Acute and chronic pancreatitis: epidemiology and clinical aspects
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Epidemiology, aetiology and outcome of acute and chronic pancreatitis: An update

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Abstract

Over the past decades several epidemiological studies have been published reporting on incidence trends, hospital admissions, etiological factors and outcome of both acute and chronic pancreatitis. Over time, the incidence of acute pancreatitis has increased in the Western countries. Also, the number of hospital admissions for both acute and chronic pancreatitis have increased. These upward time trends possibly reflect a change in the prevalence of main etiological factors (e.g. gallstones and alcohol consumption) and cofactors such as obesity and genetic susceptibility. Acute and chronic pancreatitis are associated with significant morbidity and mortality and a substantial use of health care resources. Although the case-fatality rate of acute pancreatitis decreased over time, the overall population mortality did not change for both acute and chronic pancreatitis.

This chapter will focus on recent developments in the epidemiology, aetiology, natural course and outcome of both, acute and chronic pancreatitis.
Acute pancreatitis

According to the Atlanta Symposium held in 1992, acute pancreatitis is defined as an acute inflammatory process of the pancreas that frequently involves peripancreatic tissues and/or remote organ systems. The disease spectrum of acute pancreatitis ranges from mild and self-limiting disease (80%) to a rapidly progressive fulminant illness with morbidity rates up to 33-54%. The Atlanta criteria for severity include organ failure (particularly pulmonary insufficiency, renal failure, shock) and/or local complications (necrosis, abscess, pseudocyst). The clinical course of an attack of acute pancreatitis varies from a short period of hospitalization with supportive care (analgesic treatment, fluid resuscitation, and nutritional management) to prolonged hospitalization with admittance to an Intensive Care Unit for the management of multi-organ failure, systemic inflammatory response syndrome and septic complications.

Epidemiology

Over the last decades a plethora of epidemiological studies has been published, reporting on incidence trends, hospital admissions and outcome of acute pancreatitis. Several large-scale, population-based cohort studies were published in recent years. The advantage of these population-based studies over single-center studies is the minimization of selection bias. Single-center case series, especially those from tertiary or referral centers, run the potential risk of including more complicated and sicker patients. In population-based studies, large databases are used, including national or regional hospital discharge registries or administrative databases. Obviously, from the standpoint of validity it is important that the completeness and accuracy of the information contained in these databases are verified. Remarkably though, few studies have addressed the issue of data validity of these large-scale databases. In one series it was shown that the positive predictive value for an acute pancreatitis discharge code from a nationwide discharge registry in the Netherlands was 82%. Thus, the use of such databases without a sample case review may considerably overestimate actual incidence rates.

First attack of acute pancreatitis

Large-scale cohort studies indicate increasing incidences of first attacks of acute pancreatitis in many Western countries, independent of geographical location. [Table 1] summarizes the latest (since the year 2000) published population-based studies. Although the study methodologies are somewhat heterogeneous, the data suggest that the incidence of a first attack of acute pancreatitis is relatively low in England (10 per 100.000), higher in the Netherlands, Germany and Norway (16-20 per 100.000) and considerably higher in the other Scandinavian countries (Sweden and Finland) and the
United States of America (32-44 per 100,000). The difference in incidence rates between these geographical locations is not clearly understood, but presumably reflects differences in risk factor prevalence. The differences in incidence rates in former studies were explained by a greater alcohol use in the Scandinavian countries. This explanation is now under debate. In the latest Swedish study, the incidence of alcoholic pancreatitis decreased and the proportion of alcoholic pancreatitis is comparable with the other recent published studies. Furthermore, in the USA the proportional increase of the incidence was smallest among cases with alcoholic pancreatitis. However, in that study the standardized incidence rate of alcoholic pancreatitis was probably underestimated, because the Veterans and military hospitals were not included. Other explanations

Table 1  Summary of published population-based studies reporting on incidence and mortality of first acute pancreatitis since the year 2000

<table>
<thead>
<tr>
<th>First author, Publication Year</th>
<th>Study Period</th>
<th>Country/Region</th>
<th>Incidence per 100,000/ year</th>
<th>Aetiology (%)*</th>
<th>Case Fatality (%)</th>
</tr>
</thead>
</table>

* Rounded % of causes (biliary, alcohol, idiopathic), miscellaneous causes not included  
† incidence per person-years  
‡ age-standardized incidence rates  
§ age- and sex-standardized incidence rates, idiopathic cases combined with other causes
could include differences in the individual genetic susceptibility to develop an attack of pancreatitis, differences in the use of classification criteria for the diagnosis, and variability in the completeness and accuracy of the source databases.

The incidence of a first attack of acute pancreatitis is increasing and this trend is observed worldwide. Also, all studies show increasing numbers of gallstone-related pancreatitis over time. One may speculate that an increase in the incidence of obesity, which is a well-known risk factor for gallstones, (partly) explains this trend. In this respect, ageing of the population also plays a prominent role. The incidence of gallstones rises with age and all studies report that the incidence of acute pancreatitis increases with age. Another possible contributing factor is that serum amylase/lipase values are tested more routinely and mild non-significant elevations may result in an ‘over’ diagnosis of acute pancreatitis. Finally, part of the increase could be accounted for by the introduction of endoscopic retrograde cholangiopancreatography (ERCP) in the last two and a half decades with resulting cases of post-ERCP pancreatitis. Numerically however, post-ERCP pancreatitis accounts for only a small proportion of all acute pancreatitis cases. Furthermore, in the last decade the total number of ERCPs has actually decreased because diagnostic ERCP has become virtually obsolete by the introduction of magnetic resonance cholangiopancreatography (MRCP).

**Hospital admissions for acute pancreatitis**

Beside the rising incidence of a first attack of acute pancreatitis there is also a coincidental increase of the hospitalization rate for acute pancreatitis. The reported annual incidence rates of hospital admissions include both admissions for a first and recurrent attacks of acute pancreatitis. In England, the age-standardized hospital admission rate for acute pancreatitis increased in the period 1989/90 to 1999/2000 from 14.5 to 20.7 per 100,000 inhabitants (43% increase). Another study from England confirms this upward trend. In this study hospital admissions for acute pancreatitis also increased in the period 1997/1998 to 2003/2004 with non-standardized admissions rising from 30 to 39 per 100,000 inhabitants (30% increase). In Finland, the annual incidence of acute pancreatitis discharges increased between 1987 to 2001 from 68 to 102 per 100,000 inhabitants (50% increase). In the Netherlands, the number of primary acute pancreatitis admissions also rose substantially between 1992 to 2004 by 75%. The age- and sex-standardized annual incidence rates increased from 12.3 to 18.5 per 100,000 person-years representing an increase of 50% in this twelve year time period (submitted). It is forecasted that in the Netherlands this trend will most likely continue for the near future. Finally, a nationwide retrospective hospital-based study in the USA reported an increase in the hospital admission rate between 1988 to 2003 from 40 to 70 per 100,000 inhabitants (75% increase). In 2002, acute pancreatitis was the third most common gastrointestinal discharge diagnosis in the USA. Hospitalization rates in Finland and in the USA are amongst the highest in the Western world. This is in
accordance with the above mentioned highest incidence of a first acute pancreatitis attack in the same geographical locations. Possible explanations for the trend towards an increase of hospitalizations for acute pancreatitis are identical as discussed in the previous paragraph. The numbers might be skewed if patients are re-admitted after they had an attack of acute pancreatitis and are labeled as as ‘AP’ while in fact they have a complication such as a pseudocyst.

Also patients may be readmitted for a pancreatitis recurrence because the etiological factor was not eliminated or treated, which may have been prevented by adequate treatment. For example, the increase in gallstone related pancreatitis has not been followed by an increase in the incidence of cholecystectomies in Scandinavian countries. Furthermore, in California (USA) only 43% of patients admitted with a gallstone related pancreatitis underwent a cholecystectomy during the same hospitalization. Which proportion of patients had a cholecystectomy later was not part of the study. However, it seems very likely that a substantial proportion of patients with a proper indication ultimately does not undergo a cholecystectomy.

It can be anticipated that a continuing increase of hospitalizations for acute pancreatitis will have important consequences for the allocation of national health care resources. For example, in the USA the number of patients requiring hospitalization for acute pancreatitis in 2003 was 2.5 times larger than the United States government had estimated. Health care costs associated with this disease will increase accordingly.

**Age, sex and racial distribution**

All recent large scale population-based studies report, irrespective of the aetiology, an increase in the incidence of a first attack of acute pancreatitis with increasing age. Accordingly, hospital admissions rates for acute pancreatitis increase with age. The median age of a first attack of acute pancreatitis is in the sixth decade of life in most studies. With an ageing population in most Western countries, it is therefore likely that the incidence of acute pancreatitis will increase even more. The proportion of men with a first attack of acute pancreatitis in most studies is higher than that of women. However, it appears that over time the proportion of women is rising. This is in accordance with our own data regarding the trends in hospital admissions in the Netherlands between 1992 to 2004 (submitted).

Two recent studies from the USA addressed the relationship between ethnicity on the one hand and hospital admissions for acute pancreatitis and incidence rates of a first acute pancreatitis attack on the other hand. One study identified, for the first time in a large scale nationwide study, a racial difference in the number of hospital admissions. Overall, the hospitalization rate for black people in the USA between 1988 to 2003 more than doubled compared to the rate for whites. Interestingly, over time the hospitalization rate for blacks remained steady, but a significant upward trend was ob-
served for whites. This study did not investigate etiological racial differences and incorporated a potential source of bias because recurrent attacks in the same patient were not accounted for. A second study was carried out in the state of California (USA) with an ethnically diverse population. This study also showed a significant difference in the racial incidence rates of acute pancreatitis and, importantly, the underlying aetiology and its relative frequency was addressed with some interesting outcomes. Blacks (African Americans) had the highest age- and sex-standardized incidence rate for acute pancreatitis. Moreover, Blacks had a much higher standardized incidence rate of alcoholic pancreatitis compared to whites. This suggests a greater prevalence of alcohol abuse or greater predisposition to the toxic effect of alcohol among blacks. Interestingly, Blacks also had the highest standardized incidence rate of idiopathic pancreatitis. Asians had a very low standardized incidence rate of alcoholic pancreatitis, and Hispanics had the highest incidence rate of biliary pancreatitis. In California, African Americans had a much higher incidence rate of alcoholic pancreatitis.

**Recurrent acute pancreatitis**

The term recurrent pancreatitis is used to indicate recurrent attacks of acute pancreatitis in an otherwise (between attacks) normal pancreas. However, to conclude that the pancreas is truly normal between attacks with no evidence of chronic pancreatitis can be very difficult. More in particular, it is a challenge to accurately establish the diagnosis of so-called early chronic pancreatitis before the development of frank morphologic changes and before the development of exocrine or endocrine insufficiency. It is therefore almost impossible to discriminate patients with acute attacks during the early stage of chronic pancreatitis from those with multiple episodes of acute pancreatitis. In this respect, pancreatic function testing (intubation studies) and ultrasonography have been proposed as tests with some discriminatory potential.

In spite of many published case reports and some single center series, only a few population-based epidemiological studies regarding recurrent acute pancreatitis are available. Eland et al reported that 10.6% of patients with a first attack of acute pancreatitis developed a relapse within a five years time period and 6.4% of patients with a first attack progressed to chronic pancreatitis. Etiological factors were not specified.

The largest published multi-center study to date included 1068 patients with acute pancreatitis from five different European countries and demonstrated a recurrence rate of 27% with alcohol being the most important etiological factor followed by gallstones (25%). The authors concluded that the observed percentage of recurrent acute pancreatitis is lower compared to reports from the seventies (percentages from 36% to 60%). This downward trend is consistent with the findings in a systemic review on the epidemiology of acute pancreatitis. The reported proportion of recurrent acute pancreatitis of 31% in studies performed until the mid-eighties dropped to 14.4% in the population-based studies published in the last two decades. The reasons for this finding
Aetiology of acute pancreatitis

The two most common etiological factors of acute pancreatitis are gallstones (including small gallstones and/or microlithiasis) and alcohol abuse. Together, they represent more than 80% of cases. However, the actual risk of developing acute pancreatitis for persons exposed to these etiological factors is fairly low. In Germany, over a 20-30 year period, the risk of developing a gallstone-related pancreatitis in patients with asymptomatic gallstones is estimated unlikely to be higher than 2%. In addition, the incidence of gallstone-related pancreatitis is highest among patients with small gallstones. The estimated annual risk of small gallstone carriers to develop pancreatitis is 0.05-0.2%. Similarly, only a minority of subjects who abuse alcohol develop pancreatitis. Lankisch and co-workers suggested that the risk of developing alcoholic pancreatitis in heavy alcoholic (>60 g/d for 20-30 years) is only 2% to 3%. In a recent study among male veterans in a detoxification program (high risk population of heavy drinkers) the estimated prevalence of pancreatitis (69% acute pancreatitis) is at least three percent, and the true prevalence could be four to five percent depending on the criteria used to diagnose acute and chronic pancreatitis.

Once gallstones or alcohol misuse have been excluded, the search for other etiologic factors begins. Other causes of acute pancreatitis include structural abnormalities like pancreas divisum, neoplasms, metabolic disorders, drugs, trauma, iatrogenic causes (e.g. post-ERCP pancreatitis), infections, vascular disorders (ischemia), genetic causes (e.g. trypsinogen mutations), and lastly a remaining group of cases which cannot be classified and is referred to as idiopathic pancreatitis. In the recently published AGA Institute medical position statement on acute pancreatitis it is mentioned that it should be possible to establish the etiologic cause of acute pancreatitis in at least three fourths of patients. Recent population-based studies show a considerable variation in the percentage of patients with a first attack of acute pancreatitis with unknown etiologic causes between 2-37% [table 1]. Extensive or invasive (e.g. ERCP, endoscopic ultrasound (EUS)) evaluation is not recommended in those patients with a single episode of unexplained pancreatitis who are below 40 years of age.

Several of the latest population-based studies addressed the incidence rates of various aetiologies of pancreatitis. Frey and co-workers compared the incidence rate of the three major etiologic subtypes of pancreatitis, namely, gallstone-related, alcoholic and idiopathic pancreatitis and plotted them by age. Both gallstone-related and
idiopathic pancreatitis increased dramatically with age and was highest among people older than 75 years. The incidence rate of alcoholic pancreatitis reached its maximum among patients of either sex in the age group 35 to 44 years. During the subsequent decades the incidence rate declined rapidly. This is largely in accordance with the results of Lankisch and coworkers who reported a peak incidence of alcoholic pancreatitis in the age groups 35 to 44 years for men and 25 to 34 for women.15

In a recent systematic review on the epidemiology of acute pancreatitis, the incidence rates of a first attack of acute pancreatitis by aetiology and sex shows a same pattern across the various studies.4 Gallstone related pancreatitis is more common in women (especially after the age of 65 years), alcoholic pancreatitis is more common in middle aged man and the incidence of idiopathic pancreatitis is somewhat similar in both sexes.

Outcome and case-fatality of acute pancreatitis

Overall, about 15% to 20% of patients with an acute pancreatitis progress to a severe illness with a prolonged disease course.3, 34 These severely ill patients may develop organ failure and/or local complications such as pancreatic necrosis. In patients with necrotizing pancreatitis the mortality is close to 17%, with a mortality of 12% in the case of sterile necrosis and up to 30% in infected necrosis.2 Death within the first two weeks is generally attributable to organ failure. Later in the course of the disease it is mainly due to (infected) necrosis.2

The reported case-fatality rate of a first attack of acute pancreatitis in the latest population-based studies varies between 3% to 10.7% [table 1]. Some of the studies report a progressive decline over time, together with a leveling of the case-fatality in the last

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**Table 2  Etiological factors of acute pancreatitis**

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
</tr>
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<tbody>
<tr>
<td>Biliary (eg, gallstones, microlithiasis)</td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td></td>
</tr>
<tr>
<td>Anatomic variants (eg, pancreas divisum, choledochal cyst)</td>
<td></td>
</tr>
<tr>
<td>Ampullary or ductal obstructions (eg, SOD, tumors, stricture, stones, mucus)</td>
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</tr>
<tr>
<td>Metabolic (eg, hypercalcemia, hypertriglyceridemia)</td>
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<tr>
<td>Drugs</td>
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<tr>
<td>Toxins</td>
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<tr>
<td>Trauma</td>
<td></td>
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<tr>
<td>Ischemia</td>
<td></td>
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<tr>
<td>Hypothermia</td>
<td></td>
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<tr>
<td>Infections (eg, viral, bacterial, parasites)</td>
<td></td>
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<tr>
<td>Autoimmune</td>
<td></td>
</tr>
<tr>
<td>Genetic (familial, sporadic)</td>
<td></td>
</tr>
<tr>
<td>Idiopathic</td>
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</tbody>
</table>
A recent systematic review concerning the epidemiology of a first attack of acute pancreatitis observed a downward trend of the case-fatality rate in the last three decades (from up to 20% to less than 10%). Tinto and co-workers reported in their recent study of hospital admissions in England a significant decline of the in-hospital case-fatality rate for acute pancreatitis. The case-fatality rate declined in 1989/1990 from 6.5% for men and 5.0% for women to approximately 4% in 1999/2000 for both men and women (37% and 19% decrease respectively). Recently, Frey and co-workers reported an unchanged 14- or 91 day case-fatality rate between 1994 to 2001. They suggest that in the last decade the effects of an improved management of early and late multi organ failure have leveled-off.

An interesting finding in several studies is that the overall annual population mortality rate per 100,000 has remained unchanged. It is important to keep in mind that the case-fatality is the proportion of affected cases and that population mortality is a rate per 100,000 inhabitants. Due to the detection of milder cases within a population, the case-fatality will decrease but the population mortality not.

Several epidemiological studies report an increase in case-fatality and mortality with increasing age. For example, the thirty day case-fatality rate in patients younger than 40 years was 2.1% as compared to 11.8% in those older than 60 years and even up to 18.9% in those older than 75 years. Eland and co-workers reported a very low mortality in children and young adults, but an increased mortality after 30 years of age to 14.4 per 100,000 person-years in those older than 85 years. Also, Frey and co-workers reported that advancing age has a major effect on early survival. The odds ratio of death within the first two weeks after admission for patients older than 75 years was more than 15 fold relative to patients 35 years or younger (mortality rates 5.3 and 0.3 respectively). It is likely that elderly patients are dying more often because of the presence of significant co-morbidity.

Only one recent study compared the mortality rates from different aetiologies. The 91-day case-fatality rates were not significantly different between gallstone associated pancreatitis (3.7%) and alcoholic pancreatitis (3.2%), but were significantly lower compared to idiopathic pancreatitis (5.1%). The fact that alcoholic pancreatitis is more frequent at a younger age could be a possible explanation for the lower case-fatality rate. However, after adjusting for age, race and sex, alcoholic pancreatitis was associated with a significantly higher increase in the odds of dying within 91 days compared with idiopathic and gallstone associated pancreatitis (20% and 90% higher odds respectively).

Finally, the mortality rates of recurrent acute pancreatitis are lower than the mortality rates following a first attack of acute pancreatitis. For example, Eland and co-workers reported in their population based study a case-fatality rate for relapses of 3.2% and this rate was significantly lower than the rate of 10.7% for first attacks of acute pancreatitis. Gullo and co-workers performed a multi-center study and observed a lower overall mortality among patients with a recurrent attack than among patients
with a single attack (5.9% and 8.5%, respectively). If patients with a recurrent attack died, this most often occurred during the second attack (82.4%). The mortality rates varied from 4.3% for patients with a recurrent attack of alcoholic pancreatitis and 10.0% for idiopathic recurrent pancreatitis.

**Chronic pancreatitis**

Chronic pancreatitis is an inflammatory process that leads to the progressive and irreversible destruction of exocrine and endocrine glandular pancreatic parenchyma which is substituted by fibrotic tissue, with alcohol abuse being the major etiological factor. As a result, a series of morphologic and functional alterations can be detected which are responsible for several symptoms. From the onset through to the most advanced phase the pancreas undergoes various degrees of transformation and this process can be separated into four different stages. At first, there is a pre-clinical stage with absent or uncharacteristic symptoms followed by a second stage with recurrent acute episodes of pancreatitis without definite signs of chronic pancreatitis. The third or late stage is characterized by further recurrent episodes with intermittent or constant pain in-between and signs of chronic pancreatitis such as duct dilatation and pancreatic calcification on imaging. The exocrine function of the pancreas decreases. In the fourth and final stage acute flares are often absent and the frequency and intensity of pain may have diminished. At this stage, the majority of patients have developed both exo- and endocrine insufficiency with resulting maldigestion and diabetes, respectively. Individual patients do not necessarily follow this general scheme step by step. In some patients distinct stages are skipped and some may even present at a very advanced but painless stage with maldigestion, steatorrhea and/or diabetes.

**Epidemiology**

Data regarding the epidemiology of chronic pancreatitis has been less often reported than acute pancreatitis. One important reason is probably that acute pancreatitis is more common and accounts for the major proportion of morbidity and mortality among pancreatic diseases. Another explanation may be that the diagnosis of chronic pancreatitis, especially the early stages, is more difficult to establish. At present there is no test that has been shown to reliably diagnose early chronic pancreatitis. For many years, pancreatologists have struggled to achieve a manageable classification of chronic pancreatitis. In the last five decades more than ten different and adjusted classification systems of chronic pancreatitis have been proposed to provide a basis for diagnosis, treatment and research.
imaging and functional criteria for the diagnosis of chronic pancreatitis. Each of them reflect the scientific knowledge available at a given point in time. As a consequence, one must realize that it may be inappropriate to compare results of epidemiological studies, especially if they were performed years apart using different classification systems. Furthermore, chronic pancreatitis may be misdiagnosed as acute pancreatitis and vice versa. For example, recurrent attacks of acute pancreatitis may be classified as chronic pancreatitis in absence of true signs of chronic pancreatitis. Thus, a rational, acceptable and workable classification system for chronic pancreatitis would greatly improve the quality of future (clinical) research in chronic pancreatitis.

Incidence and prevalence of chronic pancreatitis
Recent large population-based epidemiological studies concerning chronic pancreatitis are strikingly scarce and time trends of incidence rates are lacking. Dite and co-workers reported an incidence rate of 7.9 per 100,000 inhabitants per year in South and Central Moravia in the Czech Republic (1,300,000 inhabitants). They conclude that their observed incidence rate was similar to the reported incidence rates during the 1980s and 1990s in Denmark (8.7) and Germany (7.0), but higher than that of Switzerland (1.6) and Poland (4.0). In 2002, Lankisch and co-workers published their results of an epidemiological survey in a well-defined population in Northern Germany (approximately 150,000 inhabitants). The observed crude incidence rate for chronic pancreatitis was 6.4 per 100,000 inhabitants per year in the period from 1988 to 1995. A time trend is not mentioned. In France, in 2003 a nationwide prospective survey was performed among gastroenterologists to assess the incidence and prevalence rates of patients with chronic pancreatitis. Almost a quarter of all gastroenterologists participated. The crude incidence was estimated between 5.86 and 7.74 per 100,000 inhabitants. The crude prevalence of chronic pancreatitis was estimated at 26.4 per 100,000 inhabitants.

In summary, although relatively scarce, the available data point to an incidence of chronic pancreatitis in the European and probably all Western countries of approximately 6.0 per 100,000 inhabitants.

Hospital admissions for chronic pancreatitis
Hospitalization of patients with chronic pancreatitis is required in case of acute flares, emaciation due to maldigestion, treatment of complications such as pseudocysts, and to manage severe chronic pain (e.g., opioid medication, pancreaticejejunostomy). In England, the age-standardized hospital admission rate for chronic pancreatitis doubled in the period 1989/90 to 1999/2000 from 4.3 to 8.6 per 100,000 inhabitants. In contrast, the percentage of admissions leading to an operation decreased significantly (22%) during this period. It should be noted that day care admissions and endoscopic procedures were excluded in this study. It is conceivable that the proportion of chronic pancreatitis patients treated endoscopically increased, thereby avoiding operations. This upward
trend in the number of hospital admissions for chronic pancreatitis coincides with our own observations in the Netherlands. From 1992 to 2004 the number of primary chronic pancreatitis admissions increased substantially by 75.4% (from 790 to 1386).23 The overall annual incidence of chronic pancreatitis admissions rose from 5.2 to 8.5 per 100,000 person-years. The underlying aetiologies were not accounted for in this retrospective study. Both studies conclude that the upward trends will most likely continue for the near future.

It has been proposed that the frequency of chronic pancreatitis is correlated to the amount of alcohol consumption in a population.55–56 For example, in England and Wales the per capita alcohol consumption correlates strongly with the numbers of discharges of chronic pancreatitis patients six years later.56 From these data it is suggested that epidemiological trends in chronic pancreatitis might be predictable from population based statistics of alcohol consumption. However, in the Netherlands, despite the significant increase in hospital admissions for chronic pancreatitis there has only been a minimal change in alcohol consumption.57

Another explanation for the observed increase in hospital admissions is that the diagnosis of chronic pancreatitis is established more often, especially in an earlier stage of the disease, following a higher awareness among gastroenterologists in combination with more sophisticated imaging techniques (e.g. EUS, MRCP).57 However, there is a definite risk to ‘overdiagnose’ chronic pancreatitis when the diagnosis is solely based on EUS criteria. The number of EUS criteria needed to make a definitive diagnosis is debated and interobserver agreement of EUS features of chronic pancreatitis is poor to mediocre.49 Therefore, it is advisable to base the diagnosis of chronic pancreatitis on a combination of a compatible clinical history and morphological and/or functional changes.

**Age, sex and racial distribution**

In contrast to the epidemiology of acute pancreatitis the incidence rates and hospital admissions for chronic pancreatitis do not seem to rise with increasing age.55–54 Generally, the peak incidence for men and women is between the fourth and sixth decade of life. In almost all age groups there is a male predominance. In the Czech Republic, the average age of patients with chronic pancreatitis was 45.3 years.53 The median age among men and women was approximately the same. The aetiology was alcoholic in 70% of cases and men outweighed women by far (88.2%). Lankisch and co-workers described a peak incidence in men between 45 to 54 years and a small peak incidence in women between 35 to 44 years.15 When only alcoholic aetiology was considered, the observed peak incidence for men and women did not change. Also Levy and co-workers observed an overall peak incidence of patients with proven or suspected chronic pancreatitis aged between 45 to 49 years.54 Again, most patients were men (83.5%). The estimated crude incidence was minimal 9.79 and maximal 12.85 per 100,000 inhabitants in men and varied between 1.93 to 2.63 in women. In England and Wales, the hospital
admissions for chronic pancreatitis peaked in the age groups between 35 to 54 years.\textsuperscript{24} The age-standardized admission rates were consistently higher in men, except for the very old (85 years and beyond). In the period between 1989/90 to 1999/2000, the admission rates increased in all age groups, especially amongst those aged between 35-54 years. The increase was more pronounced amongst men. In contrast, in the Netherlands, the sex-standardized admission rates per 100,000 person-years increased from 7.2 to 11.4 for men (58.3\% increase) and from 3.3 to 5.7 for women (72.7\% increase) between 1992 to 2004 (submitted).

Finally, one multi-center study (three hospitals from two different countries) examined the impact of ethnicity as a risk factor for the development of chronic pancreatitis.\textsuperscript{58} The racial status of 1883 patients discharged with a first-listed diagnosis of chronic pancreatitis and alcoholic cirrhosis were compared. In comparison to white patients, black patients were two to three times more likely to be hospitalized for chronic pancreatitis than for alcoholic cirrhosis. This highly significant difference was observed in both men and women. The reason is unclear, but could be related to racial differences in diet, type or amount of alcohol consumption, smoking, or the (genetically determined) ability to detoxify substances harmful to the liver or pancreas.

Aetiology of chronic pancreatitis

In the last few decades the aetiology of chronic pancreatitis was divided into three categories: alcohol, idiopathic and ‘other’. In the Western countries alcohol abuse is the major cause of chronic pancreatitis accounting for approximately 70\%-80\% of all cases.\textsuperscript{35, 45, 46, 59, 60} About 20\% of cases is considered to relate to idiopathic pancreatitis, while the remaining 10\% is categorized as ‘other’. This latter category included cases associated with hyperparathyroidism, hypertriglyceridemia, duct obstruction, trauma, pancreas divisum, autoimmune pancreatitis and hereditary pancreatitis. Due to advancements in the scientific knowledge about the etiopathogenesis of chronic pancreatitis a new classification system was proposed in 2001.\textsuperscript{44} According to this TIGAR-O classification system, the risk factors for chronic pancreatitis are divided into six major categories including: toxic-metabolic (T), idiopathic (I), genetic (G), autoimmune (A), recurrent severe acute pancreatitis-associated (R) and obstructive (O) mechanisms [table 3]. The classification is roughly based on etiologic prevalence and was proposed to provide a base for treatment and research. However, recently a new and unifying classification system of chronic pancreatitis was introduced.\textsuperscript{52} The M-ANNHEIM classification system allows patients to be categorized according to the aetiology, clinical stage, and the severity of the disease. The M-ANNHEIM classification system is based on the assumption that chronic pancreatitis results from the interaction of multiple (M) risk factors. The risk factors are categorized into seven subcategories: alcohol consumption (A), nicotine
consumption (N), nutritional factors (N), hereditary factors (H), efferent pancreatic duct factors (E), immunological factors (I), and miscellaneous and metabolic factors (M). This classification system hopefully provides a better framework for studying the interaction of the various risk factors on the course of the disease.

As already mentioned, alcohol misuse is assumed to be the leading cause of chronic pancreatitis. However, the association between alcohol consumption and pancreatitis is complex and only in part dose-dependent. In 2006 an international consensus workshop was launched to address these matters. A confounding factor is the extreme difficulty to get reliable estimates of a person’s true alcohol consumption. Self-reports

Table 3  **TIGAR-O Classification system (version 1.0) of risk factors and aetiologies of chronic pancreatitis**

<table>
<thead>
<tr>
<th>Toxic-metabolic</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Alcoholic</td>
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<tr>
<td>• Tobacco smoking</td>
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<tr>
<td>• Hypercalcemia (hyperparathyroidism)</td>
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<tr>
<td>• Hyperlipidemia</td>
</tr>
<tr>
<td>• Chronic renal failure</td>
</tr>
<tr>
<td>• Medication (phenacetin abuse, possibly from chronic renal insufficiency)</td>
</tr>
<tr>
<td>• Toxins (organontin compounds, eg. DBTC)</td>
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<table>
<thead>
<tr>
<th>Idiopathic</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Early onset</td>
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<tr>
<td>• Late onset</td>
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<tr>
<td>• Tropical (tropical calcific pancreatitis, fibrocalculous pancreatic diabetes)</td>
</tr>
<tr>
<td>• Other</td>
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<table>
<thead>
<tr>
<th>Genetic</th>
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<tbody>
<tr>
<td>• Autosomal dominant (cationic trypsinogen, codon 29 and 122 mutations)</td>
</tr>
<tr>
<td>• Autosomal recessive/ modifier genes (CFTR;SPINK1; cationic trypsinogen (codon 16,22,23) and possible α1-antitrypsinogen mutations)</td>
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<table>
<thead>
<tr>
<th>Autoimmune</th>
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<tbody>
<tr>
<td>• Isolated autoimmune chronic pancreatitis</td>
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<tr>
<td>• Syndromic autoimmune chronic pancreatitis (Sjögren syndrome-, inflammatory bowel disease- and primary biliary cirrhosis-associated chronic pancreatitis)</td>
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</tbody>
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<thead>
<tr>
<th>Recurrent and severe acute pancreatitis</th>
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<tbody>
<tr>
<td>• Postnecrotic (severe acute pancreatitis)</td>
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<tr>
<td>• Recurrent acute pancreatitis</td>
</tr>
<tr>
<td>• Vascular diseases/ ischemic</td>
</tr>
<tr>
<td>• Postirradiation</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Obstructive</th>
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<tbody>
<tr>
<td>• Pancreatic divisum</td>
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<tr>
<td>• Sphincter of Oddi disorders (controversial)</td>
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<tr>
<td>• Duct obstruction (eg. tumor)</td>
</tr>
<tr>
<td>• Preampullary duodenal wall cysts</td>
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<tr>
<td>• Posttraumatic pancreatic duct scars</td>
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about the alcohol consumption are notoriously unreliable and underestimate the alcohol consumption. Furthermore, it remains elusive and enigmatic why some alcoholics develop pancreatitis and others do not, but, for example, develop liver cirrhosis. Most likely individual susceptibility determined by as yet undetermined genetic factors plays an important role. Nevertheless, despite these unresolved issues, epidemiological studies unequivocally demonstrate a causal link between alcohol consumption and the development of both acute and chronic pancreatitis.

Natural course and outcome of chronic pancreatitis

The most important clinical symptoms of chronic pancreatitis include (severe) abdominal pain (at least 75% of patients), exocrine and endocrine insufficiency. In addition, pancreatic cancer is the most dreaded long-term complication. The natural history of chronic pancreatitis has been difficult to characterize because of the variability in the use of diagnostic criteria, stage of the disease, and etiological factors. Furthermore, the pancreas is relatively inaccessible for histological assessment. The natural history of chronic pancreatitis may differ for various aetiologies. Only one recent prospective study has investigated the long-term evolution of alcoholic and non-alcoholic chronic pancreatitis. This series includes 343 patients with chronic pancreatitis (265 alcoholic, 67 idiopathic and 11 hereditary) and the follow-up period from disease onset ranged from 14 to 36 years. The median age at onset was 36 years for alcoholic pancreatitis and as early as 10 years in case of hereditary pancreatitis. Idiopathic pancreatitis has an early onset or ‘juvenile’ form (median age at onset 23 years) and a late onset or ‘senile’ form (at 62 years). In alcoholic and late onset idiopathic chronic pancreatitis, exocrine insufficiency develops earlier than in early onset idiopathic pancreatitis. In alcoholic chronic pancreatitis, exocrine insufficiency can develop as early as 6 years after the diagnosis. Similarly, endocrine insufficiency occurs earlier in alcoholic pancreatitis with a median time of 8 years, compared with 27 years in early onset idiopathic pancreatitis. Almost all patients (95.6%) with alcoholic pancreatitis achieved pain relief after a median time of 10 years and this coincided with the onset of exocrine and/or endocrine insufficiency (burn-out of chronic pancreatitis). However, there is still a controversy with respect to the progression of pancreatic insufficiency over time and whether there is a true correlation between pain relief and the development of pancreatic insufficiency.

Although alcohol abuse is the major cause of chronic pancreatitis, smoking has been identified as an additional independent risk factor. Recently, smoking has also been shown to be associated with progression of chronic pancreatitis. In a retrospective study among 934 subjects with chronic alcoholic pancreatitis smoking was associated with earlier age at diagnosis of chronic pancreatitis. Furthermore, the risk of the development of pancreatic calcifications and, to a lesser extent, diabetes during the course of chronic pancreatitis, was higher, independent of alcohol consumption. This study was
not able to evaluate whether smoking alone is a risk factor or risk modifier. However, in a following retrospective study among 164 patients with non-alcoholic idiopathic chronic pancreatitis smoking was also associated with a shortened time to the appearance of pancreatic calcifications and of diabetes. Future, preferably prospective, studies are needed to establish the role of smoking in the initiation and/or progression of alcohol induced pancreatic injury. Not surprisingly, there is a strong correlation between alcohol intake and smoking, with heavy drinkers often being heavy smokers and vice versa. An important message for alcoholic chronic pancreatitis patients is that smoking cessation is as important as reducing alcohol consumption. Both life-style changes do not just influence the progression of the disease, but also reduce the risk of developing pancreatic cancer. Smoking has consistently been shown to be a risk factor for the development of pancreatic cancer. Chronic pancreatitis by itself is also associated with an increased risk of developing pancreatic cancer. In a large cohort, the cumulative risk of pancreatic cancer in subjects who were followed for 10 and 20 years after the diagnosis of chronic pancreatitis was 1.8% (95% confidence interval, 1.0 to 2.6%) and 4.0% (95% confidence interval, 2.0 to 5.9%). In patients with hereditary pancreatitis who smoke the risk of pancreatic cancer is increased more than 50-fold.

There is data that supports that the survival of patients with chronic pancreatitis is reduced compared to the standard population. In a large retrospective multicenter study the overall 10 year survival rate was 70% and the 20 year survival rate 45%. The survival was significantly lower compared to the standard population. Older age at diagnosis, smoking, and drinking were major predictors of mortality in patients with chronic pancreatitis. Recently, Tinto and co-workers reported that between 1989 and 1999 the age-standardized mortality rate of chronic pancreatitis patients has remained unchanged in England. Most of the deaths are not directly related to chronic pancreatitis itself, but related to non-pancreatic effects such as alcohol and/or smoking, including cardiovascular disease and lung cancer. Mullhaupt and co-workers recently reported in their series of alcoholic and idiopathic chronic pancreatitis patients that cardiovascular, severe infection and malignancy were the three major causes of death.

Summary

Over the last decades several epidemiological studies have been published reporting on incidence trends, hospital admissions and outcome of acute pancreatitis. The incidence of first acute pancreatitis attacks and hospital admissions in the Western countries are increasing. An important contributor to this increase is gallstone-related pancreatitis, which is more common in women. Alcoholic pancreatitis is predominant in middle-aged men. Differences in incidence and aetiology between countries are related to differences in the prevalence of risk factors. Both incidence and the mortality of acute pancreatitis
increase with age. Case-fatality rates have decreased over time, but the overall population mortality has remained unchanged. Compared to a first attack of acute pancreatitis, recurrent acute pancreatitis is a milder disease with a substantially lower mortality.

Data regarding the epidemiology of chronic pancreatitis has been reported less often compared with acute pancreatitis, but the number of hospital admissions also shows a clear tendency to increase, as is, although less well established, the incidence of chronic pancreatitis. The latter seems (at least in part) related to an increase in the amount of alcohol consumption in a population and/or a higher awareness among physicians in combination with more sophisticated imaging techniques. Alcohol is the major cause of chronic pancreatitis and is mainly diagnosed in middle aged men, although this diagnosis nowadays is also made in women more often. The natural course of chronic pancreatitis differs for various aetiologies. Smoking independently affects the development of pancreatic calcifications, diabetes and ultimately, pancreatic cancer. The overall survival of chronic pancreatitis patients is reduced and most notably because of non-chronic pancreatitis associated effects of alcohol and/or smoking including cardiovascular diseases and various malignancies.

**Practice points**

- The incidence of acute and chronic pancreatitis as well as the number of hospital admissions in the Western countries are increasing
- Consequently, not only the burden for patients, but also health care costs will increase
- The increasing incidence of acute pancreatitis seems largely accounted for by an increase in patients with gallstone-related pancreatitis
- Case-fatality rate of acute pancreatitis decreased over time, but the overall population mortality did not change for both, acute and chronic pancreatitis
- There is no definite explanation for the increasing number of hospital admissions for chronic pancreatitis (more cases versus more admissions per patient)
- Smoking cessation is important in chronic pancreatitis patients, especially in heavy drinkers

**Research points**

- Initiation of large scale prospective population-based epidemiological studies
- Detailed verification of the completeness and accuracy of information contained in large databases used for epidemiological research in pancreatitis
- Investigate and establish the trend and the nature of the rise in the incidence of both acute and chronic pancreatitis
- Identify genetically determined risk factors associated with to risk to develop pancreatitis and with prognosis
- Establish which proportion of gallstone related pancreatitis is actually caused by a recurrence due to a delay or even the omission of biliary surgery (cholecystectomy / ERCP) indicated according to practice guidelines (and as such preventable)
- Determine more accurately mortality rates in various aetiologies of acute pancreatitis
- Investigate the long-term evolution of alcoholic and non-alcoholic chronic pancreatitis, documenting the amount and pattern of alcohol use (and smoking) to assess dose-response relationships
- Further establish the role of smoking in the initiation and progression of alcohol induced pancreatic injury
References


Epidemiology of Acute and Chronic Pancreatitis


