairns Health Service District and James Cook University.

8.4 Results: ***Reasons why acute pancreatitis may be considered a chronic disease.***

Over the 3.5-year study period, 153 cases were recruited for prospective data collection. By definition, all were of acute pancreatitis. Baseline characteristics are shown in Table 26.

Table 26. Demographic and aetiological characteristics of documented acute pancreatitis cases admitted to Cairns Base Hospital, 2004-2007.

Total cases (n)	153
Mean age (years)	44.7
Males (n)	94 (61.4%)
Indigenous Australians (n)	63 (41.2%)
Alcohol aetiology (n)	83 (56.9%)
Gallstone aetiology (n)	36 (24.7%)
Other/unknown aetiology (n)	27 (18.5%)
Median length of hospital stay (days)	5

An additional 134 admissions for acute pancreatitis, that did not consent for prospective data collection or were missed by the recruitment process, were recorded by the hospital's medical records department. To ascertain the true admission rate for this period, the preceding two data sources were considered along with a third source from the receipt of diagnosis-specific pathology specimens. For the census period, there were 304 admissions after merging of data sources, giving a crude admission rate of 7.6 per month. Crude ascertainment rates for discharge records and prospective identification were 44% and 52% respectively. Following capture-recapture analysis using log-linear

modelling, total admissions more than doubled to 644 (95% CI: 449-1100). The adjusted admission rate was therefore 16.1 per month (95% CI: 11.1-28.1) [309].

On further analysis of the prospectively obtained dataset (n=153), it became evident that there were at least three reasons for a significant proportion of these acute admissions to be worthy of a dedicated chronic disease management model.

1) **A considerable proportion of acute pancreatitis cases harbour underlying chronic pancreatitis**

Table 27 shows the numbers and proportions of cases exhibiting the various recognised clinical, biochemical and morphological features of chronic pancreatitis. If applying a composite diagnostic criterion of having at least one of these features present, the 54.3% of these acute cases would be diagnosed with underlying chronic pancreatitis. It should also be noted that certain data regarding diagnostic features were missing due to not being actively documented in the patient's records or non-availability of biological specimens such as a stool sample for [FE-1] estimation. The proportion of patients with underlying chronic pancreatitis may thus be even greater than that described. Absolute numbers would also likely have been considerably greater if extrapolating from the capture-recapture analysis, which would augment the overall chronic disease burden.

Table 27. Features of chronic pancreatitis in acute admissions to Cairns Base Hospital, 2004-2007.

	Percentage	Denominator (n)
2 or more previous admissions	29.0%	153
Chronic abdominal pain	31.8%	153
Steatorrhoea	14.5%	153
Otherwise unexplained weight loss	22.4%	153
[FE-1] < 200µg/g*	53.7%	67
Chronic pancreatitis (by composite criteria)	54.3%	153

* only in cases with predicted mild acute pancreatitis (Ranson score <3)

2) An attack of severe acute pancreatitis may lead to long-term structural or functional impairment.

While typically representing only approximately 10% of all acute cases, SAP has been reported to have a case fatality of up to 10-15% [310] and significantly greater health resource consumption [295]. Further, the clinical criterion by which SAP has been diagnosed may determine the likelihood of long-term deficits. Anatomical lesions such as necrosis or pseudocysts are more likely to lead to loss of endocrine or exocrine capacity, compared to purely physiological derangements or transient organ failure.

In the FNQ series, 11.2% (n=17) of cases developed severe acute pancreatitis, as defined by the Atlanta criteria,[15] subsequent to their initial presentation. Although details of the actual lesions that contributed to the SAP diagnosis were not included in the final summary data, the potential contribution of SAP to ongoing impairment can be exemplified by initial and follow-up CT scan images from a representative case of SAP (see Figures 6 and 7).

Beyond the FNQ series, the chronic sequelae of SAP have been the subject of numerous studies, although the results have been somewhat variable. This may be due to the rarity of the outcome in any particular cohort of acute admissions, as well as variable follow-up periods. For example, in a retrospective cohort study of 88 patients who had undergone necrosectomy, Connor et al [311] found that 25% of surviving patients developed exocrine insufficiency and 33% without prior diabetes developed endocrine insufficiency. By contrast, Ibars et al [312] in a prospective cohort study of 63 acute biliary pancreatitis patients found no significant difference in endocrine or exocrine function between mild and severe cases. Andersson et al [295] concluded that there was a higher prevalence of endocrine insufficiency after SAP although quality of life and exocrine function were no different. In summary, it would appear that on a case-by-case basis there should at least be vigilance for long-term complications following an attack of SAP.

3) Following an attack of acute pancreatitis, risk factors or precursors of chronic pancreatitis or recurrent acute pancreatitis may persist.

Of the FNQ cohort, the median 7-day alcohol recall was 4.5 standard drinks. This tended to be skewed downwards by the cases of gallstone-related pancreatitis. However 33% (n=51) of cases admitted to drinking in excess of three standard drinks per day. Moreover, in 56.9% (n=83) of cases, the aetiology of the acute attack was attributed to alcohol. Mean daily cigarette consumption was 12.7, with 62.3% (n=94) of the cohort being current smokers.

It has been suggested that progression to chronic pancreatitis may be accelerated by a diet poor in anti-oxidants, which would otherwise serve to quench the oxidative stress of repeated clinical or sub-clinical acute attacks. While long-term dietary data was not available for the FNQ cohort, self-reported nutrient and other intakes were recorded for the 24-hour period prior to onset of acute symptoms. After adjustment for key demographic variables, no individual nutrient or other substance showed a significant association with underlying chronic pancreatitis. However, following principal components analysis (PCA), there emerged a significant positive association with a so-called "stimulant" pattern (with positive loadings on non-nutritive substances such as coffee and tobacco) and a negative association with a "nutritive" pattern (with positive loadings on major macro- and micro-nutrient groups) [313]. This is likely to be

indicative of a pattern of binge behaviour in those with recurrent acute episodes related to alcohol. As such, this could inform a behavioural and nutritional management intervention forming part of a chronic disease management program.

Further examination of the cohort data revealed that 54.6% (n=83) of patients had a history of at least one other co-morbidity such as diabetes. This further validates the placement of this patient population within a chronic disease paradigm.

8.5 Discussion: *Towards a coherent chronic disease management strategy for pancreatitis*

The FNQ cohort has described certain clinicopathological variations of acute pancreatitis that also represent chronic pancreatitis. Since the commencement of prospective data collection for the study, the M-ANNHEIM staging classification of chronic pancreatitis has in effect affirmed this argument by its recognition of three categories that incorporate an element of acute pancreatitis [44]. Stage 0b is defined as a first episode of acute pancreatitis where clinical history or aetiological factors (such as alcohol) point to there being underlying chronic pancreatitis. Stage 0c is severe acute pancreatitis that has resulted in significant irreversible complications. Finally, stage 1a is characterized by recurrent attacks of acute pancreatitis with pain-free intervening periods.

While the data presented from the FNQ study are representative of a particular local demographic, inferences drawn may nevertheless be generalizable to other parts of Australia and the world, in that similar risk factors for chronicity prevail and a reasonably constant proportion of patients typically develop severe complications during the course of an admission. In general, the incidence of acute pancreatitis is increasing in the Western world, largely due to the upward trend in prevalence of aetiological factors, such as alcohol consumption and gallstone disease [100, 314]. The consequent increase in chronic disease burden represents an even greater public health impost, and thus merits a coherent management strategy.

In a review of hospital admissions for pancreatitis to a regional hospital in Alice Springs, Australia, Ah-Tye [71] found a significant over-representation of Indigenous patients with a preponderance of cases attributable to alcohol misuse. There was also a high re-admission rate. A population-based study from a region of northern Germany showed that a third of first attacks of acute pancreatitis were alcohol-related [67], for which a chronic disease management protocol could ostensibly be invoked. The proportion of alcohol-related cases remained reasonably constant over time for this population, although the proportion of cases with necrosis or other severe complications appeared to decrease slightly [89]. In one hospital-based study from the United Kingdom, 10% of 5312 people admitted for acute pancreatitis over a 35-year period had more than one recorded episode [72]. This was probably an underestimate of recurrence in that re-admissions within 12 months were not counted. In a 10-year retrospective case series of acute pancreatitis admissions in a Swedish hospital, Appelros et al [91] found that 38% of

admissions were in fact recurrent episodes, and that alcohol was the predominant aetiological factor for these, once again suggesting the need for a differential management pathway. These authors subsequently noted from the same series of patients a high incidence of long-term exocrine and endocrine dysfunction in those who had an episode of severe acute pancreatitis [94]. A review of hospital admissions in Ireland for acute pancreatitis between 1994 and 2004 showed an increasing incidence that was largely attributable to heavier alcohol consumption and binge drinking. This also appeared to be occurring at a younger age [314]. Even in Saudi Arabia where alcohol is a negligible aetiological factor, almost one-third of first attacks progressed to severe acute pancreatitis with ongoing morbidity such as diabetes [90].

The chronic disease paradigm was foreshadowed by the medical philosopher Georges Canguilhem, whose work titled "Le Normal et le Pathologique" [315] basically defined health as the ability to adapt to one's environment. He also coined a maxim "*Aucune guérison n'est retour à l'innocence biologique*", that no cure could guarantee a return to biological innocence. It therefore follows that (chronic) disease management involves treatment of the ongoing effects of the disease, as well as minimisation of risk factors to avert further attacks or progression. As described by Wagner et al [316], the basic principles of chronic disease management include: the use of evidence-based, planned care; reorganization of practice systems and provider roles; improved patient self-management support; increased access to expertise; and greater availability of clinical information. Andrews [317] provided a cogent argument for the application of these to depression. However some adaptation may be needed to apply them to the diverse

clinical scenarios presented by pancreatitis. The NHPAC [298] perhaps provides a more succinct and adaptable format through the four basic action areas it proposes: prevention across the continuum; early detection and early treatment; integration and continuity of prevention and care; and self-management.

8.5.1 Prevention across the continuum

Pancreatitis, like any chronic disease, lends itself well to a disease prevention framework based on the established ordinal hierarchy of prevention. *Primary prevention* involves undertaking certain practices in order to avoid the onset of the disease [318]. In the case of pancreatitis, education on lifestyle factors such as moderation of alcohol intake and cessation of smoking, at a population level, would ostensibly lead to a diminution in the incidence of acute pancreatitis episodes and eventual progression to chronic pancreatitis or long-term sequelae arising from severe acute pancreatitis in certain cases. *Secondary prevention* is defined as the prevention of recurrences or exacerbations of a disease or complications of its therapy [318]. Thus patients who present with a first attack of acute pancreatitis may be offered counselling to cease alcohol or tobacco intake, in order to prevent further attacks that would lead to a chronic disease state. In the same vein, consensus practice guidelines advocate expeditious cholecystectomy for gallstone-related cases [23]. *Tertiary prevention* aims at providing appropriate supportive and rehabilitative services to minimise morbidity and maximise quality of life when a chronic disease state is clearly present [318]. Such measures would suitably be applied to cases of established chronic pancreatitis, many of whom interface with the hospital system by

virtue of their recurrent acute attacks. Strategies would aim to optimise pain control, nutrient absorption and glycaemic control. Where available, practice guidelines may help inform management, such as those of the Australasian Pancreatic Club for exocrine insufficiency [54]. Moreover, a focus on quality of life measures and psychological management has also been recommended for these patients [319]. A fourth tier of prevention, *quaternary prevention*, basically refers to the avoidance of over-medicalization where interventions may be of limited utility or overtly unethical [320]. This may apply to cases of chronic pancreatitis that would not be amenable to invasive surgical or endoscopic procedures due to anatomical considerations or the persistence of correctable risk factors that would negate the benefits of such treatments. In cases of severe acute pancreatitis, it is generally advised to reserve surgical debridement of necrosis for cases with proven superinfection, in order minimise eventual functional deficits [25, 321]. Also, despite the usual recommendations, early cholecystectomy is not advisable for severe acute gallstone-related pancreatitis [22, 28, 322]; it should be delayed until the acute inflammatory response has settled.

Based on the work of Gordon [323] and Kumpfer and Baxley [324], there is an alternative three-tiered classification of preventive strategies, which can also be suitably applied to pancreatitis. *Universal prevention* involves the whole population at risk from known aetiological factors. In the case of pancreatitis, such interventions may comprise public health promotion campaigns advocating moderation in alcohol consumption and balanced nutritional intake. *Selective prevention* is where specific at-risk groups may be targeted based on recognised demographic or other characteristics. From the FNQ cohort

described, it would thus be reasonable to develop strategies directed at the Indigenous community or even men in general. *Indicated prevention* is defined as a screening process that aims to identify individuals with early, potentially remediable disease or those exhibiting high-risk behaviours. Specific primary, secondary or tertiary interventions would then be prescribed. Such a strategy could conceivably be applied to any patient admitted for the first time with acute alcohol-related pancreatitis. Further, those with clinical, morphological or biochemical evidence of chronic pancreatitis detected on acute admission could be offered an education and follow-up program. Indicated prevention is also implicit in the numerous guidelines that advocate early cholecystectomy following an attack of gallstone-related pancreatitis [23, 25, 321].

8.5.2 Early detection and early treatment

Another cornerstone of chronic disease management is early detection facilitating early treatment. Diagnosing chronic pancreatitis in those presenting acutely or, more broadly, those acute cases that would benefit from a chronic disease management model, is the key imperative. Early diagnosis of chronic pancreatitis *per se* (prior to onset of constant pain, malabsorption or diabetes) remains somewhat challenging, particularly if relying solely on a morphological or functional investigation to confirm the disease process. Furthermore, to detect underlying chronic pancreatitis in such a manner, opportunistically during the course of an acute admission, poses additional logistic difficulties. Faecal elastase-1 concentration ([FE-1]) is simple and non-invasive test that has been shown to have excellent sensitivity and specificity for cases outside the acute setting [59]. It has

also been shown to have good diagnostic performance for detecting incipient chronic pancreatitis in non-severe acute cases [218]. However, obtaining a stool specimen from a patient in the course of a brief acute hospital admission may be logistically difficult. From a pragmatic point of view, it may simply suffice to assume that patients who have had more than one acute attack and/or without abatement of risk factors such as alcohol abuse, effectively have chronic pancreatitis and should be offered a comprehensive management program.

8.5.3 Integration and continuity of prevention and care

Regarding an integrated and continuous program of care recommended for chronic disease, acute pancreatitis is traditionally managed in surgical units, unless Intensive Care is required for supervening severe complications. The reasons for this would seem to stem from the well-established need for prompt cholecystectomy in cases of acute biliary pancreatitis, and for surgical debridement (necrosectomy) in the relatively uncommon eventuality of infected necrotic pancreatitis [23, 27]. The predominant therapeutic paradigm of Surgery relates to an acute episode of care with the ostensible outcome of "cure" or at least of definitive abatement of prevailing symptoms, in contrast to a chronic disease paradigm, which involves repeated episodes of care with the ultimate objective being disease attenuation rather than complete resolution. Even in cases of acute pancreatitis that do not require operative intervention, it is assumed that the disease process and/or its causative factors cease when the patient is discharged. Certainly later complications ensuing from the acute episode, such as pseudocyst and pancreatic fistula,

may necessitate surgical interventions. Moreover, based on the evidence from the FNQ cohort, it would appear that a more consciously multidisciplinary approach, calling upon disciplines other than Surgery, is warranted for many of the cases that present in the acute context. For example, gastroenterological and dietetic support is required for cases of exocrine insufficiency, where prescribed treatments may include enzyme supplementation, gastric acid suppression, medium-chain triglycerides and other nutritional advice [54]. Many cases of AP, even those without severe manifestations, may have transient or permanent exocrine or endocrine deficiencies that would warrant some form of replacement therapy. In a small prospective cohort study from the United Kingdom, Boreham and Ammori [122] demonstrated that acute pancreatitis cases with necrosis were likely to have residual exocrine insufficiency and that this also correlated with endocrine insufficiency. Psychological and rehabilitative input is recommended where substance abuse remains an issue and chronic pain management where pain persists beyond the acute episode. As well as pharmacotherapy, the latter may entail radiologically or endoscopically guided ablative techniques. Furthermore, dedicated follow-up of presumed chronic cases is required to detect any deterioration in function that could be corrected or attenuated by a specific intervention. However this may be somewhat difficult in the case of entrenched chronic pancreatitis cases where alcohol abuse and other lifestyle factors mitigate against compliance.

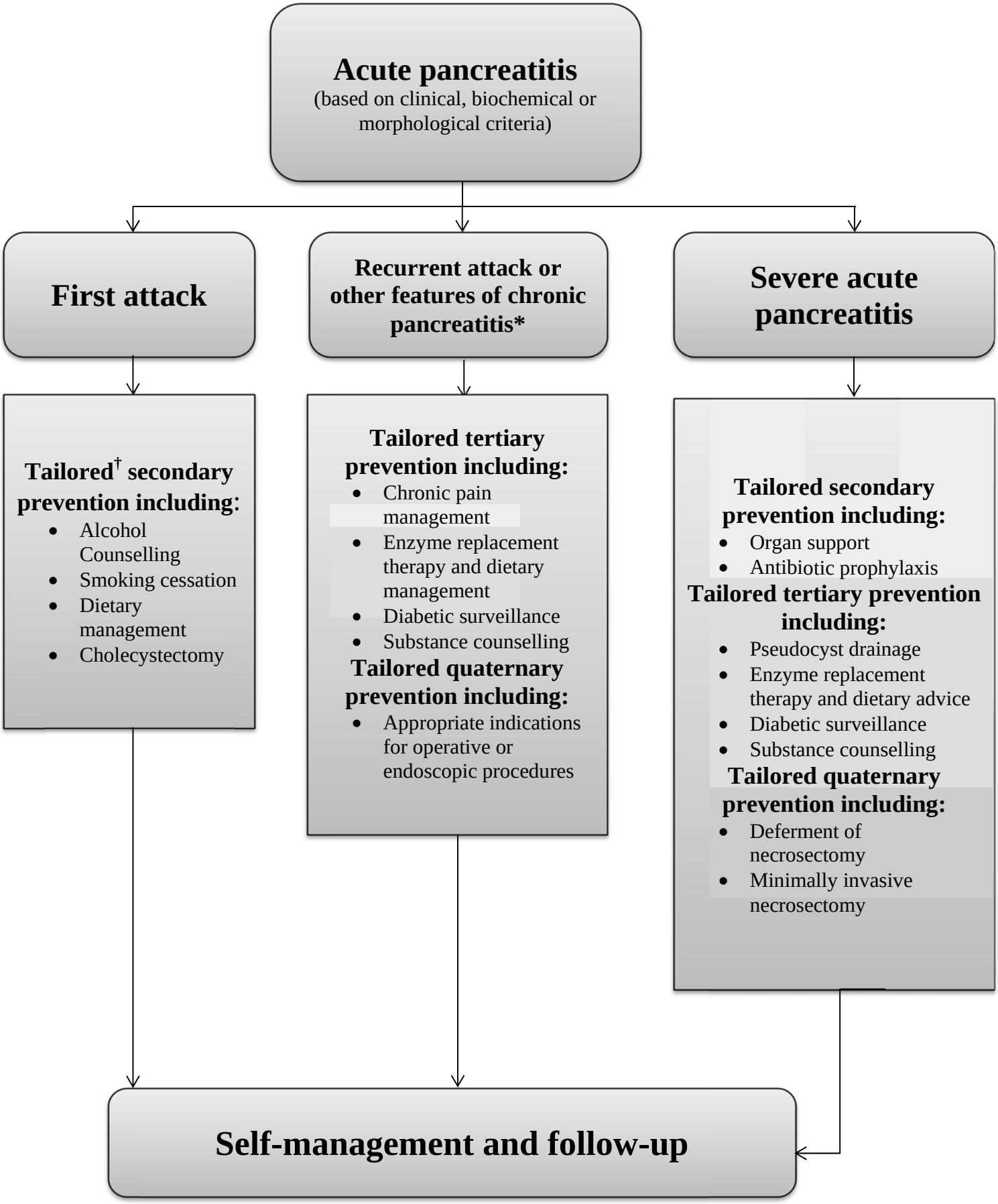
8.5.4 Self-management

The remaining "action area" for chronic disease according to the NHPAC is self-management. This has always been seen as a challenge for pancreatitis, typically because of the lifestyle factors associated with the aetiology of those cases exhibiting chronic disease characteristics. Nevertheless, active acknowledgement by clinicians and patients of the "teachable moment" may serve as the initiating point for the patient in taking responsibility for their own care [325]. Teachable moments are basically describe naturally occurring health events thought to motivate individuals to adopt risk-reducing behaviours [326]. As with key events that may be exploited to promote smoking cessation [326], an admission for acute pancreatitis could provide a trigger to increase patients' awareness of the role of alcohol, smoking and diet in the progression to chronicity. Engagement in an active follow-up process could also be actively encouraged for those with evidence of underlying chronic pancreatitis or those who had an episode of severe acute pancreatitis.

8.6 Conclusion: *Managing pancreatitis as a chronic disease*

The FNQ cohort, supported by a growing body of literature, provides a case for considering incident pancreatitis cases, by default, from within a chronic disease framework. This represents a paradigm shift from the traditional acute "surgical" model of care.

Based on the principles of chronic disease management as outlined above, a feasible, generalizable and multimodal algorithm for acute pancreatitis hospitalizations is suggested in Figure 8. Such a model of care should be embedded within a more holistic chronic disease framework, given the prevalence of co-morbidities within this patient population.


Acute pancreatitis
(based on clinical, biochemical or morphological criteria)
First attack
Recurrent attack or other features of chronic pancreatitis*
Severe acute pancreatitis
Tailored† secondary prevention including:
Alcohol Counselling
Smoking cessation
Dietary management
Cholecystectomy
Tailored tertiary prevention including:
Chronic pain management
Enzyme replacement therapy and dietary management
Diabetic surveillance
Substance counselling
Tailored quaternary prevention including:
Appropriate indications for operative or endoscopic procedures
Tailored secondary prevention including:
Organ support
Antibiotic prophylaxis
Tailored tertiary prevention including:
Pseudocyst drainage
Enzyme replacement therapy and dietary advice
Diabetic surveillance
Substance counselling
Tailored quaternary prevention including:
Deferment of necrosectomy
Minimally invasive necrosectomy
Self-management and follow-up

* May include early detection of sub-clinical exocrine insufficiency with [FE-1] testing

† "Tailored" refers to decisions based on aetiological attribution or other clinical manifestations during the course of the acute episode.

Figure 8. Chronic disease management algorithm for patients admitted with acute pancreatitis, based on three possible clinical scenarios.

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APPENDICES

1. **Ethics documentation**

    1.1. Participant information sheet and consent form

2. **Prospective data collection forms**

    2.1. Hospital admission data

    2.2. Follow-up data

3. **Standard Drinks Guide**

4. **Research output**

    4.1. Selected peer-reviewed oral communications (abstracts)

    4.2. Peer-reviewed publications

    4.3. PowerPoint slides of selected peer-reviewed oral communications and invited presentations

APPENDIX 1

1. Ethics documentation

1.1 Patient information sheet and consent form

INFORMATION TO THE PARTICIPANT

1. PURPOSE AND BACKGROUND OF THE RESEARCH/PROJECT

You have been diagnosed with pancreatitis, an inflammatory condition of the pancreas gland. We are currently conducting a survey to assess the prevalence and severity of this disease in our community, and also to determine its risk factors. This may help to prevent and treat this disease in the future and also to find out which people are most at risk for certain complications.

2. PROCEDURE/RESEARCH

You will be required to answer a few simple questions about yourself and undergo some simple measurements. The rest of the information for the survey will be obtained from the medical record of your stay in hospital. Your treatment will be in accordance with current best practice guidelines for pancreatitis and may involve taking blood samples, radiological examinations (X-rays, CAT scans, ultrasound scans), and a stool specimen.

When you are discharged, you will be asked to present for a follow-up visit to see how you have recovered from this episode. At this time you will also be required to undergo a blood test and provide another stool specimen. Any other tests and examinations at this time will be decided by the doctor looking after your case. To assist with contacting you for follow-up, we will also ask you to provide the name and contact details of two people who would normally know your whereabouts. This is entirely at your discretion; one of the people may be your General Practitioner.

All of the information gathered about you for the survey is strictly confidential and will only be known to ourselves and the hospital staff responsible for your treatment. You will not be identified by name in any reporting of the survey data. However, it may sometimes be necessary to identify you by name and date of birth should we need to obtain information from other hospitals where you seek treatment. This information will once again be treated with confidentiality.

3. BENEFITS

The treatment you receive for your pancreatitis will be in accordance with the accepted standard of care.

The survey itself will provide you with no additional individual benefits. It may however help us to improve the ways of preventing and treating pancreatitis in the future.

4. **RISKS/DISCOMFORTS**

The survey does not require you to undergo any procedures that would not normally be part of the standard treatment of your condition, except for the blood test at the follow-up visit(s). Should you not wish to have this blood test or answer any or all of the questions related to the survey, you do not have to. This will in no way affect your overall treatment.

5. **QUERIES OR COUNSELLING**

Any queries related to the survey can be directed to Dr Richard Turner at Cairns Base Hospital on (07)40506333.

Any queries related to your treatment while in hospital should be directed to the doctor(s) looking after you.

SHOULD YOU HAVE ANY QUESTIONS OR REQUIRE ANY EXPLANATIONS PLEASE ASK

CONSENT TO PARTICIPATE IN RESEARCH PROJECT

Are you an adult ie. 18 years or over? Yes [✓] No [ ]

Do you consent to take part in this research project?

Yes [✓] No [ ]

Have you read and/or had read and explained to you the information sheet which explains the nature, object and possible risks of the research project

Yes [✓] No [ ]

Do you understand the contents of the information sheet?

Yes [✓] No [ ]

Do you consent to provide one or more stool specimens, if possible, during your hospital admission and again at follow-up?

Yes [✓] No [ ]

Do you consent to the taking of an additional blood sample at follow-up to look at blood fat, glucose and vitamin levels?

Yes [✓] No [ ]

If necessary to the research project, do you authorise access to your medical and/or other files?

Yes [✓] No [ ]

Do you understand that:-

(i) your responses, the results and any report arising from this research project will remain confidential? Yes [✓] No [ ]

(ii) only persons carrying out the research project will have access to the information? Yes [✓] No [ ]

(iii) you will not be identified or named in the publication of the results and findings of the research project? Yes [✓] No [ ]

Do you understand that you may withdraw from this research project at Yes [✓] No [ ]

any stage and that your medical care will not be affected? ☑ ☐

Do you voluntarily agree to take part in the research project? Yes ☑ No ☐

Do you acknowledge that you have signed this Consent Form of your own free will and that you have not relied upon any verbal, written or visual representation or statements by the person/s conducting the research project? Yes ☑ No ☐

Have you received a copy of this Consent Form? Yes ☑ No ☐

SIGNED this 26th day of May 2006

....

Signature of the Participant

Residential Address:

Telephone Number:

Witness:

RESEARCHERS STATEMENT

I have explained to the Participant.....
the nature and purpose of the research project and the procedures used and any risks or discomfort which may result from their participation.

26-5-06

....

Signature of the Researcher Date

APPENDIX 2

2. Prospective data collection forms

2.1 Hospital admission data

NORTH QUEENSLAND PANCREATITIS STUDY: Admission data

Data field	Coding	Instructions
1. Interview details *Please specify:* *(a) Date*..... *(b) Time*..... *(c) Interviewer*.....		Use 24-hour clock.
2. Hospital UR number *Please specify*.....		Available from hospital record Include hospital prefix
3. Surname *Please specify*.....		
4. Forename(s) *Please specify*.....		
5. Date of birth *Please specify*.....		Available from hospital record
6. Gender Male Female	 1 2	Available from hospital record
7. Residential locality (a) "What place do you live in?" *Please specify*..... (b) How long have you lived there? *Please specify*.....		Verify with participant where he/she lives most of the time. Postcode is not sufficient. In years (or months)

8. Ethnicity (a) "What is your country of birth?" Australia Other *(please specify)*..... (b) "Do you identify yourself as any of the following?" Aboriginal Torres Strait Islander Aboriginal and Torres Strait Islander None of these	 1 2 1 2 3 4	
9. Marital status "Do you live – - alone?" - with spouse / partner / family?" - with non-family members?"	 1 2 3	
10. Employment (a) "What is your current work situation?" Full-time Part-time Casual Student Domestic duties Unemployed / other welfare benefits Retired (b) "What work do you do in the job where you work the most hours?" OR if retired / not employed: "What work do you do when you were last employed?" *Please specify*.....	 1 2 3 4 5 6 7	Accept more than one answer if appropriate. Ask about nature of work.

11. Education "How far have you gone with your education so far?" Left before Year 8 Completed Year 8 Completed Year 10 Completed Year 12 Trade / apprenticeship Certificate / diploma University / bachelor's degree or higher Other *(please specify)*.....	 1 2 3 4 5 6 7 8	Read options to participant If not part of Australian education system, estimate equivalent level.
12. Date of admission *Please specify:* *(a) Date*..... *(b) Day of week*.....		As indicated in hospital notes.
13. Date of discharge *Please specify*.....		As indicated in hospital notes
14. Presumed aetiology Alcohol Gallstones Hyperlipidemia Not stated / idiopathic Other *(please specify)*.....	 1 2 3 4 5	As indicated in doctor's notes on admission (or within first 24 hours)

15. Duration of disease (a) "What year were you first admitted to hospital with a diagnosis of pancreatitis?" *Please specify*…… (b) "Before this time, how many times have you been admitted to hospital with a diagnosis of pancreatitis?" *Please specify*……		Corroborate by referring to hospital notes were applicable. Approximate if patient is uncertain as to exact year. Corroborate by referring to hospital notes were applicable. Approximate if patient is uncertain as to exact number.
16. Presenting symptoms (a) "What symptoms caused you to come into hospital in this occasion?" Pain Vomiting Other *(please specify)*…… (b) "How long had the main symptom been present when you came into hospital?" (hours / days / months) *Please specify*……	 1 2 3	Corroborate by referring to hospital notes if necessary. More than one answer is acceptable. Corroborate by referring to hospital notes if necessary.

17. Co-morbidities		
(a) "Do you suffer from any other illnesses or conditions?"		Corroborate any information by referring to hospital notes if necessary.
No Yes *(please specify: disease – duration)* …… …… …… …… ……	1 2	Ask specifically about chronic conditions e.g. diabetes mellitus, hyperlipidemia ("high cholesterol"), heart / lung / kidney disease, etc. Include approx. duration of any chronic conditions in years.
(b) "Have you previously had any abdominal operations?"		Briefly describe operation in participant's own words if name not known and record not available.
No Yes *(please specify)*…… …… …… ……	1 2	
(c) "Do you usually take any medications?"		Include any non-oral medications (e.g. insulin, eye drops, topical applications, etc.), vitamin supplements, and natural / herbal preparations.
No Yes *(please specify)*…… …… …… ……	1 2	

18. Family history		
(a) "Has anyone in your family been diagnosed with pancreatitis?"		Specify that only "blood" relatives are to be included.
No	1	
Yes *(please specify relationships)*	2	
.....		
.....		
.....		
.....		
(b) "Has anyone in your family ever had any chronic illnesses or conditions?"		Ask specifically about chronic conditions (e.g. diabetes mellitus, hyperlipidemia ["high cholesterol"], heart / lung / kidney disease, etc.) and cancers (specify organ of origin)
No	1	
Yes *(please specify relationships - conditions)*	2	
.....		
.....		
.....		
.....		
.....		
.....		
(c) "Has anyone in your family been a heavy drinker?"		If necessary, define as drinking that lead to any medical, psychological or social problems.
No	1	
Yes *(please specify relationship)*	2	
.....		
.....		
.....		
.....		

19. Symptoms of chronicity		
(a) "Prior to this admission, and excluding any other admissions for pancreatitis, have you ever suffered from abdominal pain?"		
Never	1	
Sometimes	2	
All the time – at the same intensity	3	
All the time – with flare-ups	4	
(b) "If you do have chronic abdominal pain, how would you rate its intensity on a scale of 1 to 10?"		Show visual analogue scale
(i)"On average"		
Please specify.....		
(ii)"At its worst"		
Please specify.....		
(c) "Do you usually have loose, frothy or bulky bowel motions?"		"Usually" can be clarified as "on most days" or "on most days of the week", etc.
No	1	
Yes	2	
(d) "Over the last 12 months, has your weight changed?"		If participant is unsure of change in kilograms, ask about fit of his/her clothes.
No – stayed the same	1	
Yes – decreased	2	
Yes – increased	3	

20. Anthropometric measures (a) Weight (kg) *Please specify*…… (b) Height (cm) *Please specify*…… (c) Waist circumference (cm) *Please specify*…… (d) Hip circumference (cm) *Please specify*……		Obtain from hospital notes if available; otherwise measure with minimal excess clothing and footwear. Free-standing or recumbent if patient is unable to stand. Take at narrowest point between lower costal border and iliac crest; at end of normal expiration and arms at sides. Take at level of greatest posterior protuberance of buttocks (patient standing and not tensed).

21. Alcohol history		
(a) "What did you drink in the 7 days before you developed the pain (or other symptom if applicable) that made you come into hospital?"		Record on relevant worksheet. Refer to picture card to assess volumes if necessary.
(b) "In a normal week, how much would you have to drink?" *Please specify beverage and volume units*.....		Refer to picture card if necessary.
(c) "If in the last week or so you have drunk more than you usually do, was there a reason for this?"		
Not applicable No / don't know Yes *(please specify)*.....	1 2 3	
(d) "How old were you when you first started drinking?"		
Not applicable Age *(please specify)*.....	1 2	
(e) "How long ago did you stop drinking?" *(if applicable)* *Please specify*.....		Express as years or months
(f) "Why did you stop drinking?" *(if applicable?)* *Please specify*.....		

22. Tobacco history (a) How many cigarettes do you usually smoke per day?" *Please specify*..... (b) "How long have you been smoking?" *Please specify*..... (c) "How long ago did you stop smoking?" (if applicable) *Please specify*..... (d) "Why did you stop smoking?" *(if applicable)* *Please specify*.....		Record equivalent in packets of tobacco per week if applicable. Alternative question: "How old were you when you first started smoking?" Express as years or months Alternative question: "When did you stop smoking?" (then calculate length of time, etc.)
23. Dietary history "What did you eat in the 24 hours prior to the onset of your symptoms?"		Record on relevant worksheet.

24. Contact details (a) Patient *(i) Postal address*..... .... *(ii) Telephone number*..... *(iii) E-mail*..... (b) Contact person 1 *(i) Name*..... ..... *(ii) Postal address*..... .... *(iii) Telephone number*..... *(iv) E-mail*..... (c) Contact person 2 *(i) Name*..... ..... *(ii) Postal address*..... .... *(iii) Telephone number*..... *(iv) E-mail*.....		Complete as applicable. Verify any contact information in hospital notes directly with the patient. Contact persons should ideally include patient's local health care provider (GP, community clinic, etc.) and a friend/relative who lives at another address. Information can be obtained from hospital notes where applicable.

Additional comments

INVESTIGATION RESULTS: Hospital admission

Investigation	*Date/time*	*Result*	*Instructions*
Serum lipase (U/L) *on admission*			First level taken since admission or diagnosis
Serum C-reactive protein (U/L) *within 48 hours*			Highest level in first 48 hours after admission or diagnosis
Serum glucose (mmol/L) *on admission*			First level taken since admission or diagnosis; "BSL" also acceptable
Serum glucose (mmol/L) *within 48 hours*			Highest level in first 48 hours after admission or diagnosis; "BSL" also acceptable
Serum lactate dehydrogenase (LD) (U/L) *on admission*			First level taken since admission or diagnosis
Serum aspartate transaminase (AST) (U/L) *on admission*			First level taken since admission or diagnosis
Serum aspartate transaminase (AST) (U/L) *within 48 hours*			Highest level in first 48 hours after admission or diagnosis

Investigation	*Date/time*	*Result*	*Instructions*
Serum alanine transaminase (ALT) (U/L) *within 48 hours*			Highest level in first 48 hours after admission or diagnosis
Serum albumin (g/L) *within 48 hours*			Lowest level in first 48 hours after admission or diagnosis
Serum cholesterol (mmol/L) *on admission*			First fasting level taken since admission or diagnosis
Serum triglyceride (mmol/L) *on admission*			First fasting level taken since admission or diagnosis
White blood cell count (x 10^9/L) *on admission*			First level taken since admission or diagnosis
Hematocrit *on admission*			First level taken since admission or diagnosis
Hematocrit *within 48 hours*			Lowest level in first 48 hours after admission or diagnosis
Serum urea (mmol/L) *on admission*			First level taken since admission or diagnosis
Serum urea (mmol/L) *within 48 hours*			Highest level in first 48 hours after admission or diagnosis

Investigation	*Date/time*	*Result*	*Instructions*
Serum calcium (mmol/L) *within 48 hours*			Lowest level in first 48 hours after admission or diagnosis
Arterial pO2 (mmHg) *within 48 hours*			Lowest level in first 48 hours after admission or diagnosis
Arterial base excess (mmol) *within 48 hours*			Greatest negative value in first 48 hours after admission or diagnosis
Est. fluid balance (L) *within 48 hours*			Highest level in first 48 hours after admission or diagnosis; refer to patient chart or fluid balance sheet.
Red cell folate (ng/ml) *on admission*			Requested with routine blood tests within 24 hours of admission or consenting to participate.

Investigation	*Date/time*	*Result*	*Instructions*
Faecal elastase-1 (mcg/g) *during admission*			Where possible, collect each stool specimen for the first week of the admission, then weekly thereafter, where applicable. Avoid mixing urine with faeces.

Investigation	*Date/time*	*Result*	*Instructions*
Abdominal X-ray *on admission*		1. Not done 2. Normal study 3. Ileus/sentinel loop/colon cut-off 4. Pancreatic calcification 5. Other*(specify)*…… …… ……	First imaging since admission; private imaging done just prior to admission should also be included. Seek reports in patient's chart (Investigation or Correspondence sections) or X-ray packet.
Abdominal ultrasound *on admission*		1. Not done 2. Normal study 3. Gallstones 4. CBD >6mm diameter 5. CBD stone 6. Pancreatic calcification 7. Dilated/irregular pancreatic duct 8. Pancreatic edema 9. Pancreatic mass/tumour 10. Fluid collection(s) 11. Other*(specify)*…… …… ……	First imaging since admission; private imaging done just prior to admission should also be included. Seek reports in patient's chart (Investigation or Correspondence sections) or X-ray packet.

Investigation	*Date/time*	*Result*	*Instructions*
Abdominal CT scan *on admission*		1. Not done 2. Normal study 3. Pancreatic edema 4. Pancreatic necrosis *(specify %)*..... 5. Pancreatic necrosis with gas bubbles 6. Fluid collection 7. Pseudocyst 8. Ascites/generalised intra-peritoneal fluid 9. Pancreatic calcification 10. Dilated/irregular pancreatic duct 11. Pancreatic mass/tumour 12. Other*(specify)*.....	First imaging since admission; private imaging done just prior to admission should also be included. Seek reports in patient's chart (Investigation or Correspondence sections) or X-ray packet.

Investigation	*Date/time*	*Result*	*Instructions*
Abdominal CT scan *after baseline*		1. Not done 2. Normal study 3. Pancreatic edema 4. Pancreatic necrosis *(specify %)*…… 5. Pancreatic necrosis with gas bubbles 6. Fluid collection 7. Pseudocyst 8. Ascites/generalised intra-peritoneal fluid 9. Pancreatic calcification 10. Dilated/irregular pancreatic duct 11. Pancreatic mass/tumour 12. Other*(specify)*…… …… ……	Include any abdominal CT scan done after initial one. Complete additional forms if necessary. Seek reports in patient's chart (Investigation or Correspondence sections) or X-ray packet.

Investigation	*Date/time*	*Result*	*Instructions*
Upper endoscopy *during admission*		1. Not done 2. Normal study 3. Esophagitis 4. Esophageal varices 5. Gastritis 6. Gaastric erosions 7. Gastric ulcer(s) 8. Duodenal ulcer(s) 9. Other*(specify)*…… …… ……	Where performed at any time during the course of the admission; also include any procedure done just prior to admission. Seek reports in patient's chart (Investigation or Correspondence sections) or X-ray packet.

Investigation	*Date/time*	*Result*	*Instructions*
ERCP *during admission*		1. Not done 2. Attempted but unsuccessful 3. Normal study 4. CBD stone(s) seen 5. Endoscopic sphincterotomy performed 6. CBD stone(s) extracted 7. Pancreatic calcification 8. Dilated pancreatic duct(s) 9. Obstructed/strictured pancreatic duct(s) 10. Irregular/tortuous pancreatic duct(s) 11. Intraductal pancreatic calculi 12. Cavities in pancreas 13. Other abnormality *(specify)*…… …… …… …… …… ……	Where performed at any time during the course of the admission; also include any procedure done just prior to admission. Seek reports in patient's chart (Investigation or Correspondence sections) or X-ray packet.

7-DAY ALCOHOL RECALL (WORKSHEET)

Day	Type of drink	Amount*	Grams ethanol
1			
2			
3			
4			
5			
6			
7			

TOTAL _____

* *Express as glasses, bottles, casks – specifying volume if necessary*

24-HOUR DIETARY RECALL

Time	Meal / Snack / Beverage	Composition	Portion size / Amount	Preparation details

2.2Follow-up data

North Queensland Pancreatitis Survey

Cairns Base Hospital

First Name _____ Surname _____

Date of Birth _____ Hospital No _____

Date Survey Done _____ I will drop off a sample to the laboratory ☐ yes ☐ no

Have you been diagnosed with any new illnesses or conditions since you were last admitted with pancreatitis? (Please describe)

Enlarged liver.

Are you taking any new medications since you were last admitted with pancreatitis? (If yes please name the medication and reason for use)

No.

Have you had any operations or procedures since you were last admitted with pancreatitis?

No.

Since you were last admitted with pancreatitis have you had any abdominal pain? Please tick

- ☐ Never
- ☐ Sometimes mild pain
- ☑ Sometimes severe pain
- ☐ All the time mild pain
- ☐ All the time severe pain
- ☐ Some pain all the time with flare ups of severe pain

Have you had consistently unusual bowel motions?

- ☑ No
- ☐ Loose
- ☐ Frothy
- ☐ Bulky
- ☐ Other Sometimes diahorreah.

Since your admission for pancreatitis has your weight changed?

- ☐ No stayed the same
- ☐ Yes increased
- ☑ Yes decreased

What is your weight now?

_____ kg

I have provided a tape measure

Could you please measure your waist (around where belly-button is)

_____ cm

And your hips (around where your buttocks are the biggest)

_____ cm

North Queensland Pancreatitis Survey

Cairns Base Hospital

Are you a cigarette smoker?

- ☐ No
- ☒ Yes How many a day usually? 15 cigs
- ☐ Former smoker - When did you stop smoking? _____
  Why did you stop? _____

In a normal week how much alcohol would you have to drink?

- ☐ None
- ☐ Former alcohol drinker When did you stop drinking? _____
  Why did you stop? _____
- ☐ I usually have the following (please include type of drink and amount)

4 casks / week.
12 rums / week.

- ☐ In the past week I have had the following (please include type of drink and amount)

5-6 casks
1½ bottle of rum.

What have you eaten in the last 24 hours? (Please include size of meal any type and any additions like milk, margarine, sugar and non-alcoholic drinks)

0. 2 litres / water
4 mugs black coffee.

Could we try to contact you in another 6 months for another survey?

- ☐ No
- ☐ Yes The best phone number for me is _____

THANKYOU VERY MUCH please send this survey (and tape measure) in the envelope provided.

DESCRIPTION

ALC:
Usually drink 4 casks white wine and 12 rums per week.
This week had 5-6 casks and 1.5 bottles rum.

CIG:
15/day

MEDS:
No new meds since last admitted with panc.

FOODS

Water In A Beverage	2 L
Coffee,black,NFS	4 mug(240ml)

ANALYSIS SUMMARY

	Avg/Day	EAR	EAR(%)	Alerts
Weight (g)	2960			
Energy (kJ)	48			
Protein (g)	1			
Total Fat (g)	0			
- Saturated Fat (g)	0			
- Polyunsaturated Fat (g)	0			
- Monounsaturated Fat (g)	0			
Cholesterol (mg)	0			
Carbohydrate (g)	1			
Sugars (g)	0			
Starch (g)	1			
Water (g)	2951			
Alcohol (g)	0			
Dietary Fibre (g)	1			
Thiamin (mg)	0.00			
Riboflavin (mg)	0.10			
Niacin (mg)	4.80			
Niacin Equivalents (mg)	5.76			
Vitamin C (mg)	0.00			
Total Folate (ug)	0.00			
Total Vitamin A Equivalents (ug)	0.00			
Retinol (ug)	0.00			
Beta Carotene Equivalents (ug)	0.00			
Sodium (mg)	38.40			
Potassium (mg)	355.20			

	Avg/Day	EAR	EAR(%)	Alerts
Magnesium (mg)	58.40			
Calcium (mg)	39.20			
Phosphorus (mg)	28.80			
Iron (mg)	0.96			
Zinc (mg)	0.00			
kJ from Protein (%)	50			
kJ from Fat (%)	0			
kJ from Carbohydrate (%)	50			
kJ from Alcohol (%)	0			
kJ from Others (%)	18			
Fat as Mono (%)	?			
Fat as Poly (%)	?			
Fat as Saturated (%)	?			
Glycemic Index ()	?			
Glycemic Index Level (Diet) ()	?			
Glycemic Index Level (Food) ()	?			
Glycemic Load ()	?			
Unassigned Carbohydrate (%)	100			
Assigned Carbohydrate (g)	0.0			
Glycemic Index of Assigned Carbohydrate ()	?			
Glycemic Load of Assigned Carbohydrate ()	0			

RATIO ENERGY FROM PROTEIN, FAT, CARBOHYDRATE AND ALCOHOL

RATIO POLY, MONO AND SATURATED FATS

APPENDIX 3

3. **Standard Drinks Guide**

NUMBER OF STANDARD DRINKS – BEER

1.1
285ml
Full Strength
4.8% Alc. Vol

0.8
285ml
Mid Strength
3.5% Alc. Vol

0.6
285ml
Low Strength
2.7% Alc. Vol

1.6
425ml
Full Strength
4.8% Alc. Vol

1.2
425ml
Mid Strength
3.5% Alc. Vol

0.9
425ml
Low Strength
2.7% Alc. Vol

1.4
375ml
Full Strength
4.8% Alc. Vol

1
375ml
Mid Strength
3.5% Alc. Vol

0.8
375ml
Low Strength
2.7% Alc. Vol

1.4
375ml
Full Strength
4.8% Alc. Vol

1
375ml
Mid Strength
3.5% Alc. Vol

0.8
375ml
Low Strength
2.7% Alc. Vol

34
24 x 375ml
Full Strength
4.8% Alc. Vol

24
24 x 375ml
Mid Strength
3.5% Alc. Vol

19
24 x 375ml
Low Strength
2.7% Alc. Vol

These are only an approximate number of standard drinks. Always read the container for the exact number of standard drinks.

NUMBER OF STANDARD DRINKS – WINE

1.5
150ml
Average
Restaurant Serving
of Red Wine
13% Alc. Vol

1
100ml
Standard Serve
of Red Wine
13% Alc. Vol

0.8
60ml
Standard Serve
of Port
17.5% Alc. Vol

1.4
150ml
Average
Restaurant Serving
of White Wine
11.5% Alc. Vol

0.9
100ml
Standard Serve
of White Wine
11.5% Alc. Vol

1.4
150ml
Average Restaurant
Serve of Champagne
12% Alc. Vol

7.1
750ml
Bottle of Champagne
12% Alc. Vol

7.7
750ml
Bottle of Red Wine
13% Alc. Vol

41
4 Litres
Cask Red Wine
13% Alc. Vol

21
2 Litres
Cask Red Wine
13% Alc. Vol

6.8
750ml
Bottle of White Wine
11.5% Alc. Vol

36
4 Litres
Cask White Wine
11.5% Alc. Vol

18
2 Litres
Cask White Wine
11.5% Alc. Vol

28
2 Litres
Cask of Port
17.5% Alc. Vol

These are only an approximate number of standard drinks. Always read the container for the exact number of standard drinks.

NUMBER OF STANDARD DRINKS – SPIRITS

1
30ml
High Strength
Spirit Nip
40% Alc. Vol

22
700ml
High Strength
Bottle of Spirits
40% Alc. Vol

1.1
275ml
Full Strength
RTD*
5% Alc. Vol

1.2
330ml
Full Strength
RTD*
5% Alc. Vol

2.6
660ml
Full Strength
RTD*
5% Alc. Vol

1.5
275ml
High Strength
RTD*
7% Alc. Vol

1.8
330ml
High Strength
RTD*
7% Alc. Vol

3.6
660ml
High Strength
RTD*
7% Alc. Vol

1
250ml
Full Strength
Pre-mix Spirits
5% Alc. Vol

1.2
300ml
Full Strength
Pre-mix Spirits
5% Alc. Vol

1.5
375ml
Full Strength
Pre-mix Spirits
5% Alc. Vol

1.7
440ml
Full Strength
Pre-mix Spirits
5% Alc. Vol

1.4 – 1.9
250ml
High Strength
Pre-mix Spirits
7% – 10% Alc. Vol

1.6
300ml
High Strength
Pre-mix Spirits
7% Alc. Vol

2.1
375ml
High Strength
Pre-mix Spirits
7% Alc. Vol

2.4
440ml
High Strength
Pre-mix Spirits
7% Alc. Vol

These are only an approximate number of standard drinks. Always read the container for the exact number of standard drinks.

* Ready-to-Drink

D002X10(08)

APPENDIX 4

4.1Selected peer-reviewed oral communications (abstracts)

Epidemiology – making an impact

The Joint Scientific Meeting of the Australasian Epidemiological Association (AEA) and the International Epidemiological Association (IEA) Western Pacific Region

Hotel Grand Chancellor
Hobart, Australia
August 2007

4.2 Peer-reviewed publications

HPB, 2006; 8: 223–226

Taylor & Francis
Taylor & Francis Group

Using faecal elastase-1 to screen for chronic pancreatitis in patients admitted with acute pancreatitis

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Abstract
Background: Patients presenting with acute pancreatitis may have co-existing chronic pancreatitis, the accurate diagnosis of which would potentially guide appropriate management. Gold standard tests are often invasive, costly or time-consuming, but the faecal elastase-1 assay has been shown to be comparatively accurate for moderate and severe exocrine deficiency. This study aimed to evaluate fecal elastase-1 concentration [FE-1] against clinical criteria for chronicity in an acute setting. *Patients and methods:* [FE-1] was performed on patients admitted with acute onset of epigastric pain and a serum lipase at least three times the upper limit of normal. Clinical diagnosis of chronic pancreatitis was defined by the presence of specific clinical, pathological or radiological criteria. A [FE-1] value of <200 μg/g was similarly considered indicative of chronic exocrine insufficiency. Thus a 2×2 table comparing [FE-1] and clinical diagnosis was constructed. *Results:* After exclusion of liquid stool specimens, 105 stool specimens from 87 patients were suitable for [FE-1] determination. [FE-1] was evaluated against the clinical diagnosis of chronic pancreatitis, initially for the whole sample, and then after exclusion of cases of moderate and severe acute pancreatitis (Ranson score >2). The latter analysis, based on an exocrine insufficiency threshold of 200 μg/g, yielded a sensitivity of 79.5%, specificity of 98.0%, positive predictive value of 96.9% and negative predictive value of 86.0%. *Conclusion:* [FE-1] is an accurate screening tool for underlying chronic exocrine insufficiency when taken in the course of a hospital admission for mild acute pancreatitis.

Key Words: *Faecal elastase-1, diagnostic tests, chronic pancreatitis, acute pancreatitis*

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Feature

What is the 'real' admission rate of acute pancreatitis in a regional Australian population?

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Abstract

Objective. Capture-recapture analysis was used to more accurately quantify the admission rate for acute pancreatitis in a regional hospital setting, in comparison to the usual method of case ascertainment. Reasons for differences in capture for the various methods were also sought.

Methods. Admissions for acute pancreatitis were enumerated over a 40-month period using three data sources: hospital classification of admission diagnoses, prospective case identification, and receipt of diagnosis-specific pathology specimens. Capture-recapture analysis was applied with log-linear modelling to account for likely dependency between data sources. Covariates were noted to explain capture probability by the various data sources and for eventual stratification in the analysis process.

Results. For the census period, there were 304 admissions after merging of data sources, giving a crude admission rate of 7.6 per month. Crude ascertainment rates for discharge records and prospective identification were 44% and 52% respectively. Following log-linear modelling, total admissions more than doubled to 644 (adjusted admission rate 16.1 per month). Of the covariates considered, admissions of less than three days' duration and those occurring in December and January were significantly associated with increased capture by the hospital discharge records data source.

Conclusions. In this clinical setting, admissions for acute pancreatitis are grossly underestimated by the standard case ascertainment method. The reasons for this are not clear. Hospital discharge records are nevertheless more effective than prospective case ascertainment for certain cases, such as brief admissions and those in holiday periods.

What is known about the topic? Capture–recapture analysis was originally developed in animal ecology, but has since been used to estimate both prevalent and incident cases of human disease.

What does this paper add? This study exposes possible deficiencies in the single-source case ascertainment methods used by most hospitals to enumerate incident cases. It is the first time that capture–recapture techniques have been used to estimate acute pancreatitis admissions.

What are the implications for practitioners? To obtain accurate admissions estimates for diseases such as acute pancreatitis, capture–recapture analysis with multiple data sources is advisable. One possible solution may be to conduct intermittent prospective censuses to complement existing retrospective ascertainment methods. On a more general level, clinical staff should be better trained to provide more accurate and detailed information in case records.

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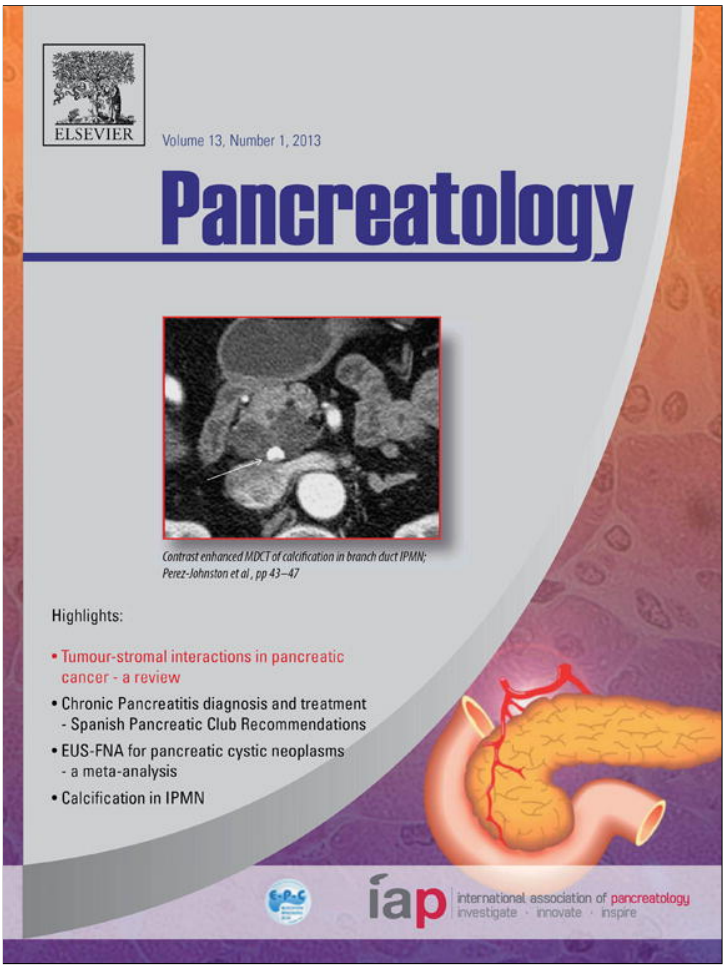

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Original article

Intake patterns of food nutrients and other substances associated with chronic pancreatitis☆

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ABSTRACT

Background/objectives: While alcohol is considered the most common aetiological factor for chronic pancreatitis, the intake of various nutrient and other substances is thought to act as cofactors in the pathogenesis of the disease due to modulation of oxidative stress. This study examined incident cases of acute pancreatitis to determine the dietary and other intakes that characterize those harbouring underlying chronic pancreatitis.

Methods: Cases of acute pancreatitis presenting to a single institution were prospectively recruited ($n = 153$). The presence of chronic pancreatitis was defined by a composite of clinical, biochemical and radiological criteria. Information was obtained on the intake of dietary macro- and micronutrients, coffee, tobacco and alcohol in the period just prior to the acute exacerbation. Univariate and multivariate analyses of association were undertaken. Principal components analysis (PCA) was employed to elicit patterns of intake.

Results: After adjustment for key demographic variables, no individual nutrient or other substance showed a significant association with chronic pancreatitis. However, following PCA there emerged a significant positive association with a so-called "stimulant" intake pattern and a negative association with a so-called "nutritive" pattern.

Conclusions: Preceding an acute exacerbation, patients with underlying chronic pancreatitis are more likely to substitute food-based intake for combinations of other substances, such as tobacco and coffee. This finding may have application in the clinical setting as part of a chronic disease management protocol.

☆ Institution(s) where research was conducted: James Cook University, Cairns Base Hospital.

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http://dx.doi.org/10.1016/j.pan.2012.12.004

ORIGINAL ARTICLE

ANZJSurg.com

Clinical predictors of severe acute pancreatitis: value-adding the view from the end of the bed

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Key words
central obesity, pancreatitis, prognosis, smoking.

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Accepted for publication 12 August 2013.

doi: 10.1111/ans.12390

Abstract

Background: Research into clinical determinants of severe acute pancreatitis remains important for therapeutic and preventive purposes. To contribute to prognostication, this study aimed to define clinical risk factors for the development of severe acute pancreatitis.

Methods: Study design was a prospective cohort study, using multiple logistic regression. From March 2004 to July 2007, 153 cases of acute pancreatitis were recruited in a regional Australian hospital. Data were collected regarding demographic and clinical characteristics. The outcome measure was severe acute pancreatitis, as defined by composite consensus criteria.

Results: After adjustment for potential confounders, there was a significant positive association with waist circumference and a negative association with current smoking status.

Conclusion: The study confirms other work suggesting central adiposity as a risk factor for severe acute pancreatitis. The finding of a possible protective effect for smoking may be physiologically plausible but merits further confirmatory research.

Pancreatic Disorders & Therapy

Turner, Pancreatic Dis Ther 2013, 3:2
http://dx.doi.org/10.4172/2165-7092.1000118

Review Article Open Access

Acute Pancreatitis is a Chronic Disease

Richard Turner*

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Abstract

Based on the example of a cohort of patients treated at a regional Australian hospital, it is evident that many incident acute pancreatitis cases merit consideration as a chronic disease process, for a number of reasons:

• A considerable proportion of acute cases harbour underlying pancreatitis.

• An attack of severe acute pancreatitis may lead to long-term structural or functional impairment.

• Following an attack of acute pancreatitis, risk factors or precursors of chronic pancreatitis or recurrent acute pancreatitis may persist.

As such, it is argued that cases of acute pancreatitis should by default be managed from the perspective of a chronic disease paradigm. A management strategy based on a prevention hierarchy is proposed.

Keywords: Acute pancreatitis; Chronic disease; Chronic pancreatitis; Severe acute pancreatitis

Abbreviations: AP: Acute Pancreatitis; CI: Confidence Interval; CP: Chronic Pancreatitis; [FE-1]: Faecal elastase-1 concentration; FNQ: Far North Queensland; NHPAC: National Health Priority Action Council; SAP: Severe Acute Pancreatitis

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Citation: Turner R (2013) Acute Pancreatitis is a Chronic Disease. Pancreatic Dis Ther 3: 118. doi:10.4172/2165-7092.1000118

4.3 PowerPoint slides of selected peer-reviewed oral communications and invited presentations

Epidemiology, clinical outcomes and resource costs of pancreatitis in northern Queensland

R.C. Turner, M. von Papen, P.K. Donnelly

Department of Surgery, James Cook University Clinical School, North Queensland, Australia

Presented at the biennial Scientific Meeting of the International Hepato-Pancreatico-Biliary Association, Brisbane, May 2000.

Methodology

- Retrospective
- 12 month period (1997)
- Primary diagnosis pancreatitis
- 3 tertiary referral hospitals

- DATABASE
  - demographics
  - pathophysiology
  - severity criteria (Ranson)
  - treatment
  - clinical outcomes

North Queensland

- Area >600 000 km^2
- Population >600 000

  Approx. 8% Aboriginal or Torres Strait Islander
- 3 public secondary / tertiary referral hospitals

Descriptive data

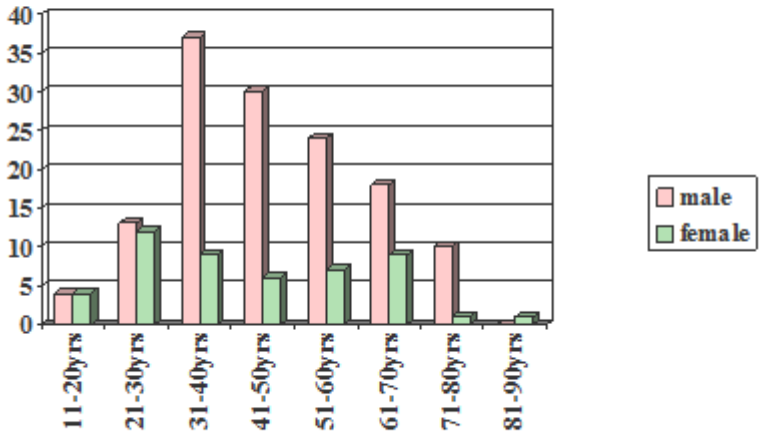
- 227 admissions (155 patients)
- 87 first admissions:

  Crude incidence = 14.7 per 100 000 / yr

  (indigenous : non-indigenous = 43.9 : 12.1)
- Mean age of admissions = 45.3 yrs (SD 15.7)
- Male : female = 78 : 22
- Indigenous admissions: 39%
- Alcoholic etiological attribution: 68%
- Chronic pancreatitis: 53%

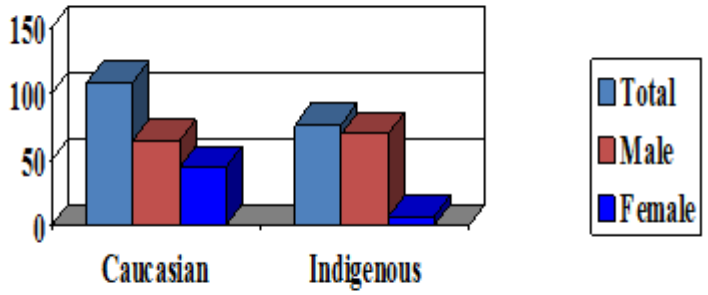
Age-gender distribution

(Y-axis = no. of patients)



Ethnicity

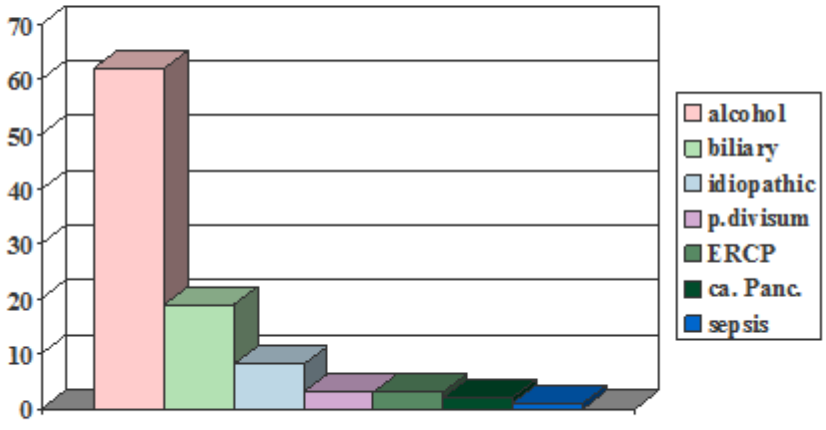
(y-axis = no. of patients)



Relative incidence Indigenous : Caucasian = **8**

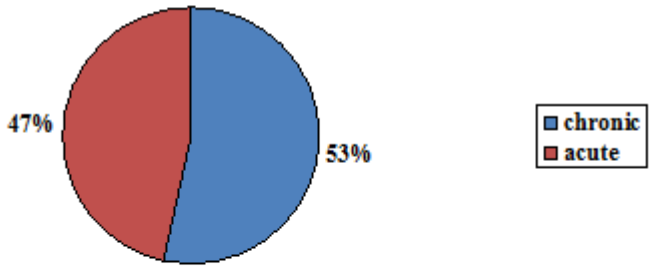
Aetiology

(Y-axis = % of admissions)



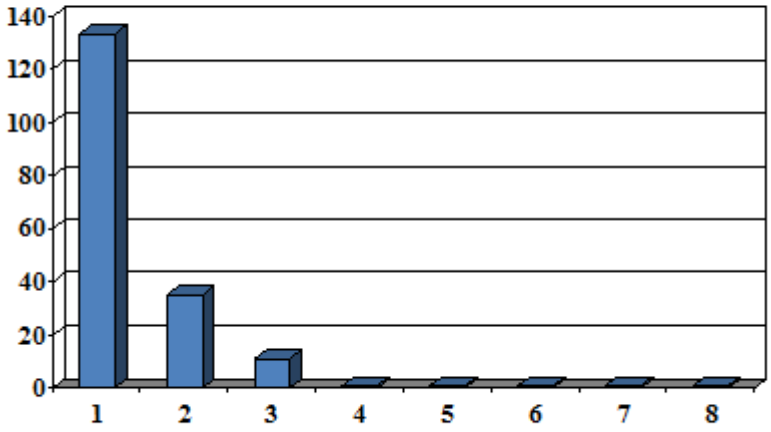
Acute or chronic pancreatitis?

(Admissions)



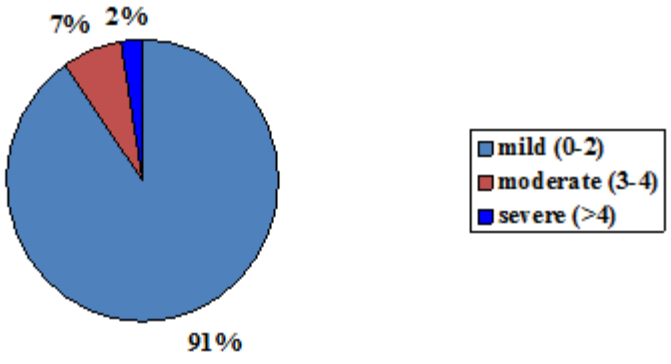
Admissions in 12 months

(Y-axis = no. of patients)



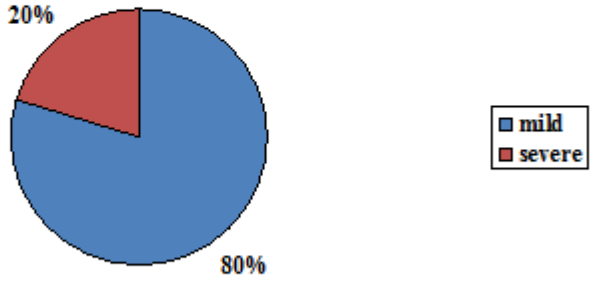
Predicted severity of admissions

(Ranson's score)



Actual severity of admissions

(Atlanta criteria)



Conclusions

- Pancreatitis is frequently encountered in northern Queensland
- Alcohol consumption is the commonest cause
- Males and indigenous people are disproportionately over-represented
- Most cases are mild and do not require surgery
- A considerable proportion of cases is thought to be chronic.

ADDENDUM:

(included in a subsequent presentation to the Australasian Pancreatic Club)

What are the determinants of chronic pancreatitis in the acute hospital population?

Univariate analyses

VARIABLE	CHRONIC	NON-CHRONIC	P-value
Age (mean)	46.5 (± 18.4)	44.2 (± 12.9)	0.1424
Male	90.0%	64.2%	**<0.00001**
Indigenous	52.9%	22.6%	**<0.0001**
Se. amylase (med.)	276	1138	**<0.0001**
Etiol. (alcohol)	92.2%	38.7%	**<0.00001**
Alcohol intake (med.)	70	5	**<0.00001**
Ranson (med.)	0	1	**0.001**
Severe status	19.0%	21.7%	0.615
Admissions (med.)	4	0	**<0.00001**

Multivariate analysis

(Generalised estimating equations)

Variable	Coefficient	P-value
Male gender	0.681	0.163
Indigenous	1.097	**0.005**
Alcohol intake	0.004	0.503
Alcohol aetiol.	-0.534	0.173
Se. amylase	-0.0007	**0.000**
Ranson score	0.074	0.771

Limitations…

- Retrospective data collection
- Missing confounders
- Need for an objective case definition

Using faecal elastase-1 to screen for chronicity in patients admitted with acute pancreatitis

A pilot study

Richard Turner, Robyn McDermott
James Cook University School of Medicine
Cairns. Australia

Presented at the biennial Scientific meeting of the European Hepato-Pancreatico-Biliary Association, Heidelberg, May 2005.

Acute or chronic pancreatitis?

- Separate disease processes…
- Acute episodes may occur in isolation or on a background of permanent or progressive disease.
- Progressive chronic disease may occur in the absence of acute episodes.

Chronic pancreatitis

- True prevalence is largely unknown.
- Those presenting with acute attacks are a relatively high prevalence subgroup.
- Gold standard tests are often invasive, expensive or time-consuming.
  e.g. ERCP, biposy, secretin-caerulein test
- Diagnostic criteria are probability and/or aetiology based.
  e.g. Japan Pancreas Society diagnostic criteria, Zurich classification for alcoholic chronic pancreatitis.

Faecal elastase-1

- ELISA method (Schebo®, Giessen)
- Stable during intestinal transit, at 4-8°C for 3 days and at -20°C for 12 months.
- >90% sensitivity and specificity for chronic pancreatitis (*Stein et al* 1993, 1996, 1997; *Löser et al* 1995, 1996)
- Exocrine insufficiency if <200 µg E1/g stool
- False positives may be due to liquid stools.

Research question

- *Does the [FE-1] of a stool specimen obtained opportunistically during the course of an acute episode of pancreatitis accurately reflect baseline exocrine function (or the presence of chronic pancreatitis)?*

Clinical setting

- Cairns Base Hospital in Far North Queensland, Australia
- Approximately 250,000 people over >500,000 sq. km between 18°S and 9°30'S
- 12% are indigenous Australians.

Patients and methods

- Consecutive admissions for acute pancreatitis - based on characteristic abdominal pain and elevated serum lipase.
- First available stool specimen analysed for [FE-1] by ELISA method (Schebo®)
- Liquid stool specimens were excluded.
- Exocrine insufficiency if [FE-1] < 200µg/g

Diagnostic performance criteria were assessed w.r.t. "gold standard" clinical case definition...

One or more of the following:

- chronic epigastric pain
- >4 acute admissions in previous 5 years (where alcohol-related)
- steatorrhoea
- otherwise unexplained weight loss
- positive imaging

Results I

- 105 stool specimens from 87 patients.
- Between April 2001 and May 2004.
- 84.8% classified as mild acute pancreatitis by Ranson's score
- 39.0% had [FE-1] < 200μg/g

Results I

	Mild	Moderate / severe	TOTALS
[FE-1] ≥ 200µg/g	58	6	64
[FE-1] < 200µg/g	31	10	41 *(39%)*
TOTALS	89 *(84.8%)*	16	105

Results II

	Diagnosis +	Diagnosis -	TOTALS
Test +	32	9	41
Test -	9	55	64
TOTALS	41	64	105

Results II

- Sensitivity 78.0%
- Specificity 76.6%
- Positive predictive value 78.0%
- Negative predictive value 85.9%

- Diagnostic efficiency 82.9%

Moderate / severe acute pancreatitis...

- Exocrine "shock" or necrosis may lead to an acute fall in [FE-1]

- Therefore, exclusion of specimens where Ranson score >2

- Majority of false positives were eliminated.

Results III

	Diagnosis +	Diagnosis -	TOTALS
Test +	**31**	**1**	**32**
Test -	**8**	**49**	**57**
TOTALS	**39**	**50**	**89**

Results III

- Sensitivity 79.5%
- Specificity 98.0%
- Positive predictive value 96.9%
- Negative predictive value 86.0%

- Diagnostic efficiency 89.9%

Conclusions I

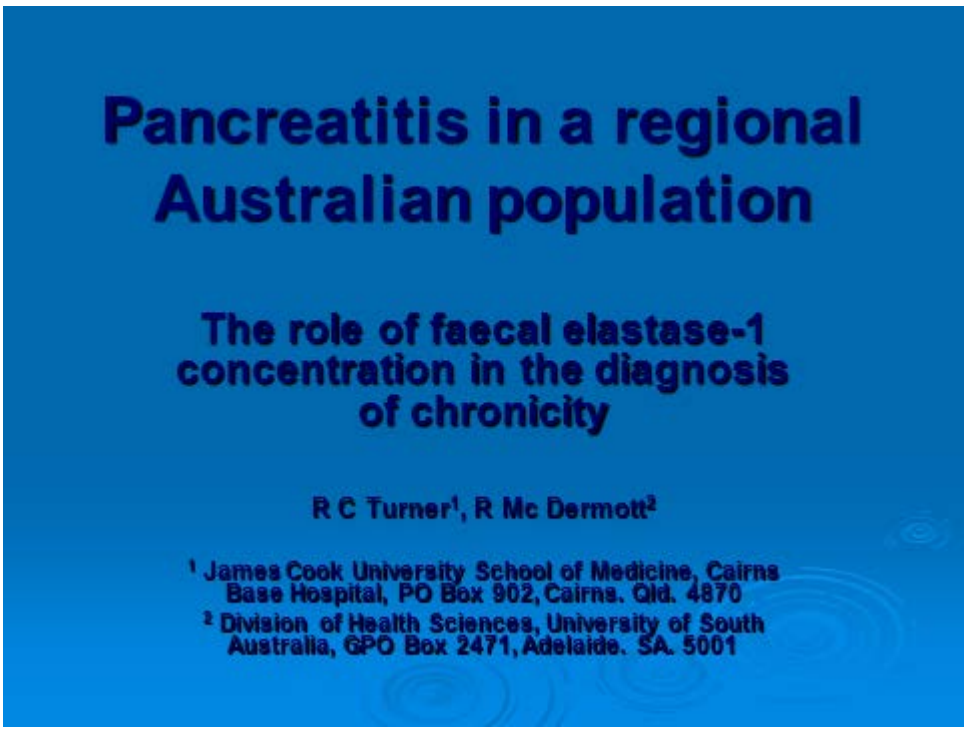
- [FE-1] accurately diagnoses underlying chronicity in patients admitted with mild acute attacks of pancreatitis.

Conclusions II

- Patients with severe acute pancreatitis should be followed up to detect irreversible exocrine impairment.

Conclusions III

- Those with consistently subnormal [FE1] should be offered a different management pathway to that of purely acute pancreatitis.



Presented at the Australian Health and Medical Research Congress, Brisbane, November 2008.

Pancreatitis

Acute

- Inappropriate intraparenchymal activation of digestive enzymes.
- Autodigestion, variable local and systemic inflammatory response
- May be severe (fatal or with local complications) or mild (self-limiting and reversible)
- Main etiological factors: alcohol, gallstones

Chronic

- Progressive fibrosis and acinar atrophy (irreversible)
- Due to necrosis-fibrosis sequence or "insidious" fibrosis
- Results in chronic pain, exocrine insufficiency (malabsorption), and endocrine insufficiency (diabetes)
- May co-exist with acute attacks

Diagnostic tests for chronic pancreatitis

Functional

- Secretin-caerulein
- Secretin-cholecystokinin
- Lundh meal
- Pancreolauryl test
- Faecal chymotrypsin
- Faecal elastase-1

Morphological

- Histology (biopsy)
- ERCP
- MRCP
- Endoscopic ultrasound
- CT scan

Faecal elastase-1 [FE-1]

- Exclusively produced by pancreas
- Stable at room (or body) temperature for 72 hrs and at -20°C for up to 12 months
- Stool concentration measured by ELISA
- Mild-moderate exocrine insufficiency if [FE-1] <200µg/g
- Sensitivity and specificity w.r.t. "gold standard" tests >90%

Diagnostic test evaluation: [FE-1]

Location	Cairns Base Hospital, Queensland, Australia
Census period	March 2004 – February 2007
Inclusion criteria	Hospitalisation with acute pancreatitis; first available stool specimen for [FE-1] measurement
Exclusion criteria	Liquid stools specimens Severe acute pancreatitis
Reference	Consensus-based clinical criteria

Clinical criteria for chronic pancreatitis

At least one of:

- Chronic epigastric pain
- Recurrent acute admissions
- Steatorrhea
- Weight loss
- Medical imaging features

(Diabetes NOT a criterion)

Results: [FE-1] vs clinical diagnosis

Exclusion of liquid stools and Ranson score >2

	Clinical diagnosis +	Clinical diagnosis -	TOTALS
[FE-1] <200µg/g	38 44	3 27	41 71
[FE-1] ≥200µg/g	9 12	68 83	77 95
TOTALS	47 56	71 110	118 166

Measures of discrimination
(n = 118)

Measure	*Value*	*95% C.I.*
Sensitivity	81%	68-90
Specificity	94%	85-98
Positive predictive value	92%	80-97
Positive likelihood ratio	14.4	5.5-37.6

Discussion points I

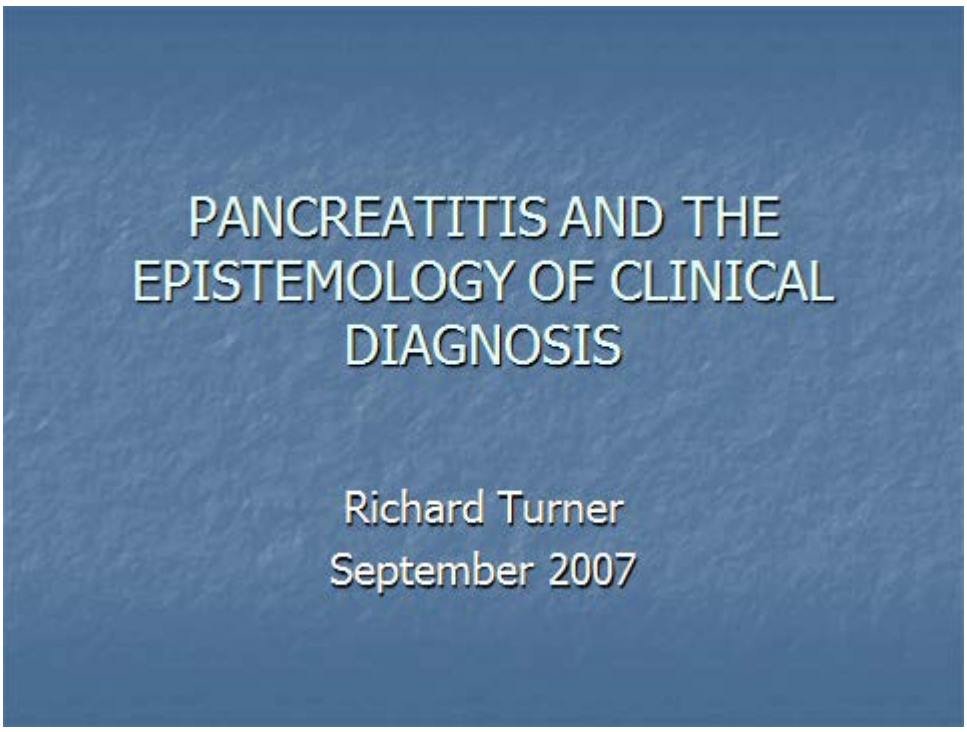
- Based on [FE-1]<200µg/g, approx. prevalence of chronic pancreatitis in tested sample is 40% (95% CU: 31-49)
- Selection bias in intention-to-test population:
  - Non-available stool specimen
  - Non-evaluable stool specimen
  - Severe acute pancreatitis

Discussion points II

- Exocrine insufficiency, as measured by [FE-1], is a "proxy" measure of chronic pancreatitis; the high prevalence of diabetes in the target population may be a confounder.
- The use of a "soft" reference standard in diagnostic test evaluation is valid and practical – provided strict case definition criteria are applied.

Conclusions

- [FE-1] is an accurate and feasible means of opportunistic screening for chronic pancreatitis in this high-prevalence population.
- Such screening may provide the evidence base for more appropriate management protocols.
- Longitudinal follow-up of the cohort will provide further useful information.



Presented at the University of South Australia, School of Health Sciences (weekly seminar program), Adelaide, October 2008.

PANCREATITIS

"Acute or chronic inflammation of the pancreas…"

EPISTEMOLOGY

"the branch of philosophy which investigates the origin, nature, methods, and limits of human knowledge"

[Gr. *episteme* knowledge + O + LOGY]

DIAGNOSIS

Gr. *dia* = to know + *gignoskein* = between

The (normal) pancreas

- Intra-abdominal gland located retroperitoneally in the abdominal cavity
- Dual exocrine and endocrine functions
  - digestive enzymes
  - glucose homeostasis
  - other endocrine functions

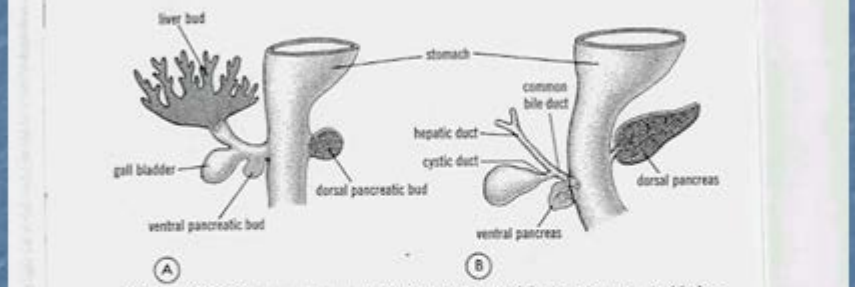


Figure 13-23. *Successive stages in the development of the pancreas. A, At 30 days (approximately 5 mm.); B, 35 days (approximately 7 mm.). The ventral pancreatic bud is initially located close to the hepatic diverticulum, but later migrates posteriorly around the duodenum in the direction of the dorsal pancreatic bud.*

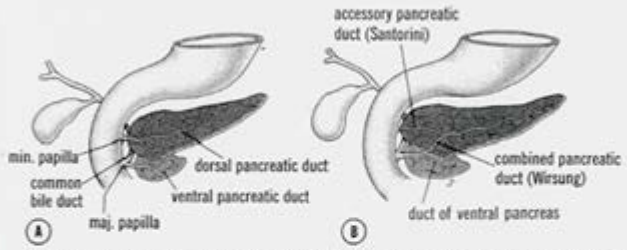
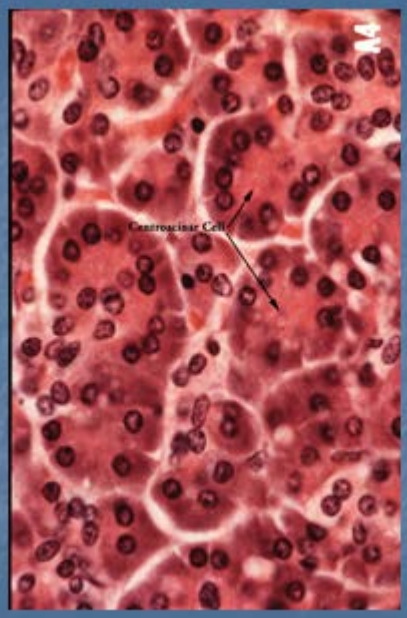


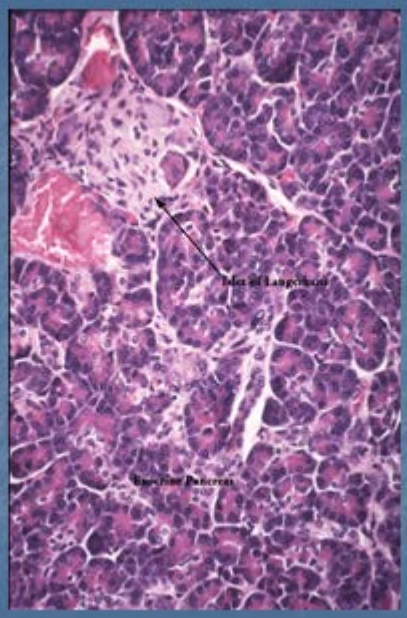
Figure 13-24. *A, The pancreas during the sixth week of development (approximately 10 mm.). The ventral pancreatic bud is in close contact with the dorsal pancreatic bud. The dorsal pancreatic duct enters the duodenum at the minor papilla and the ventral pancreatic duct at the major papilla. B, Drawing showing the fusion of the pancreatic ducts. The common pancreatic duct (Wirsung) now enters the duodenum in combination with the common bile duct at the major papilla. The accessory pancreatic duct (Santorini) enters the duodenum at the minor papilla (modified after Starck).*

The (normal) pancreas

Histology

- acini → lobules
- ductules → → → ducts
- islets of Langerhans


Centroacinar Cell


Islet of Langerhans

The (normal) pancreas

Physiology of exocrine secretion

- Composition of pancreatic juice
  - water
  - bicarbonate
  - sodium and other electrolytes
  - digestive enzymes
- Stimuli for secretion
  - neural: vagus nerve
  - hormonal: secretin, cholecystokinin

What prevents the pancreas from auto-digesting under normal circumstances?

- Pro-enzymes activated by enterokinase in duodenum
- Separate storage in acinar cells of lysosomal enzymes and digestive enzymes
- production of protease inhibitors
- low intracellular calcium concentrations

PANCREATITIS

ACUTE	CHRONIC
▪ Inappropriate intra-parenchymal activation of digestive enzymes	▪ Progressive fibrosis and distortion of the pancreatic parenchyma
▪ Variable local and systemic effects	▪ Associated with pain, malabsorption and diabetes
▪ Potentially reversible	▪ Irreversible
▪ Due to gallstones, alcohol, and other etiological factors	▪ Due largely to alcohol and certain rare etiological factors

ADVICE…

When seeking an area for research, to gain rapid expertise and unique personal kudos, choose something that is relatively unpopular, unloved, and even downright irritating for most practitioners…

Epidemiology, clinical outcomes and resource costs of pancreatitis in northern Queensland

R.C. Turner, M. von Papen, P.K. Donnelly

Department of Surgery, James Cook University Clinical School, North Queensland, Australia

Aims of the study

- To describe the incidence, demographics, and clinical outcomes of pancreatitis in northern Queensland.
- To assess the impact on the local health economy.
- To identify subgroups that may benefit from therapeutic or preventive interventions.

Methodology

- Retrospective
- 12 month period (1997)
- Primary diagnosis pancreatitis
- 3 tertiary referral hospitals

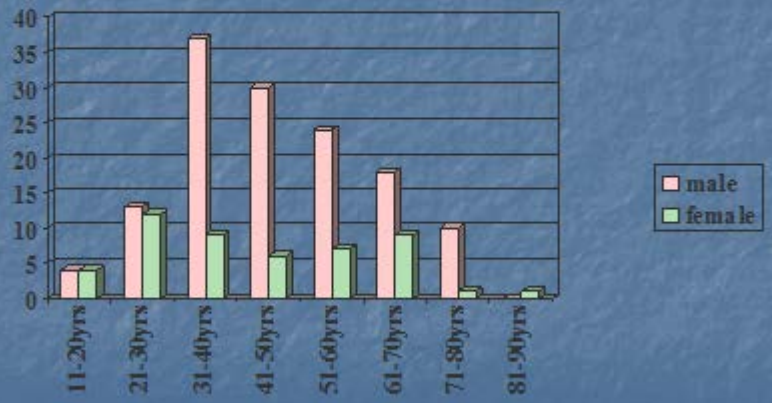
- DATABASE
  - demographics
  - pathophysiology
  - severity criteria (Ranson)
  - treatment
  - clinical outcomes

Pancreatitis in northern Queensland

Catchment population	553 385 (7% indigenous)
Admissions	293
Patients	185
First presentation	97
INCIDENCE	17.5 per 100000

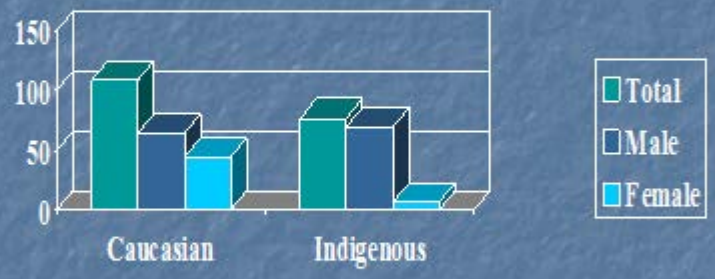
Age-gender distribution

(Y-axis = no. of patients)



Ethnicity

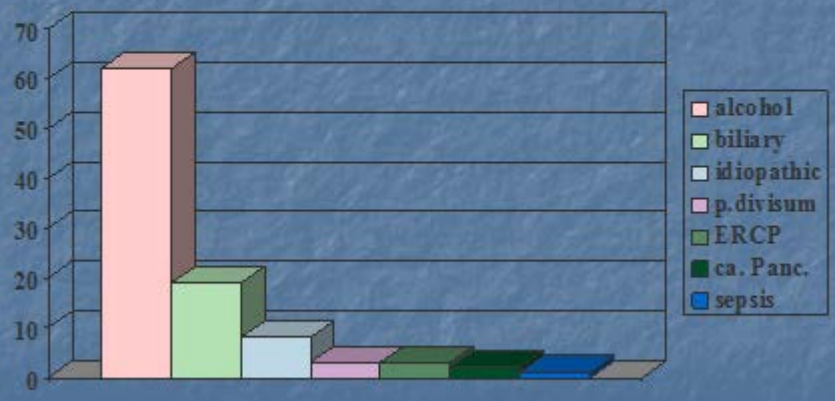
(y-axis = no. of patients)



Relative incidence Indigenous : Caucasian = **8**

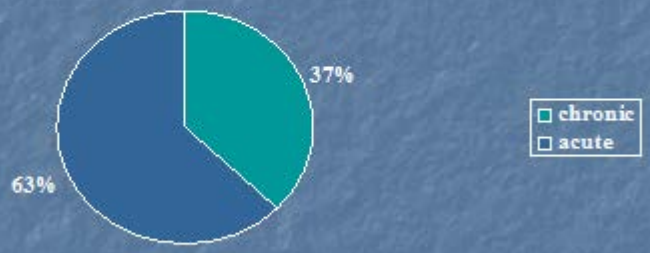
Aetiology

(Y-axis = % of admissions)



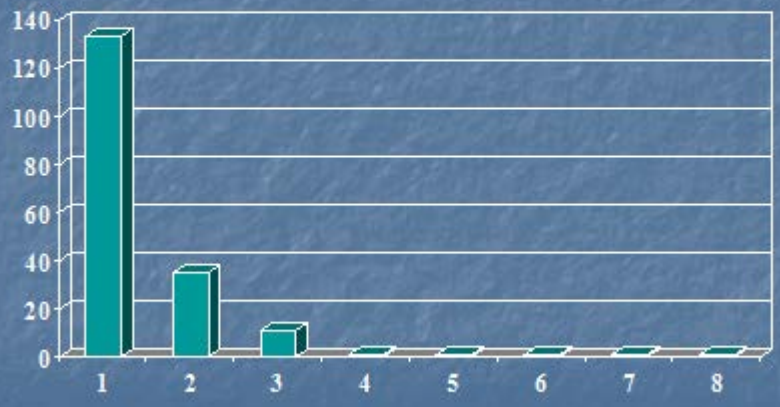
Acute or chronic pancreatitis?

(Actual patients)



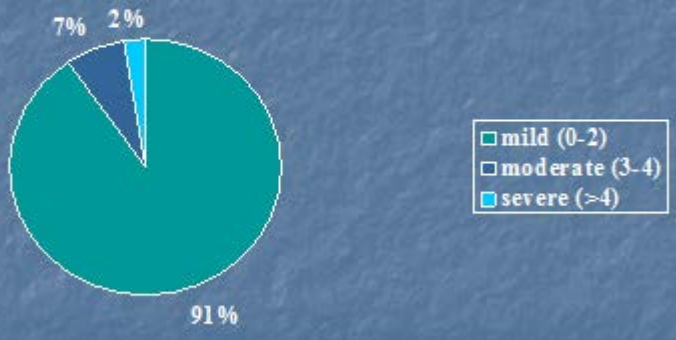
Admissions in 12 months

(Y-axis = no. of patients)



Severity of admission episodes

(Ranson's score)



Conclusions

- Pancreatitis is frequently encountered in northern Queensland
- Alcohol consumption is the commonest cause
- Males and indigenous people are disproportionately over-represented
- Most cases are mild and do not require surgery
- A considerable proportion of cases is thought to be chronic.

How do we "objectively" diagnose CHRONIC PANCREATITIS?

CLINICAL DIAGNOSIS

- The differentiation of a pathological state from a non-pathological state
- The differentiation between two pathological states *(or the distinction of a pathological state arising within another pathological state)*

Nosology

- Disease is typically defined in terms of clinical features or biological outcomes.
- Such definitions are the result of repeated observations and description.
- Variable combinations of clinical features that may occur simultaneously or sequentially, become unified as a "disease", based on the common biological end-point in which they result.

Chronic pancreatitis: clinical diagnostic features

- Pain
  - Epigastric ± radiation to back
  - Continuous or intermittent
- Loss of exocrine function (malabsorption)
  - Steatorrhea
  - Weight loss
- Diabetes
  - Insulin-dependent

The temporality of clinical diagnosis

A PRIORI	*A POSTERIORI*
Clinical observations: symptoms and signs	Disease evolution: longitudinal follow-up
Diagnostic tests: morphological and functional measurements	Response to treatment

DIAGNOSTIC TESTS

- To increase the certainty of clinical suspicion
- To detect a disease process early in its evolution (prior to manifestation of typical clinical features)
- To be utilised in the context of prognostic and therapeutic imperatives
- May measure only one biological process within a multi-process disease ("proxy measure")

THE BIOLOGICAL "AXES" OF DIAGNOSTIC TESTS

MORPHOLOGICAL

- Complex visual images
- Categorical or discrete numerical data
- May diagnose >1 biological process and >1 disease

FUNCTIONAL

- Quantifiable measurements
- Continuous numerical data (which can also be categorised)
- Usually diagnose 1 biological process, but sometimes >1 disease

DIAGNOSTIC TESTS w.r.t. OBSERVER ROLE

OBSERVATIONAL	EXPERIMENTAL
▪ Observations are made of spontaneously occurring phenomena	▪ Active modification of the external milieu to elicit a measurable response
▪ No interventions are performed	▪ Involves some form of intervention – with varying degrees of invasiveness

CHOICE OF DIAGNOSTIC TESTS

Influenced by:

- Efficacy
- Diagnostic and therapeutic imperatives
- Cost
- Ethical issues: risk vs benefit
- ?? Vested interests

CHRONIC PANCREATITIS: DIAGNOSTIC TESTS

	Morphological	Functional
Observational	▪MRCP ▪CT scan	▪Faecal elastase-1 ▪Faecal chymotrypsin ▪Faecal fat quantification
Experimental	▪ERCP ▪Pancreatic biopsy (histology)	▪Secretin-cerulein test ▪Pancreolauryl test ▪^{13}C-substrate breath tests

[FAECAL ELASTASE-1]

- ELISA method (Schebo®, Giessen)
- Stable during intestinal transit, at 4-8°C for 3 days and at -20°C for 12 months.
- >90% sensitivity and specificity for chronic pancreatitis (*Stein et al* 1993, 1996, 1997; *Löser et al* 1995, 1996)
- Exocrine insufficiency if <200 μg E1/g stool
- False positives may be due to liquid stools.

Opportunistic screening for chronic pancreatitis in northern Queensland

Using faecal elastase-1 to define the at-risk population with a view to better management

Richard Turner
James Cook University School of Medicine

Research question

- *Does the [FE-1] of a stool specimen obtained opportunistically during the course of an acute episode of pancreatitis accurately reflect baseline exocrine function (or the presence of chronic pancreatitis)?*

Clinical setting

- Cairns Base Hospital in Far North Queensland, Australia
- Approximately 250,000 people over >500,000 sq. km between 18°S and 9°30'S
- 12% are indigenous Australians.


CAIRNS BASE HOSPITAL

Methods


Far North Queensland
Pancreatitis Study
Faecal elastase-1
study

Faecal elastase-1 pilot study

- Consecutive admissions for acute pancreatitis - based on characteristic abdominal pain and elevated serum lipase.
- First available stool specimen analysed for [FE-1] by ELISA method (Schebo®)
- Liquid stool specimens were excluded.
- Exocrine insufficiency if [FE-1] < 200μg/g

Diagnostic performance criteria were assessed w.r.t. "gold standard" clinical case definition...

One or more of :

- chronic epigastric pain
- >4 acute admissions in previous 5 years
- steatorrhoea
- otherwise unexplained weight loss
- positive imaging

Results I

- 105 stool specimens from 87 patients.
- 84.8% classified as mild acute pancreatitis by Ranson's score
- 39.0% had [FE-1] < 200μg/g

Results II

	Diagnosis +	Diagnosis -	TOTALS
Test +	32	9	41
Test -	9	55	64
TOTALS	41	64	105

Results III

Measure of discrimination	%	95% c.i.
Sensitivity	78	63 – 89
Specificity	86	74 – 93
Positive predictive value	78	62 – 89
Positive likelihood ratio	5.6	3.0 – 10.4
Prevalence	39	30 – 49

Moderate / severe acute pancreatitis...

- Exocrine "shock" or necrosis may lead to an acute fall in [FE-1]
- Therefore, exclusion of specimens where Ranson score >2
- Majority of false positives were eliminated.

Results III

	Diagnosis +	Diagnosis -	TOTALS
Test +	31	1	32
Test -	8	49	57
TOTALS	39	50	89

Results IV

Measure of discrimination	%	95% c.i.
Sensitivity	79	63 – 90
Specificity	98	88 – 100
Positive predictive value	97	82 – 100
Positive likelihood ratio	39.7	5.7 – 278.5
Prevalence	44	33 – 55

Conclusions

- **[FE-1] accurately diagnoses underlying chronicity in patients admitted with mild acute attacks of pancreatitis.**
- Patients with severe acute pancreatitis should be followed up to detect irreversible exocrine impairment.
- Those with consistently subnormal [FE1] have should be offered a different management pathway to that of purely acute pancreatitis.

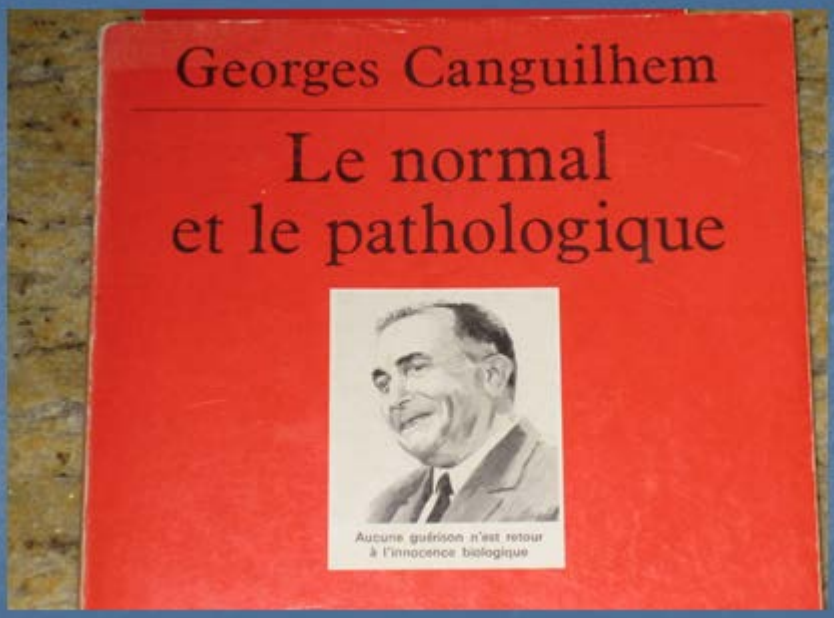
But why not look at it the other way around?

i.e.

Evaluate the clinical case definition criteria with respect to [FE-1]...

Epistemological rules for clinical diagnosis

1. ***What is amenable to diagnosis?***
   - *Definitions of disease /pathological states*
2. ***How can it be diagnosed?***
   - *Diagnostic thinking*
   - *Evaluation of diagnostic tests or methods*
   - *Diagnostic algorithms*
3. ***Why should it be diagnosed?***
   - *Rationale or intent*



Definitions of disease

- Alterations in physiological status are indeed quantitative but are viewed qualitatively by the patient and practitioner – so the organism itself has a role in determining its (desired) milieu.
- A variety of factors may come into play when determining this qualitative judgement: the role of "expertise", cultural mores, etc.
- Pathological thresholds may nevertheless be determined by quantitative methods e.g. ROC curves, etc.

TWO OPPOSING DOCTRINES…

ONTOLOGICAL	FUNCTIONAL
Absolute distinction between health and disease	Disease is part of an homogeneous state or physiological continuum
Categorical data…	Continuous data…
? Acute pancreatitis	? Chronic pancreatitis
?? Surgeons	?? Physicians

DIAGNOSTIC THINKING

ANALYTICAL

- Probabilistic
- Descriptive
- Criteria-based
- Anatomic
- Pathophysiologic
- Biopsychosocial

NON-ANALYTICAL

- Experience
- Expertise

Evaluation of diagnostic tests: "Phase I"

Reliability…

- Intra-observer reproducibility
- Inter-observer reproducibility

Evaluation of diagnostic tests: "Phase II"

Validity…

- Against a reference test ("gold standard")
  - Sensitivity, specificity, PPV, NPV, accuracy
  - Positive and negative likelihood odds ratios
- Longitudinal reproducibility (test-retest)
  - Inter-class correlation coefficient
  - kappa

Epistemological questions…

- *How is a reference test determined?*
- *What if there is no established reference?*
- *What if the reference test is not feasible?*
- *Can tests measuring different biological processes occurring within the same disease be directly compared?*

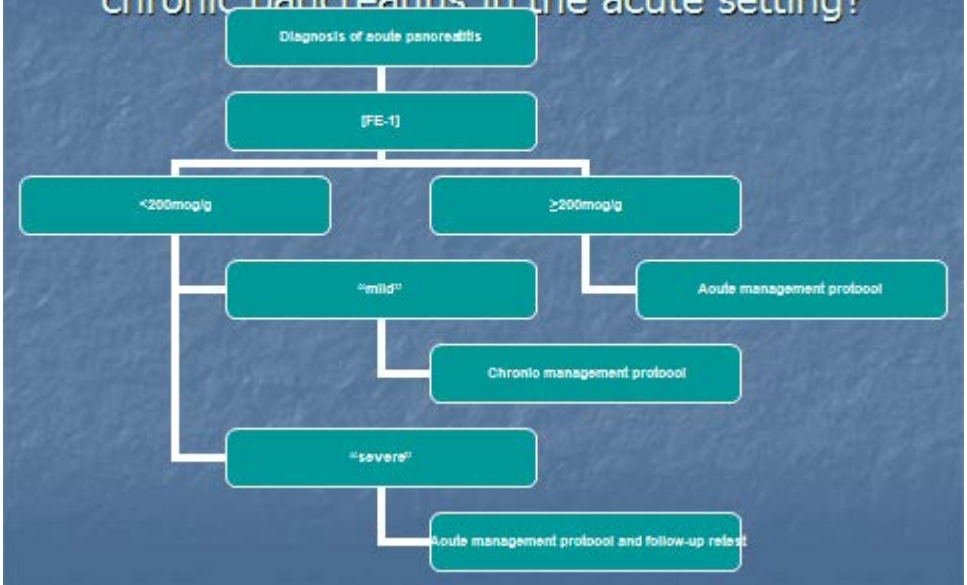
Evaluation of diagnostic tests: "Phase III"

- Clinical outcome evaluation
- Cost-effectiveness evaluation
- Randomised controlled trials

Diagnostic algorithms

- Serial hypothesis testing aimed at progressively increasing diagnostic probability to a level that is clinically acceptable i.e. where the benefits of a particular course of management outweigh the risks.
- Undifferentiated → → differentiated
- Should also be subject to evaluation…

A diagnostic / treatment algorithm for chronic pancreatitis in the acute setting?



Rationale for diagnosis

The whole notion of diagnosis implies the need to give a phenomenon or set of phenomena a definitive name (label), and in doing so, by virtue of preceding (collective) experience, predict the natural history (evolution) of the process and propose appropriate interventions to ameliorate its course.

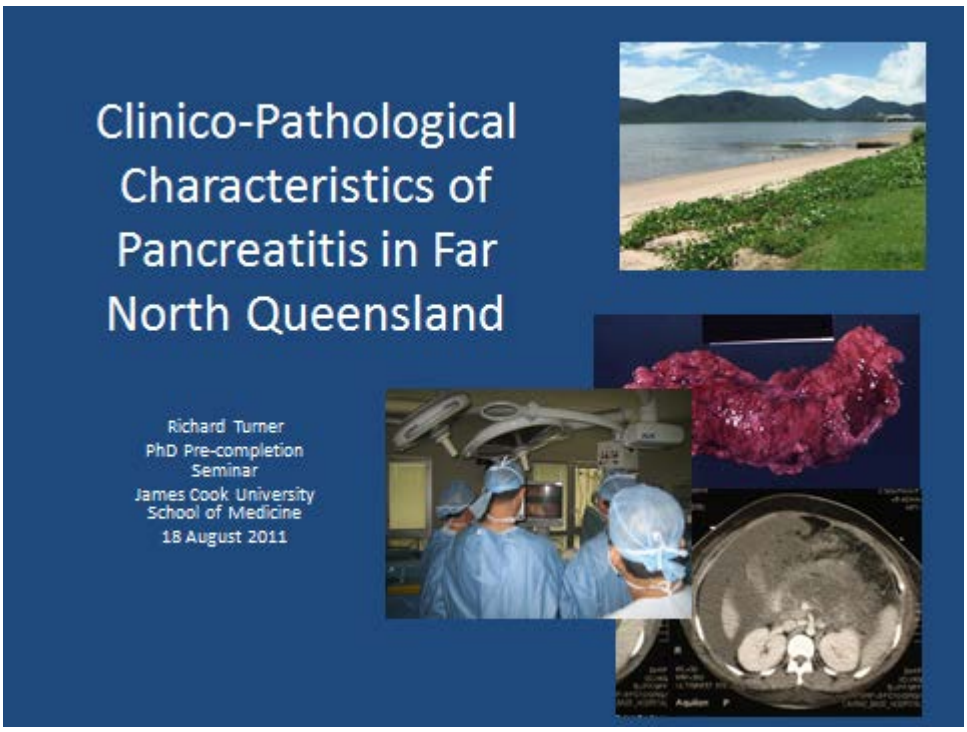
CHRONIC PANCREATITIS:
PROGNOSTIC AND THERAPEUTIC IMPERATIVES FOR DIAGNOSIS…

- Chronic disease management – justification of a more appropriate clinical pathway.
- Preventive research – co-factors in the causation of (chronic) pancreatitis.
- Diabetes mellitus – what proportion of cases can be attributed to chronic pancreatitis?

ADVICE…

When seeking an area for research, to gain rapid expertise and unique personal kudos, choose something that is relatively unpopular, unloved, and even downright irritating for most practitioners…

but don't expect to be awash with funding.



Presented as a Pre-Completion Seminar at James Cook University, Cairns, August 2011.

The aim of this body of work

- To use observational epidemiology to characterise pancreatitis in a regional hospital population with a view to informing improved clinical practice.

- 3 studies will be presented:
  - Retrospective case audit
  - Diagnostic evaluation for [FE-1]
  - Prospective cohort study

PANCREATITIS

ACUTE

- Inappropriate intra-parenchymal activation of digestive enzymes
- Variable local and systemic effects
- Potentially reversible
- Due to gallstones, alcohol, and other etiological factors

CHRONIC

- Progressive fibrosis, distortion and loss of pancreatic parenchyma
- Associated with pain, malabsorption and diabetes
- Irreversible
- Due largely to alcohol and certain rare etiological factors
- Role of oxidative stress

Management of pancreatitis

- Acute hospital admission for supportive management
- Cholecystectomy if evidence of gallstones
- Presume alcoholic aetiology if patient drinks and no evidence of other aetiological factors: *"Stop drinking because you must be sensitive to it".*

Epidemiology and clinical outcomes of pancreatitis in northern Queensland

R Turner
Department of Surgery,
North Queensland
Clinical School

Aims of the study

- To describe the incidence, demographics, and clinical outcomes of pancreatitis in northern Queensland.
- To identify subgroups that may benefit from therapeutic or preventive interventions.

Methods

- Retrospective audit of case records
- 12-month period (1997)
- Primary diagnosis pancreatitis (ICD codes)
- 3 tertiary referral hospitals: Cairns, Townsville, Mackay

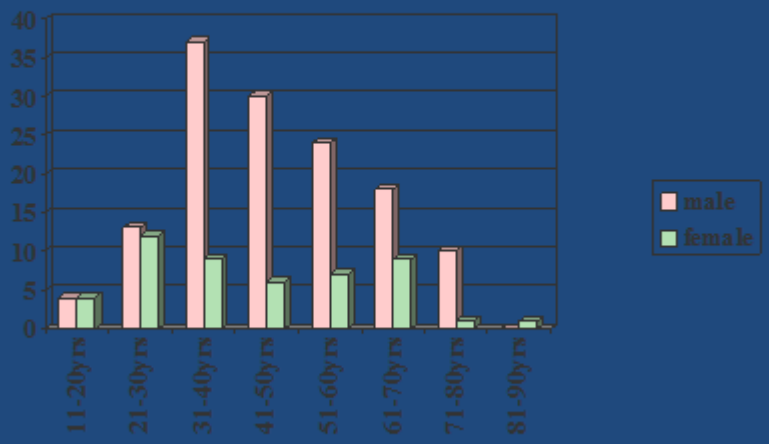
- Data collection
  - demographics
  - pathophysiology
  - aetiological attribution
  - severity criteria (Ranson)
  - treatments
  - clinical outcomes: chronic pancreatitis, severe acute pancreatitis
- Data analysis
  - Descriptive statistics

Patient characteristics

- 227 admissions (155 patients)
- 87 first admissions:
  Crude incidence = 14.7 per 100 000 / yr
  (indigenous : non-indigenous = 43.9 : 12.1)
- Mean age of admissions = 45.3 yrs (SD 15.7)
- Male : female = 78 : 22
- Indigenous admissions: 39%
- Alcoholic etiological attribution: 68%
- Chronic pancreatitis: 53%
- Predicted severe acute pancreatitis: 9%

Age-gender distribution

(Y-axis = no. of patients)



Conclusions

- Pancreatitis is frequently encountered in northern Queensland.
- Alcohol consumption is the commonest attributed cause.
- Males and indigenous people are disproportionately over-represented.
- Most cases are mild.
- A considerable proportion of cases is thought to be chronic.

Limitations…

- Retrospective data collection
  - Incomplete and/or inaccurate ascertainment of explanatory variables
- Missing confounders
  - Certain potential explanatory variables not captured by medical records
- Need for an objective case definition
  - Variable and imprecise diagnostic criteria for outcome variable (chronic pancreatitis)

CHRONIC PANCREATITIS: DIAGNOSTIC TESTS

	Morphological	Functional
Observational	•MRCP •CT scan	•Faecal elastase-1 •Faecal chymotrypsin •Faecal fat quantification
Experimental	•ERCP •Pancreatic biopsy (histology)	•Secretin-cerulein test •Pancreolauryl test •^{13}C-substrate breath tests

[FAECAL ELASTASE-1]

- ELISA method (Schebo®, Giessen)
- Stable during intestinal transit, at 4-8°C for 3 days and at -20°C for 12 months.
- >90% sensitivity and specificity for chronic pancreatitis*
- Exocrine insufficiency if <200 µg E1/g stool*
- False positives may be due to liquid stools.

**Stein et al* 1993, 1996, 1997; *Löser et al* 1995, 1996

Opportunistic screening for chronic pancreatitis in northern Queensland

Using faecal elastase-1 to define the at-risk population with a view to better management

Richard Turner
James Cook University School of Medicine

Research questions

- *Does the [FE-1] of a stool specimen obtained opportunistically during the course of an acute episode of pancreatitis accurately reflect baseline exocrine function (or the presence of chronic pancreatitis)?*
- *What is the diagnostic accuracy of this test against a "gold standard" clinical diagnosis?*

Methods

- Cairns Base Hospital 2001-2003
- Convenience sample of admissions for acute pancreatitis*
- First available stool specimen analysed for [FE-1] by ELISA method (Schebo®)
- Liquid stool specimens were excluded.
- Exocrine insufficiency if [FE-1] < 200µg/g

* *based on characteristic abdominal pain and elevated serum lipase*

Diagnostic performance criteria were assessed w.r.t. "gold standard" clinical case definition...

One or more of :

- chronic epigastric pain
- >4 acute admissions in previous 5 years
- steatorrhoea
- otherwise unexplained weight loss
- positive imaging

Results

- 105 stool specimens from 87 patients.
- 84.8% classified as mild acute pancreatitis by Ranson's score
- 39.0% had a clinical diagnosis of chronic pancreatitis
- 39.0% had [FE-1] < 200µg/g

Accuracy of [FE-1] against clinical diagnosis of chronic pancreatitis

Measure of discrimination	%	95% c.i.
Sensitivity	78	63 – 89
Specificity	86	74 – 93
Positive predictive value	78	62 – 89
Positive likelihood ratio	5.6	3.0 – 10.4
Prevalence	39	30 – 49

Moderate / severe acute pancreatitis...

- Exocrine "shock" or necrosis may lead to an acute decrease in [FE-1]*
- Therefore, exclusion of specimens where Ranson score >2
- Majority of false positives were eliminated.

* Boreham and Ammori, 2003

Accuracy of [FE-1] against clinical diagnosis of chronic pancreatitis in predicted non-severe acute cases

Measure of discrimination	%	95% c.i.
Sensitivity	79	63 – 90
Specificity	98	88 – 100
Positive predictive value	97	82 – 100
Positive likelihood ratio	39.7	5.7 – 278.5
Prevalence	44	33 – 55

Conclusions

- **[FE-1] accurately diagnoses underlying chronicity in patients admitted with mild acute attacks of pancreatitis.**
- [FE=1] may equally be used in conjunction with other (clinical) diagnostic criteria.
- Patients with severe acute pancreatitis should be followed up to detect irreversible exocrine impairment.
- Those with consistently subnormal [FE1] have should be offered a different management pathway to that of purely acute pancreatitis.

Pancreatitis in FNQ : a prospective cohort study

Richard Turner
James Cook University School of Medicine

Aims

- To identify and characterise incident cases of acute pancreatitis that have co-existent chronic pancreatitis
- To explore potential determinants of underlying chronic pancreatitis in this study cohort

METHODS

- Case-comparison study with prospective data collection
- Incident cases of acute pancreatitis at Cairns Base Hospital, 2004-2007
- OUTCOME MEASURE = chronic pancreatitis*
- Potential determinants including:

  socio-demographics, 24-hour dietary recall (Foodworks 2007™), alcohol intake parameters, aetiological attribution, parameters of smoking.
- Analysis (STATA 9.2)
  - Descriptive statistics
  - Univariate comparisons
  - Multiple logistic regression
  - Principal Components Analysis

* CP defined as having at least one of the following: chronic pain, >4 previous admissions, otherwise unexplained weight loss, steatorrhea, consistent imaging, [FE-1]<200

FNQ hospital-recruited cohort

Total cases	153
Mean age (yrs)	44.7
% male	61.4
% indigenous	41.2
% alcoholic aetiology	54.4
% severe acute pancreatitis	11.2
% chronic pancreatitis	54.3

Potential associations with the presence of underlying chronic pancreatitis

(* non-parametric continuous variables)

VARIABLE	CP absent	CP present	P-value
Age, years	46.0	43.4	0.2887
Male sex, %	47.9	72.9	0.0014
Indigenous, %	33.8	45.9	0.1257
Current smoker, %	48.4	73.9	0.0016
Cigarettes/d	8.9	15.6	0.0005
Cigarette-years	10.5	500	0.0000
7-day alcohol intake, g*	3.0	8.0	0.4987
Average alcohol intake, g/week*	30	80	0.3304
Coffee intake, cups/d	0.45	0.94	0.0411
Energy intake kj	5713	4211	0.0095
Fat intake, g/d*	48.0	24.5	0.0021
Carbohydrate intake, g/d	115.8	89.1	0.0379
Protein intake, g/d	59.6	45.9	0.0323
Folate, µg/d*	145.7	98.7	0.0174
Vitamin A, µg/d*	445.6	278.0	0.0699
Vitamin C, mg/d*	35.4	25.3	0.1367

Adjusted risk of chronic pancreatitis

Itemised nutrients and other intakes adjusted for sex, indigeneity and BMI.

Variable	IRR	95% CI
Male gender	1.42	0.997 – 2.036
Indigenous	1.25	0.923 – 1.716
BMI	0.96	0.933 – 0.995
7-day alcohol	0.99	0.998 – 1.000
Cigarettes/day	1.01	0.999 – 1.028
kj/24h	0.99	0.999 – 1.000
Fat/24h	0.99	0.978 – 0.998
Protein/24h	1.01	0.998 – 1.011
Carbohydrate/24h	0.99	0.997 – 1.003
Folate/24h	0.99	0.998 – 1.000
Vitamin A/24h	0.99	0.999 – 1.000
Vitamin C/24h	1.00	0.998 – 1.003
Coffee/24h	1.08	0.999 – 1.176

Principal components analysis

- Intake of 24-hr macro and micronutrients, cigarettes/day and 7-day alcohol, and daily coffee were included.
- 3 components had eigenvalues >1
- After oblique rotation, based on factor loadings >0.4, these could be described as:

"nutritive" = all macro and micronutrients
"stimulant" = cigarettes and coffee
"abusive" = cigarettes and alcohol

Adjusted risk of chronic pancreatitis

Principal components of intake adjusted for age, sex, indigeneity, and BMI

Variable	IRR	95% CI
Age (years)	1.00	0.99 – 1.00
Male gender	1.38	0.95 – 2.00
Indigenous	1.43	1.04 – 1.98
BMI	0.96	0.93 – 0.99
"nutritive" pattern	0.83	0.71 – 0.97
"stimulant" pattern	1.16	1.05 – 1.29
"abusive" pattern	0.97	0.82 – 1.14

Conclusions

- Alcohol consumption of itself or combined with smoking is not significantly associated with underlying chronic pancreatitis in this cohort of acute incident cases.
- PCA suggests that prior to an acute exacerbation, those with chronic pancreatitis are more likely to forego food nutrients for other ingested agents such as tobacco and coffee.
- There are limitations to causal inference for chronic pancreatitis *per se* due to the non-directional nature of the data.
- PCA with actual food items may yield more clinically meaningful results.
- Longitudinal data collection is desirable…

What this body of work demonstrates…

Acute pancreatitis in FNQ should largely be managed as a chronic disease

BECAUSE

- Over 50% of incident cases have evidence of underlying chronic pancreatitis.
- Many of the factors that modify the course of the disease are themselves chronic disease states – alcoholism, poor dietary/intake habits, obesity.
- Modifiable factors have broader implications for other chronic diseases and for general wellbeing.
- An acute episode is a "teachable moment"…

The data presented informs chronic disease management strategies by:

- Providing a practical means by which chronic pancreatitis can be diagnosed in an acute setting*.
- Identifying variables associated with chronic pancreatitics, which may:
  - Inform preventive/therapeutic strategies
  - Further identify at-risk groups or individuals
- Describing "non-chronic" cases that may also benefit from a chronic disease management plan.
- Showing that in cases of alcohol attribution, a more complex therapeutic message is required ie. more than "go to rehab".

* QHPS now performs this assay.

Chronic disease management would comprise:

- An ongoing care plan – with specific preventive and therapeutic interventions
- Follow-up
- Multidisciplinary care
- (Not necessarily focused on one disease)

There are challenges to a chronic disease management paradigm in this population:

- For many patients, an acute care service is the only contact with the health sector.
- Obstacles to follow-up may be psychological, cultural and geographical.
- Dedicated multidisciplinary care is logistically difficult.
- Further health service delivery research is required…

Refereed works

Published articles

Turner RC, McDermott R. Using faecal elastase-1 to screen for chronic pancreatitis in patients admitted with acute pancreatitis. *HPB.* 2006, **8**: 223-226

Published abstracts (oral communications)

Turner RC, von Papen M, Donnelly PK. Epidemiology, clinical outcomes and resource costing of pancreatitis in northern Queensland. *ANZJ. Surg.* 2001, **70**: A97.

Turner RC, McDermott R. Fecal elastase-1 concentration as a screening tool for chronicity in acute pancreatitis admissions (abstract). *J. Gastrointest. Surg.* 2005, **9**(4): 603

Turner RC, McDermott R. Pancreatitis in a regional Australian population: the role of faecal elastase-1 concentration in the diagnosis of chronicity (abstract). *Australasian Epidemiologist* 2007, **14**(3): 32

Publication plan

Original articles

- *Intake patterns associated with acute exacerbations of chronic pancreatitis*
- *Determinants of severe acute pancreatitis in a regional Australian cohort*
- *The use of capture-recapture analysis to determine the true admission rate for pancreatitis in the public hospital sector*

Opinion/letters

- *Acute pancreatitis is a chronic disease*
- *Pancreatitis and the epistemology of clinical diagnosis*

Thesis: Table of Contents

- Case studies
- Pancreatitis –pathogenesis and management
- Epidemiology of pancreatitis in North Queensland
- Diagnosis of chronic pancreatitis
- Prospective data collection in Far North Queensland.
- Determinants of severe acute pancreatitis
- Determinants of chronic pancreatitis
- Acute pancreatitis as a chronic disease.
- Bibliography
- Acknowledgements

Acknowledgements

- Professor Robyn McDermott
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- Mr Mel Cutuli
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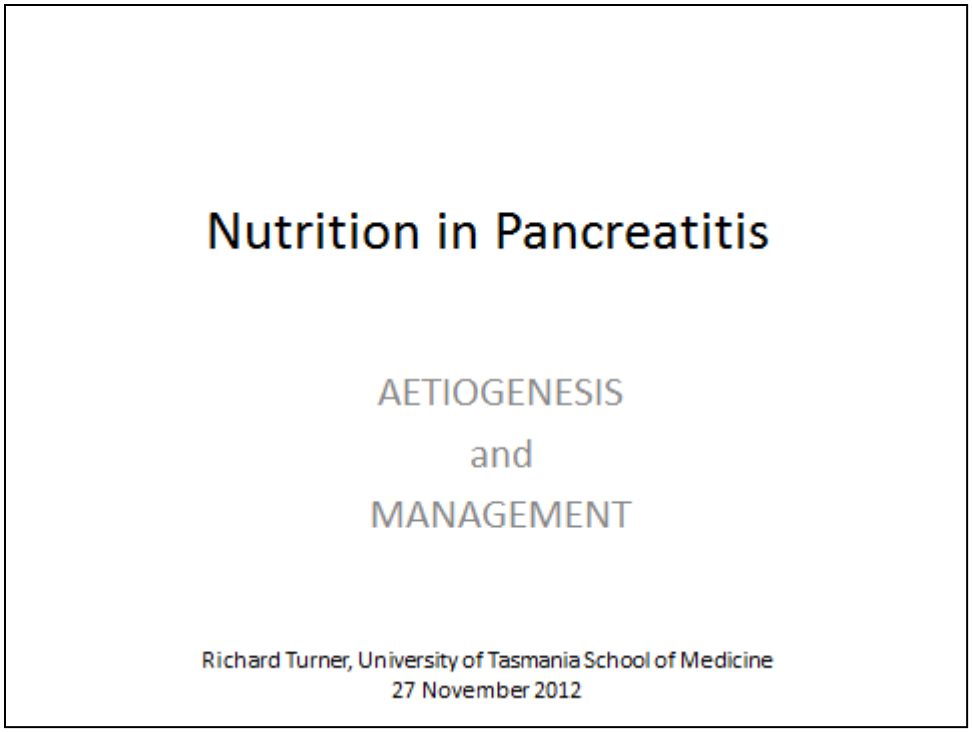
- Ms Ann Carroll
- Ms Stella Green
- Professor Adrian Esterman
- Dr Laima Brazionis
- Dr Katina d'Onise

- Abacus Diagnostics
- James Cook University / Cairns Clinical School
- Cairns Base Hospital



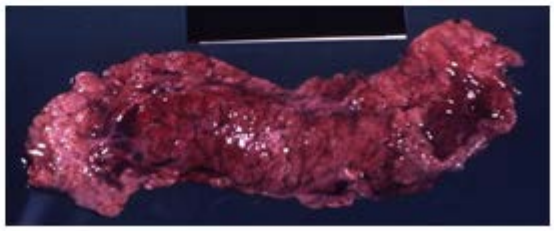
Presented as an invited lecture for the Australasian Pancreatic Club at the Australian Health and Medical Research Congress, Adelaide, November 2012.

Overview

1. Definitions
2. Chronic pancreatitis
   a. Nutrition in aetiogenesis
   b. Nutrition as therapy
3. Acute pancreatitis
   a. Nutrition in aetiogenesis
   b. Nutrition as therapy
4. Conclusion

The pancreas

- "ALL FLESH"
- Facilitates nutrition through exocrine and endocrine functions
- Also (in disease states…) responds to nutritional intakes



Nutrition

- Definition: The process by which an organism assimilates food and uses it for growth and activity.

- ENTERAL
  - Oral
  - Tube feed
- PARENTERAL

Nutrients

- Definition: Sources of nutrition esp. specific molecular constituents of food; *Diet* is an individual's typical or habitual nutrient intake.

- **MACRONUTRIENTS** = nutrients providing energy: **carbohydrates, protein, fat**

- **MICRONUTRIENTS** = substances required in minute amounts for proper growth and development: **vitamins, minerals**

- **NON-NUTRIENTS** = non-pharmaceutical dietary ingredients that the body can function without, and may be non-digestible: **antioxidants, prebiotics/fibre, probiotics, synbiotics**

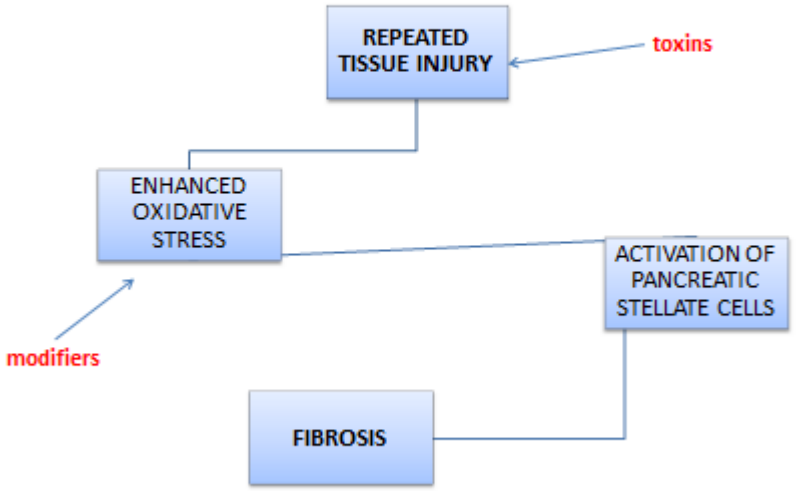
Bioavailability

- Definition: Proportion of administered substance that is absorbed and becomes available in the circulation for use or storage.

- Depends on:
  - Digestion
  - Absorption
  - Interaction with other intakes

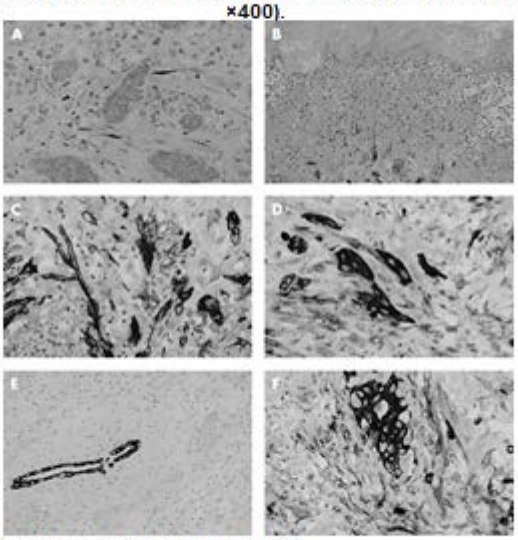
Chronic pancreatitis: AETIOGENESIS

"Manchester model"



Braganza JM. A framework for the aetiogenesis of chronic pancreatitis. Digestion 1998; 59(Suppl 4): 1-12.

(A) Loose regenerating tissue of a hypercellular regenerative sphere contains several desmin reactive cells representing elongated forms of pancreatic stellate cells (desmin immunostain, ×400).



Zimmermann A et al. Gut 2002;51:674-678

Chronic pancreatitis: AETIOGENESIS
Macronutrient studies

Durbec and Sarles, 1978	Multicentre cohort study	Quadratic relationship with lipid intake
Wilson et al, 1985	Case-control study	No difference in fat/protein intake
Balakrishnan et al, 1988	Case-control study	Low fat intake implicated
Mezey et al, 1988	**Case-control study**	**Refuted high fat/protein intake**

Chronic pancreatitis: AETIOGENESIS
Antioxidant studies

Kalvaria et al, 1986	Case-control study	Lower serum vit. E levels
Segal et al, 1995	Case-control study	Decreased serum antioxidant levels
Morris-Stiff et al, 1999	Case-control study	Decreased serum antioxidant levels
de las Heras-Castaño et al, 2005	Animal study	Cyclosporin-induced CP attenuated by antioxidants
Girish et al, 2009	Case-control study	Lower erythrocyte zinc levels

Chronic pancreatitis: AETIOGENESIS
"Novel" dietary studies

- Specific non-nutrients
- Factor analysis of dietary intakes

Assessment of cassava toxicity in patients with tropical chronic pancreatitis.

Girish BN, Rajesh G, Vaidyanathan K, Balakrishnan V.
Department of Physiology, Amrita Institute of Medical Sciences, AIMS Ponekkara P.O, Cochin - 682041, Kerala, India.

Trop Gastroenterol. 2011 Apr-Jun;32(2):112-6.

"Significant reduction in rhodanese activity with concomitant decrease in sulfur containing amino acids and antioxidants such as glutathione suggests that TCP patients are at higher risk of defective detoxification of cyanogens. However there was no difference between cassava consumers and non-consumers."

INTAKE PATTERNS OF FOOD NUTRIENTS AND OTHER SUBSTANCES ASSOCIATED WITH CHRONIC PANCREATITIS *(pending review)*

Turner RC, Brazionis LB, McDermott R.

FNQ hospital-recruited cohort

Total cases	**153**
Mean age (yrs)	44.7
% male	61.4
% indigenous	41.2
% alcoholic aetiology	54.4
% severe acute pancreatitis	11.2
% chronic pancreatitis	54.3

Adjusted risk of chronic pancreatitis

Itemised nutrients and other intakes adjusted for sex, indigeneity and BMI.

Variable	IRR	95% CI
Male gender	1.42	0.997 – 2.036
Indigenous	1.25	0.923 – 1.716
BMI	0.96	0.933 – 0.995
7-day alcohol	0.99	0.998 – 1.000
Cigarettes/day	1.01	0.999 – 1.028
kj/24h	0.99	0.999 – 1.000
Fat/24h	0.99	0.978 – 0.998
Protein/24h	1.01	0.998 – 1.011
Carbohydrate/24h	0.99	0.997 – 1.003
Folate/24h	0.99	0.998 – 1.000
Vitamin A/24h	0.99	0.999 – 1.000
Vitamin C/24h	1.00	0.998 – 1.003
Coffee/24h	1.08	0.999 – 1.176

Potential associations with the presence of underlying chronic pancreatitis

(* non-parametric continuous variables)

VARIABLE	CP absent	CP present	P-value
Age, years	46.0	43.4	0.2887
Male sex, %	47.9	72.9	0.0014
Indigenous, %	33.8	45.9	0.1257
Current smoker, %	48.4	73.9	0.0016
Cigarettes/d	8.9	15.6	0.0005
Cigarette-years	10.5	500	0.0000
7-day alcohol intake, g*	30	8.0	0.5725
Average alcohol intake, g/week*	25	80	0.2858
Coffee intake, cups/d	0.45	0.94	0.0411
Energy intake kj	5713	4211	0.0095
Fat intake, g/d*	48.0	24.5	0.0021
Carbohydrate intake, g/d	115.8	89.1	0.0379
Protein intake, g/d	59.6	45.9	0.0323
Folate, µg/d*	145.7	98.7	0.0174
Vitamin A, µg/d*	445.6	278.0	0.0699
Vitamin C, mg/d*	35.4	25.3	0.1367

Principal components analysis

- Intake of 24-hr macro and micronutrients, cigarettes/day and 7-day alcohol, and daily coffee were included.
- 3 components had eigenvalues >1
- After oblique rotation, based on factor loadings >0.4, these could be described as:

"nutritive" = all macro and micronutrients
"stimulant" = cigarettes and coffee
"abusive" = cigarettes and alcohol

Adjusted risk of chronic pancreatitis

Principal components of intake adjusted for age, sex, indigeneity, and BMI

Variable	IRR	95% CI
Age (years)	1.00	0.99 – 1.00
Male gender	1.38	0.95 – 2.00
Indigenous	1.43	1.04 – 1.98
BMI	0.96	0.93 – 0.99
"nutritive" pattern	0.83	0.71 – 0.97
"stimulant" pattern	1.16	1.05 – 1.29
"abusive" pattern	0.97	0.82 – 1.14

Chronic pancreatitis: THERAPY
Exocrine insufficiency

- Malabsorption = reduced bioavailability
  - Macronutrients esp. fat
  - Micronutrients esp. fat-soluble vitamins
- Diagnosis
  - Clinical assessment
  - Function tests
- Dietary aversion
  - Conditioning
  - Lifestyle

Chronic pancreatitis: THERAPY
ESPEN Guidelines

Statements

- Protein energy undernutrition occurs only in terminal phases
- 30-50% of patients have increased energy expenditure.
- Degree of undernutrition *probably* correlates with complications and adversely impacts outcome. (Level IV)
- Goal of nutritional therapy is to correct malabsorption and prevent undernutrition.

Recommendations

- Nutritional therapy and pain relief positively impact nutritional status. Caloric intake increases following attenuation of postprandial pain. (Grade C)
- >80% can be treated by normal diet with enzyme supplements. (Grade B)
- 10-15% require oral nutritional supplements (Grade C)
- 5% require tube feeding (Grade C)

Meier et al. *Clinical Nutrition* 2006; 25:275-284

Pancreatic exocrine insufficiency: THERAPY
APC Guidelines

Management of pancreatic exocrine insufficiency: Australasian Pancreatic Club recommendations.

Toouli J, Biankin AV, Oliver MR, Pearce CB, Wilson JS, Wray NH; Australasian Pancreatic Club.

Dept of Surgery, Flinders Medical Centre, Adelaide, SA, Australia, jim.toouli@flinders.edu.au

Med J Aust. 2010 Oct 18; 193(8): 461-476

Chronic pancreatitis: THERAPY Prevention

- Quenching oxidative stress?

Antioxidant therapy does not reduce pain in patients with chronic pancreatitis: the ANTICIPATE study.

Siriwardena AK, Mason JM, Sheen AJ, Makin AJ, Shah NS.
Hepatobiliary Surgery Unit, Manchester Royal Infirmary, Manchester, United Kingdom. ajith.siriwardena@cmft.nhs.uk

Gastroenterology 2012; 143(3): 655-663

"Thus, at the point of presentation with symptoms, with evidence of likely irreversible pancreatic parenchymal and functional alteration, the potential time point for disease modification by exogenous antioxidant supplementation may be past."

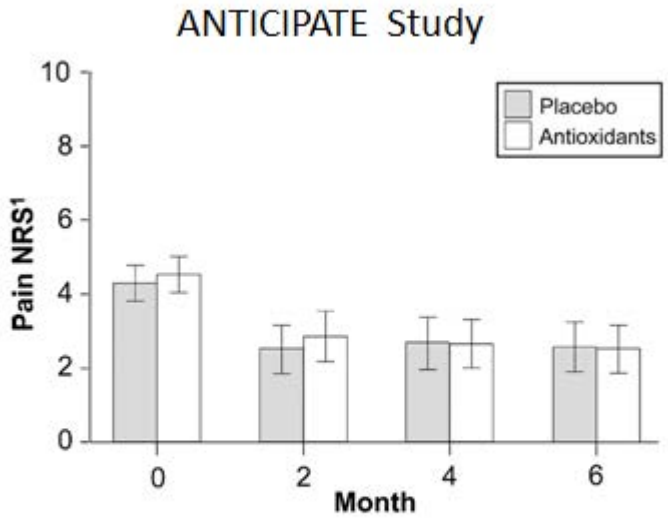
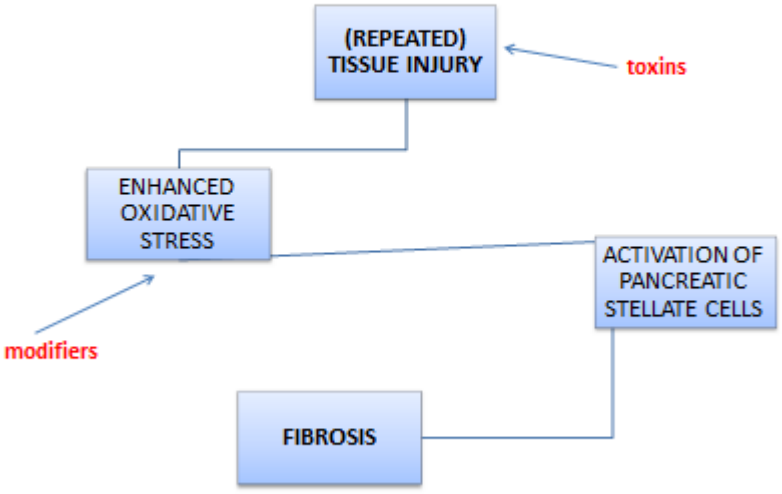


Figure 1. Clinic NRS pain scores. 1Mean pain score on the day of the clinic, on a numerical rating scale 0–10 (bars show 95% CI).

Acute pancreatitis: AETIOGENESIS "Manchester model"



Braganza JM. A framework for the aetiogenesis of chronic pancreatitis. Digestion 1998; 59(Suppl 4): 1-12.

Acute pancreatitis: AETIOGENESIS

Initiation

- Lipid surge hypothesis?

Progression

- Antioxidant bioavailability?
- Nourishment of gut mucosa
- Composition of gut flora

Lipid intolerance does not account for susceptibility to alcoholic and gallstone pancreatitis.

Haber PS, Wilson JS, Apte MV, Hall W, Goumas K, Pirola RC.
Gastrointestinal Unit, Prince of Wales and Prince Henry Hospitals, Sydney, Australia.

Gastroenterology. 1994 Mar;106(3):742-8.

Acute pancreatitis: THERAPY Objectives

1. Reversing catabolic state
2. Addressing functional insufficiency
3. Protecting gut mucosal barrier

A prospective evaluation of pancreatic exocrine function in patients with acute pancreatitis: correlation with extent of necrosis and pancreatic endocrine insufficiency

Boreham B, Ammori BJ.

BasilA. Ammori, FRCS, MD, Manchester Royal Infirmary, Oxford Road, Manchester M13 9WL. UK

E-mail: Bammori@aol.com

Pancreatology 2003; 3(4): 303-308

"Pancreatic exocrine insufficiency is a common occurrence in patients recovering from severe acute pancreatitis, and its severity correlates with the extent of pancreatic necrosis and the severity of concomitant pancreatic endocrine insufficiency."

Enteral vs parenteral nutrition

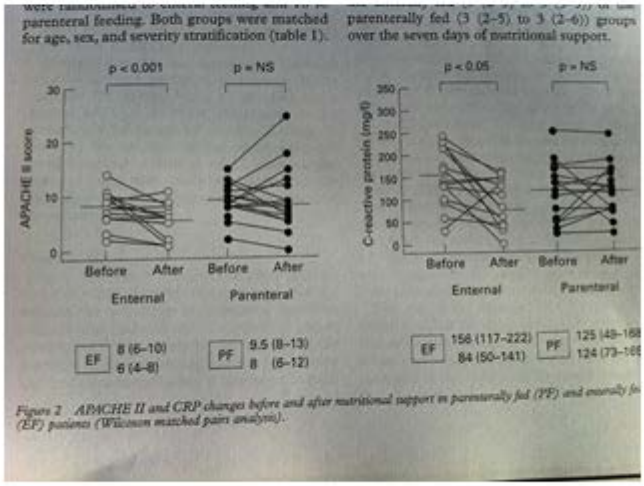


Figure 2 APACHE II and CRP changes before and after nutritional support in parenterally fed (PF) and enterally fed (EF) patients (Wilcoxon matched pairs analysis).

Windsor et al. *Gut* 1998; 42:431-435

Acute pancreatitis: THERAPY

ESPEN Guidelines: mild acute pancreatitis

Statements

- Mild pancreatitis has little impact on nutritional status or metabolism (Level IIa)

Recommendations

- Enteral nutrition (tube feeding) is not recommended if patient can tolerate normal food within 5-7 days. (Grade B)

Meier et al. *Clinical Nutrition* 2006; 25:275-284

Acute pancreatitis: THERAPY

ESPEN Guidelines: severe acute pancreatitis

Statements

- In severe necrotizing pancreatitis, energy expenditure and protein catabolism are increased (Level IIa)
- Severe undernutrition is likely to adversely affect outcome (Level ?)

Recommendations

- Enteral feeding (by gastric or jejunal route) is indicated if possible. (Grade B)
- Parenteral nutrition may be used (to supplement enteral feeds) in in cases of intestinal failure or fistulae, etc. (Grade A)
- Standard formulae can be used if tolerated. (Grade C)

Meier et al. *Clinical Nutrition* 2006; 25:275-284

Acute pancreatitis: THERAPY

Nutritional supplements

Probiotic prophylaxis in predicted severe acute pancreatitis: a randomised, double-blind, placebo-controlled trial.

Besselink MG, van Santvoort HC, Buskens E, Boermeester MA, van Goor H, Timmerman HM, Nieuwenhuijs VB, Bollen TL, van Ramshorst B, Witteman BJ, Rosman C, Ploeg RJ, Brink MA, Schaapherder AF, Dejong CH, Wahab PJ, van Laarhoven CJ, van der Harst E, van Eijck CH, Cuesta MA, Akkermans LM, Gooszen HG; Dutch Acute Pancreatitis Study Group.

Department of Surgery, University Medical Center Utrecht, Utrecht, Netherlands.

Lancet. 2008 Feb 23;371(9613):651-9. Epub 2008 Feb 14.

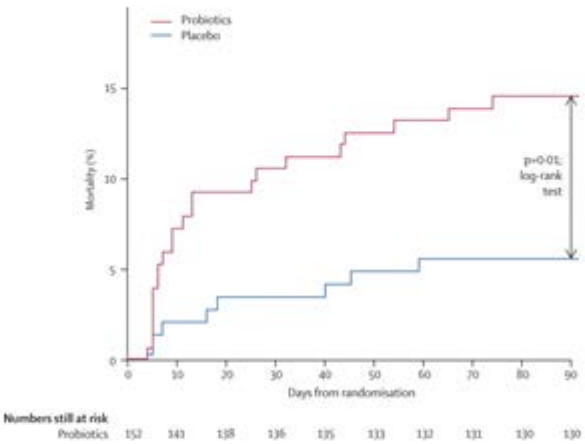


Figure 2. Kaplan–Meier time-to-event analysis for mortality in the first 90 days after randomisation. A follow-up of longer than 90 days was obtained in 266 (90%) patients. Three deaths occurred after 90 days: two in the probiotics group (day 112 and 125) and one in the placebo group (day 140).

CONCLUSIONS

- Nutritional research continues to inform – directly and indirectly – clinical practice in both acute and chronic pancreatitis.
- Guidelines for nutritional replacement therapy are generally well established and promulgated.
- Guidelines for preventive nutrition should be the goal of ongoing research.
- The efficacy of any nutritional intervention likely depends on early diagnosis or prognostication.