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Acute pancreatitis: from treatment to prevention

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CHAPTER 9

Structured alcohol cessation support program versus current practice in acute alcoholic pancreatitis (PANDA): *study protocol for a multicenter cluster randomized controlled trial*

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ABSTRACT

Background/objectives: The most important risk factor for recurrent pancreatitis after an episode of acute alcoholic pancreatitis is continuation of alcohol use. Current guidelines do not recommend any specific treatment strategy regarding alcohol cessation. The PANDA trial investigates whether implementation of a structured alcohol cessation support program prevents pancreatitis recurrence after a first episode of acute alcoholic pancreatitis.

Methods: PANDA is a nationwide cluster randomized superiority trial. Participating hospitals are randomized for the investigational management, consisting of a structured alcohol cessation support program, or current practice. Patients with a first episode of acute pancreatitis caused by harmful drinking (AUDIT score >7 and <16 for men and >6 and <14 for women) will be included. The primary endpoint is recurrence of acute pancreatitis. Secondary endpoints include cessation or reduction of alcohol use, other alcohol-related diseases, mortality, quality of life, quality-adjusted life years (QALYs) and costs. The follow-up period comprises one year after inclusion.

Discussion: This is the first multicenter trial with a cluster randomized trial design to investigate whether a structured alcohol cessation support program reduces recurrent acute pancreatitis in patients after a first episode of acute alcoholic pancreatitis, as compared with current practice.

INTRODUCTION

Alcohol is considered the second leading cause of acute pancreatitis in the Western world, responsible for approximately 20% of cases of acute pancreatitis (1). The prevalence of recurrent acute pancreatitis (ranging from 18% to 46%) and chronic pancreatitis (ranging from 13% to 26%) is high in patients recovered from their first episode of alcoholic pancreatitis (2-11). Continued alcohol use is considered the main preventable risk factor for developing these events (2, 9, 11-13). Harmful drinking brings a large physical and psychosocial burden for patients as well as a financial burden for society (14, 15). Therefore, alcohol cessation should be as much a priority in treating acute alcoholic pancreatitis as cholecystectomy in acute biliary pancreatitis.

There is increasing evidence that (brief) motivational interventions (MI) to assist in alcohol cessation are effective, particularly when performed in a hospital setting (16, 17). The rationale for this success lies in the impact of hospitalization, making patients aware of their underlying alcohol problem and increasing motivation to change. Although guidelines recommend “dedicated” follow-up visits after acute alcoholic pancreatitis, no guidance is available on the optimal content of this follow-up treatment (18). Therefore, the opportunity to perform MI in this patient group is often missed, placing this group at risk for further harm (19).

To date, one single-center randomized controlled trial (RCT) has studied the effect of in-hospital repeated versus single-session MI on alcohol cessation in acute alcoholic pancreatitis patients (20). In this study by Nordback et al., a 61,9% reduction was observed in pancreatitis recurrence in favor of patients receiving a second MI at a six month-interval. Although this reduction of pancreatitis recurrence is impressive, the extra scheduled visit to the outpatient clinic might be difficult to adopt in every healthcare system, and might also overlook the distinct and potential value of the general practitioner, who has a long-standing relationship with the patient and unique experience in cessation support. Moreover, in this traditional RCT design (20), only patients meeting a certain threshold level of motivation to quit or reduce alcohol use were likely to willing to participate, which may have led to an overestimation of the treatment effect. Finally, the effect of alcohol cessation on quality of life, QALYs and costs have not been studied.

The fact that the incidence of acute alcoholic pancreatitis is still on the rise (21, 22), and no cost-effective prevention programs have yet been described in international guidelines, warrants the need for new evidence. The multicenter cluster randomized PANDA trial aims to determine whether a structured alcohol cessation support program in patients with a first episode of acute alcoholic pancreatitis is superior to

the current practice with regard to recurrent acute pancreatitis. We hypothesize that enhanced efforts aimed at reducing alcohol use, by providing a structured program including an in-hospital MI, reduces the risk of pancreatitis recurrence in these patients and therefore reduces readmissions and costs, and improves quality of life, as compared to the current practice.

METHODS

This trial protocol is written in accordance with the Standard Protocol Items: Recommendation for Interventional Trials (SPIRIT) guidelines (23).

Design

PANDA is a multicenter two-level cluster randomized superiority trial with an equal allocation ratio. To date, 33 Dutch hospitals are participating in the trial, including academic hospitals, large teaching hospitals and regional hospitals, each representing one cluster. Before participation, all potential hospitals must complete a survey about their current support treatment during the initial admission for their patients with acute alcoholic pancreatitis (19), and hospitals that already implemented an alcohol cessation support program similar to our intervention program are excluded. The participating clusters will be stratified by type of hospital (academic versus non-academic) and in the case of hospitals with multiple physical locations, all locations will be included in the same cluster.

Study population

The subjects of this trial are hospitalized adult patients with a first episode of acute pancreatitis, according to the Revised Atlanta Criteria (24). The Alcohol Use Disorders Identification Test (AUDIT) (see additional file 1), a 10-item screening tool in the validated Dutch translation, is to be performed in all patients to detect harmful drinking (25). All patients are screened for other potential etiologies by the standard diagnostic work-up as described in the International Association of Pancreatology (IAP)/ American Pancreatic Association (APA) guidelines of 2013 (see additional file 2 and 3) (18). Patients who fulfil the eligibility criteria will be informed about the trial.

The inclusion criteria are:

1. First episode of acute pancreatitis requiring admission
2. AUDIT score >7 for men and >6 for women, indicating likelihood of harmful drinking
3. Age of 18 years or older

4. Written informed consent for participation

The exclusion criteria are:

1. Diagnosis of any etiology other than alcoholic
2. AUDIT score >15 for men and >13 for women, indicating likelihood of alcohol dependence
3. Chronic pancreatitis (according to the M-ANNHEIM criteria) (26)
4. Non-Dutch speaker

All included patients are treated according to the protocol of the treatment arm of the hospital to which they are admitted.

Intervention arm

The alcohol cessation support program is based on the guideline “Problematic Alcohol Use” of the Dutch College of General Practitioners and the guideline “Alcohol Use Disorders” of the Dutch Psychiatric Association and consist of five components, see below (27, 28). The program will be carried out by a multidisciplinary team of clinicians (i.e. gastroenterologists and surgeons), psychosocial healthcare providers available for in-hospital consultation whom are already trained for psychosocial interventions (i.e. psychiatrists, psychiatric nurses, medical psychologist and social workers) and primary care physicians. All the clinicians and psychosocial healthcare providers will be offered motivational interviewing training, as MI training is essential for providing MI effectively (29). This 4-h interactive training is given by one experienced MI trainer, who is also an addiction psychologist, and focusses on the four processes of MI including engaging, focusing, evoking and planning. To homogenize the program, the research group has compiled a standard operation procedure (SOP) (see additional file 4). Therefore, the overall framework will be identical in all study sites; however, some details may differ between sites because of logistic reasons or different local protocols.

1. *Medical phase*: if applicable, the clinician optimizes medical treatment of the effects of alcohol use, i.e. supplementation of vitamins and treatment of withdrawal symptoms.
2. *Education phase*: the clinician provides the patient with psychoeducation, including information on the relationship between alcohol use, acute pancreatitis and relapses, and give the following advice: stop drinking alcohol completely and seek for supportive treatment in primary care. A brochure ‘*Everything you need to know about alcohol*’ from the Trimbos Institute, Netherlands Institute of Mental Health and Addiction, is also provided (30).
3. *Motivational phase*: the psychosocial healthcare provider provides a patient-centered intervention following the principles of motivational interviewing: listen with empathy, develop discrepancy between patient’s drinking behavior and

goals, adjust to patient's resistance, support their self-efficacy and respect their autonomy. The primary task is to elicit patient's motivation to change drinking behavior and seek for further treatment in the setting of primary care.

4. *Discharge phase:* the clinician contacts the patient's primary care physician by telephone before discharge to ensure continuity of care. This verbal communication must include information about the reason for hospitalization, the medical treatment provided, the patient's harmful behavior of drinking and his or her motivation to change this behavior.
5. *Home phase:* the study coordinator informs the patient's primary care physician about their enrolment in the PANDA by sending a letter. This letter focusses on the awareness of their own guidelines "Problematic alcohol use" and to promote adherence of this guideline.

Control arm

Current practice has been described in the previously published survey (19). This survey among 35 Dutch hospitals showed a lack in clear protocols for the treatment of acute alcoholic pancreatitis patients and a lack of uniformity in the approach of this treatment within the departments of gastroenterology. In 17% of hospitals, psychosocial health care providers were routinely engaged in the treatment process. In the control arm, usual care will be provided at the discretion of the clinicians.

Primary endpoint

The primary endpoint is recurrence of acute pancreatitis (irrespective of etiology) within 1 year after inclusion. Recurrence of acute pancreatitis is defined as a new episode of acute pancreatitis after complete resolution of all symptoms associated with the previous episode, as defined by the 2013 revised Atlanta criteria (24).

Secondary endpoints

Secondary endpoints are cessation of alcohol use (modified AUDIT score of 0 at any time point during follow-up), clinically relevant reduction of alcohol use (modified AUDIT score ranging between 1 and 7 (men) or 1 and 6 (women) at any time point during follow-up), AUDIT-score at 1 year follow-up, self-reported alcohol use, development of other alcohol-related diseases, mortality, quality of life, QALYs and total direct and indirect costs. The AUDIT questionnaire is modified during follow-up to provide adequate information to assess the first two secondary endpoints, since this questionnaire includes questions regarding the alcohol use behavior in the past year. Therefore, all questions in the questionnaire at 3, 6 and 9 months follow-up are modified to only apply to the period after inclusion (see additional file 5).

Sample size

The sample size was calculated to detect a reduction in the recurrence rate of 62% from 25% in the control arm to 10% in the intervention arm. A recurrence rate of 25% for current practice is based on previous Dutch Data (2). The expected 62% reduction in favor of the intervention arm is based on the RCT from Nordback et al. (20). The sample size was calculated with a two-sided significance level (α) of 0.05, a power of 80% and an intra-cluster correlation of 0.05, which is often used in cluster RCTs. A drop-out rate of 10% was chosen based on previous research of the Dutch Pancreatitis Study Group (DPSG) in which the drop-out rate was less than 5% (31-36). The required sample size for different numbers of participating hospitals (i.e. clusters) are displayed in table 1. Assuming 33 participating hospitals, this will result in a sample size of 320 patients.

Table 1. Sample size

Number of clusters	N per cluster	N
27	13	351
28	12	336
30	11	330
32	10	320
35	9	315
38	8	304
42	7	294

Ethics

The PANDA is conducted in accordance with the 2013 Declaration of Helsinki and Guideline for Good Clinical Practice. The need for ethical approval was waived by the Medical Ethics Committees United (MEC-U). In addition, local board approval will be obtained from all the participating hospitals (see additional file 6).

Statistical aspects

All included patients will be evaluated for primary and secondary endpoints at one year after inclusion. The primary analysis is based on intention-to-treat principles. All analysis will be performed in SPSS or RStudio. A two-sided p value lower than 0.05 is considered statistically significant.

Baseline variables are age, sex, body mass index (BMI), American Society of Anesthesiologist's (ASA) classification, previous alcohol-related comorbidities, AUDIT score, nicotine use, severity of acute pancreatitis, length of hospital admission, motivation to change drinking habits and confidence in ability to change (scale 1-10). Categorical

data will be presented in number and percentage and numerical data as mean with standard deviation (SD) or in case of a skewed distribution as median with interquartile range (IQR).

The primary endpoint, recurrence of acute pancreatitis, will be presented as number with percentage. In subgroup analysis, the Chi-square test or the Fisher's exact test with 95% confidence interval (CI) will be used. A subgroup analysis will include predictors for the primary endpoint (sex, other alcohol-related comorbidities, AUDIT score, nicotine use, severity of acute pancreatitis and motivation level). If the subgroups differ statistically significant in one or more baseline variables, this will be adjusted in a logistic regression analysis.

Secondary endpoints will be presented as number with percentage with 95% CI, as mean with SD or median with IQR. For categorical data (cessation of alcohol use, clinically relevant reduction of alcohol use, development of other alcohol-related diseases, mortality), the Chi-square test or the Fisher's exact test will be used. For numerical data (quality of life, AUDIT score, self-reported alcohol use), the (un-) paired *t*-test, Mann-Whitney *U* test will be used. For quality of life, subgroup analysis will be made for patients with and without pancreatitis recurrence, who achieved and not achieved cessation or clinically relevant reduction of alcohol use.

The economic evaluation will comprise a cost-effectiveness analysis and a cost-utility analysis. The primary endpoint in the cost-effectiveness analysis, are the cost per prevented pancreatitis recurrence. Other medical costs generated in hospitals, resource utilization outside of the hospitals and production loss will also be assessed using the Medical Consumption Questionnaire (MCQ) and Productivity Cost Questionnaire (PCQ). For the cost-utility analysis, costs per additional QALY will be measured using the EQ-5D.

DISCUSSION

Acute alcoholic pancreatitis has a high recurrence rate as it is notoriously difficult to stop harmful drinking (6, 9, 11), which puts patients at increased risk for severe acute pancreatitis, chronic pancreatitis and pancreatic malignancies. Previous research has suggested that in-hospital motivational interventions are effective in reducing the risk of pancreatitis recurrences (20). The PANDA trial is the first cluster randomized controlled trial designed to determine whether implementation of a structured alcohol cessation support program improves the rate of recurrent acute pancreatitis after a follow-up period of one year when compared to current practice.

Previously, it has been shown that cessation of alcohol prevents against recurrent acute alcoholic pancreatitis (9, 11). In two Finnish studies, no recurrent attacks have been observed in patients who achieved abstinence after the first episode while respectively, 33% and 34% of non-abstainers developed at least one relapse. Other risk factors associated with recurrences were younger age and mild severity of the initial episode (10). Notably, another study has suggested that the disease course of acute pancreatitis may affect the patients' motivation for behavior change, since two-thirds of patients who survived a severe attack reduced their excessive alcohol use or achieved abstinence (37). In line with this theory, the impact of an admission related to alcohol may also provide a teachable moment for patients, making them more receptive to change through MI. MI is an intentionally directive counselling approach to elicit intrinsic motivation within a patients to achieve behavior change, while maintaining the patient's autonomy. In MI, patients are encouraged to explore the cons of continuing current behavior and the pros of behavior change, and if ambivalence is evident, supported to move in the direction of change (38). This approach, introduced by Miller and Rollnick (39), and initially developed to treat alcoholism in addiction care, is now widely used in the treatment of many lifestyle problems, also in the hospital setting (40-42). There are several systematic reviews and meta-analyses reporting on the effect of brief in-hospital MI in heavy alcohol users and found that interventions are beneficial regarding alcohol use, alcohol-related injuries and mortality during a follow-up time of 6 to 12 months (17, 43). Therefore, (inter)national guidelines recommend brief MI in the hospital setting in all patients with harmful drinking (27, 28, 44). A recent national survey performed prior to this trial showed that face-to-face consultations between hospitalized acute alcoholic pancreatitis patients and psychosocial healthcare providers was part of standard care in only 17% of hospitals (19). Thus, in current practice MI is suboptimally implemented. Since the success of MI is associated with skills and knowledge acquired through MI training (45, 46), training and involving psychosocial healthcare providers seems crucial.

The rate of pancreatitis recurrences was significantly less in the repeated-intervention arm of the previously mentioned RCT of Nordback et al. compared to the control arm (single-intervention arm), but the reported alcohol consumption did not differ between the two arms (20). The authors described the difficulties that they experienced evaluating alcohol consumption, since several of the subjects did not want to keep a diary for a period of two years. To overcome this problem, the Timeline Followback method is used to retrospectively assess the number of drinking days and the total amount of drinks consumed in the past 2 weeks at five time points (47). Furthermore, quality of life, QALYs and costs were not evaluated in this study. PANDA will be the first trial assessing whether a structured alcohol cessation support program prevents pancreatitis recurrence, to further reduce cost and improve quality

of life, in which the continuing alcohol consumption level after diagnosis is strictly monitored through 3-monthly validated questionnaires.

It is not clear which level of alcohol intake determines whether the most likely etiology is alcoholic pancreatitis (48-55). Multiple undefined criteria for acute alcoholic pancreatitis are used in literature, such as excessive alcohol use, alcohol misuse, heavy alcohol use, binge-drinking *et cetera* (9, 11). In some studies, the limit of alcohol intake was set at four units in the last two days prior to the start of acute pancreatitis (56, 57). For PANDA, we used the validated AUDIT-questionnaire as a screening tool (25). Patients that scored an AUDIT between 8 and 15 (for women between 7 and 13), suggesting a strong likelihood of harmful drinking, will be eligible to enroll. In patients with harmful drinking behavior and acute pancreatitis, other etiological factors may co-exist, such as gallstones, hypertriglyceridemia or genetic mutations, and should first be ruled out (58, 59). The standard diagnostic work-up is described in the IAP/APA guidelines and includes extensive clinical history (i.e. use of drugs, recent trauma or ERCP, family history), laboratory tests including calcium and triglycerides and transabdominal ultrasound (18). Because pancreatitis recurrence is the primary endpoint, we have chosen not to include patients with two or more potential etiologies.

In the PANDA trial design, patients with alcohol dependence, defined as an AUDIT higher than 15 (for women higher than 13), will be excluded. Since alcohol-dependent patients should be offered referral to an addiction specialist (44), it is considered unethical to not intervene when referral does not follow for alcohol-dependent patients in the control arm. Moreover, population heterogeneity becomes more pronounced if both patients with harmful drinking and alcohol dependence will be included (60).

Participating hospitals, instead of patients, are randomized as clusters between the intervention program and control program to prevent confounding and contamination. This methodology has several advantages. First, in a cluster RCT design, more patients are likely to give informed consent for data collection and to fill out questionnaires, including those less intrinsically motivated patients that would refuse participation in a traditional RCT. Thus, subjects are more likely to be an adequate reflection of the actual population of acute alcoholic pancreatitis patients, increasing external validity of study findings. Second, in a traditional RCT design, patients are more likely to proactively self-educate using the information in the patient information letter, than they would in case of a cluster randomized design. Lastly, the nature of an intervention program implicates a high risk of contamination on the clinician level, because it may prove to be difficult for a clinician, trained to execute a proactive program, to withhold some easily completed steps from the patients in the control group. Both

contamination on the clinician level and patient level may lead to an underestimation of the treatment effect. Therefore, a cluster randomized trial design is considered the preferred design for the PANDA trial. Additionally, clusters are stratified based on type of hospital (academic versus non-academic), because of expected low versus high rates of first admissions related to acute alcoholic pancreatitis.

Recurrence of acute pancreatitis, irrespective of etiology, within one year after inclusion is the primary endpoint. In the longest follow-up study of acute alcoholic pancreatitis patients, 46% developed a recurrent attack in 10 to 20 years, of whom 70% within three years (10). However, the study from Nordback et al. found a statistically significant difference in the occurrence of first relapse after 6 months between the repeated-intervention arm (2%) and the single-intervention arm (13%) (20). To assess the association between alcohol intake after the first episode and recurrence of disease, subjects are asked to fill out the AUDIT-questionnaire at four time points, at 3, 6, 9 and 12 months, after inclusion. Extending the follow-up period can lead to reduced compliance with completion of questionnaires.

A potential drawback of the PANDA trial design is that it only includes hospitals in the Netherlands, which may limit the applicability of our alcohol cessation program, primarily based on Dutch guidelines, to other countries and cultures. Additionally, our deliberate decision to not focus on concurrent nicotine use is driven by both the philosophy of treating one ‘addiction’ at a time and practical feasibility considerations. Lastly, in a trial involving a rare condition such as the initial occurrence of acute alcoholic pancreatitis, patient recruitment is expected to be challenging.

CONCLUSION

The PANDA trial is a multicenter, cluster randomized superiority trial to investigate whether implementation of a structured alcohol cessation support program reduces recurrent acute pancreatitis in patients with acute alcoholic pancreatitis, as compared with current practice.

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Additional file 1. AUDIT questionnaire

Instruction: the next questions are about your use of alcoholic drinks, such as beer, wine, gin and the like in the last year. Question 2 and 3 refer to the glasses that are usually used to drink. These are called standard drinks. A bottle of beer is a little bit more: 1.2 standard drinks, and half a liter of beer is 2 standard drinks. A whole bottle of wine is 8 standard drinks. Your answers will be handled confidentially, so please be honest. Circle the text in the panel that matches your answer to the question the most.

Questions:	0	1	2	3	4
How often do you have a drink containing alcohol?	Never	Monthly or less	2-4 times a month	2-3 times a week	4 or more times a week
How many standard drinks containing alcohol do you have on a typical day when drinking?	1 or 2	3 or 4	5 or 6	7 to 9	10 or more
How often do you have six or more drinks on one occasion?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
During the past year, how often have you found that you were not able to stop drinking once you had started?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
During the past year, how often have you failed to do what was normally expected of you because of drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
During the past year, how often have you needed a drink in the morning to get yourself going after a heavy drinking session?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
During the past year, how often have you had a feeling of guilt or remorse after drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
During the past year, have you been unable to remember what happened the night before because you had been drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
Have you or someone else been injured as a result of your drinking?	No		Yes, but not in the past year		Yes, during the past year
Has a relative or friend, doctor or other health worker been concerned about your drinking or suggested you cut down?	No		Yes, but not in the past year		Yes, during the past year

Additional file 2. Definitions of etiology

Alcoholic pancreatitis: pancreatitis caused by an excess intake of alcohol, diagnosed when no other etiology is demonstrated by standard work-up and the patient has an AUDIT score > 7.

Biliary pancreatitis: pancreatitis caused by biliary stones, microlithiasis or sludge, diagnosed when one of the following features is present on transabdominal ultrasound:

- a. Gallstones, microlithiasis and/or biliary sludge, either in the gall bladder, ductus cysticus, intrahepatic bile ducts or in the common bile duct, and/or
- b. A dilated common bile duct of more than eight mm in patients 75 years old or younger or more than ten mm in patients older than 75 years at diagnosis of acute pancreatitis

Chronic pancreatitis: a chronic inflammation of the pancreatic parenchyma, defined as typical clinical history of chronic pancreatitis (such as recurrent pancreatitis or abdominal pain, except for primary painless pancreatitis) and one or more of the following:

1. Pancreatic calcifications
2. Moderate or marked ductal lesions, defined as two or more of the following abnormal features on transabdominal ultrasound, CT or MRI/MRCP, according to the Cambridge classification:
 - a. Main pancreatic duct abnormalities, either enlargement or increased echogenicity of the duct wall (mandatory)
 - b. Pancreatic enlargement
 - c. Cavities
 - d. Duct irregularities including intraductal fillings defects, calculi or duct obstruction
 - e. Focal acute pancreatitis
 - f. Parenchymal heterogeneity
 - g. Irregularities of pancreatic head or body contour
3. Moderate or marked ductal lesions, defined as five or more of the following abnormal features on endoscopic ultrasound:
 - a. Enlarged gland size
 - b. Cysts
 - c. Echo-poor lesions (focal areas of reduced echogenicity)
 - d. Echo-rich lesions (more than three mm in diameter)
 - e. Accentuation of lobular pattern (e.g., echo-poor normal parenchyma surrounded by hyperechoic strands)
 - f. Increased duct wall echogenicity

- g. Irregularity of the main pancreatic duct (e.g., with narrowing of the duct)
- h. Dilation of the main pancreatic duct
- i. Visible side branches (e.g., with dilation)
- j. Calcification (of the pancreatic duct)
4. Marked and persistent exocrine insufficiency defined as pancreatic steatorrhea markedly reduced by enzyme supplementation
5. Typical histology of an adequate histological specimen

Note: during initial diagnostic work-up during admission ‘marked and persistent exocrine insufficiency’ cannot be evaluated properly. Therefore, this part of the definition of chronic pancreatitis will not be applicable during standard work-up. Obtaining histology is also not part of standard work-up.

Cystic fibrosis related pancreatitis: cystic fibrosis is an autosomal recessive disorder caused by a mutation in the CFTR gene, resulting in defective chloride channels in epithelial cells, diagnosed by either a concentration in sweat of chloride greater than 60 mmol/L on repeated analysis, confirmation of a CFTR gene mutation, or both. Cystic fibrosis related pancreatitis is caused by defective ductular and acinar pancreatic secretion, diagnosed when a patient with a history of cystic fibrosis presents with an acute pancreatitis in the absence of another origin.

Familial pancreatitis: acute pancreatitis from any cause that occurs in a family with an incidence that is greater than would be expected by chance alone, given the size of the family and the standardized incidence of pancreatitis within the Dutch population, defined as acute pancreatitis in patients who have two or more direct blood-related family members (parents, children or siblings) who have had an episode of acute pancreatitis.

Hereditary pancreatitis: otherwise unexplained pancreatitis in an individual from a family in which the pancreatitis phenotype appears to be inherited through a disease-causing gene mutation expressed in an autosomal dominant pattern, defined as pancreatitis in patients with a known mutation in the PRSS1 gene, the SPINK1 gene, the CFTR gene, the CTRC gene, the CLDN2 gene or the CPA1 gene, or if the patient has a direct family member (parents, children, siblings) with one or more of the above mentioned mutations and has at least one direct family member who has had an episode of acute pancreatitis or has chronic pancreatitis.

Hypercalcemic pancreatitis: acute pancreatitis caused by hypercalcemia and diagnosed when no signs of a biliary pancreatitis are found in standard work-up and the patient

has a blood serum calcium level of at least 12 mg/dl or 3 mmol/l, corrected for the serum albumin level, as first measured during admission.

Hypertriglyceridemic pancreatitis: acute pancreatitis based on hypertriglyceridemia and diagnosed if a biliary etiology is not demonstrated by standard work-up and the patient has a blood serum triglyceride level of at least 1000 mg/dl (or 11.2 mmol/l) under fasting conditions, as first measured during admission.

Idiopathic acute pancreatitis is considered to be present if no etiology is found in standard work-up (see all definitions).

Medication associated pancreatitis: acute pancreatitis is considered when the patient uses one or multiple drug(s) listed in the table below, the drug has been started or increased in dosage within a reasonable temporal sequence, in principle 1 month before the onset of the pancreatitis, and has a positive dechallenge (a drug reaction that is confirmed by stopping the drug).

Drugs associated with acute pancreatitis

Definite association: Acetaminophen, asparaginase, azathioprine, bortezomib, capecitabine, carbamazepine, cimetidine, cisplatin, cytarabine, didanosine, enalapril, erythromycin, oestrogens, furosemide, hydrochlorothiazide, interferon alfa, itraconazole, lamivudine, mercaptopurine, mesalazine, olsalazine, methyl dopa, metronidazole, octreotide, olanzapine, opiates, oxyphenbutazone, pentamidine, pentavalent antimony compounds, phenformin, simvastatin, steroids, sulfasalazine, co-trimoxazole

Pancreas divisum: a congenital malformation of the main pancreatic duct (Wirsung's duct) with two separate ducts (a separate ventral duct of Wirsung and a dorsal duct of Santorini) as opposed to one main duct (of Wirsung).

Post-ERCP pancreatitis: pancreatitis caused by mechanical injury from instrumentation and hydrostatic injury from contrast injection during ERCP, diagnosed if a patient develops a pancreatitis within 24 hours of an ERCP without indications of another origin.

Postoperative pancreatitis: pancreatitis caused by perioperative hypoperfusion of the pancreas, diagnosed if a patient develops a pancreatitis within 24 hours of abdominal surgery in the absence of indications for another origin.

Posttraumatic pancreatitis: pancreatitis caused by pancreatic injury due to trauma to the abdomen, diagnosed when the patient describes a typical blunt trauma to the upper abdomen and pancreatic trauma is visible on imaging.

Additional file 3. Definition of standard diagnostic work-up

1. A detailed personal history, including questions on:
 - a. Known gallstone disease
 - b. Alcohol use
 - c. Recent start of or changes in use of drugs associated with acute pancreatitis
 - d. Known hyperlipidemia
 - e. Known cystic fibrosis
 - f. Recent major abdominal trauma
 - g. Recent abdominal surgery
 - h. Recent ERCP
2. A detailed family history, including questions on:
 - a. Familial pancreatitis
 - b. Hereditary pancreatitis
3. Laboratory tests, including:
 - a. Blood serum triglycerides level
 - b. Blood serum calcium level, corrected for the serum albumin level
 - c. Blood serum liver enzymes level on admission
4. Imaging via transabdominal ultrasound

Additional file 4. SOP intervention program*Medical phase (treating physician)*

- o If applicable, start or continue vitamin suppletion
- o If applicable, start or continue treatment of withdrawal symptoms

Education phase (treating physician)

- o Provide the patient with information about the relationship between pancreatitis and alcohol use by 1) make connection 2) ask permission 3) speak in the third person and 4) connect again. For example:
 - Make connection: *what do you already know about acute pancreatitis?*
 - Ask permission: *may I tell you something about this disease?*
 - Speak in third person: *many people who develop acute pancreatitis have an alcoholic cause. Previous research show that 25% of these patients will have recurrent attacks, but that this rate can be reduced to near 0% when someone managed to stop drinking alcohol. For this reason, we advise to stop drinking alcohol completely in all patients who have suffered from acute pancreatitis.*
 - Connect again: *what is your perspective on this?*
- o Make clear that the primary care physician can offer supportive treatment regarding alcohol use and encourage the patient to visit primary care
- o In case the patient is not motivated to seek for further treatment in primary care, refer to e-mental health (www.thuisarts.nl/alcohol) or support groups (Alcoholics Anonymous)
- o Provide the brochure ‘*Everything you need to know about alcohol*’ from the Trimbos Institute

Motivation phase (by psychosocial professional)

- o Ask open-ended questions (without judging) about patient’s alcohol use and evaluate whether the patient use change talk (statements about change) or sustain talk (statements about sustaining drinking behavior without change).
- o Evoke change talk with the patient. Ask about the disadvantages of continuing alcohol use and the advantages of changing alcohol use. Examples of evocative questions: *If you were successful in making this change, what would be different? What are worse things that might happen if you do not make this change?*
- o Identify patient’s motivation to change and confidence in ability to change. Ask scale questions (1-10) or other evocative questions: *On a scale from zero to ten, how important is it to you to change? Why are you at X and not a lower number? On a scale from zero to ten, how confident are you that you could change? Why are you at X and not a lower number? Why do you think it is important to change?*

- o Explore patient's individual treatment goals, such as cessation or reduction of alcohol use or change in drinking habits: *if you decide to change, what would you like to achieve? What changes were you thinking about making? When have you made a significant change in your life before? What strengths do you have that would help you to achieve a change?*
- o Empower the patient
- o Motivate the patient to seek for further treatment, for example in the setting of primary care

Discharge phase (treating physician)

- o Direct contact with general practitioner regarding imminent discharge
- o Share summary of the reason of hospitalization, the medical treatment provided, the patient's problematic behavior of drinking, his or her motivation to change and eventually, treatment goals to achieve the desired change
- o Advise the general practitioner to contact the patient after discharge

Home phase (study coordinator)

- o Send a letter with information about this study to the general practitioner and promote awareness and adherence of their own guidelines on Problematic alcohol use

Additional file 5. Modified AUDIT questionnaire

Instruction: the next questions are about your use of alcoholic drinks, such as beer, wine, gin and the like since your admission for acute pancreatitis. Question 2 and 3 refer to the glasses that are usually used to drink. These are called standard drinks. A bottle of beer is a little bit more: 1.2 standard drinks, and half a liter of beer is 2 standard drinks. A whole bottle of wine is 8 standard drinks. Your answers will be handled confidentially, so please be honest. Circle the text in the panel that matches your answer to the question the most.

Questions:	0	1	2	3	4
How often do you have a drink containing alcohol?	Never	Monthly or less	2-4 times a month	2-3 times a week	4 or more times a week
How many standard drinks containing alcohol do you have on a typical day when drinking?	1 or 2	3 or 4	5 or 6	7 to 9	10 or more
How often do you have six or more drinks on one occasion?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
How often have you found that you were not able to stop drinking once you had started?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
How often have you failed to do what was normally expected of you because of drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
How often have you needed a drink in the morning to get yourself going after a heavy drinking session?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
How often have you had a feeling of guilt or remorse after drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
Have you been unable to remember what happened the night before because you had been drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
Have you or someone else been injured as a result of your drinking?	No		Yes, but not since my admission for acute pancreatitis		Yes, also since my admission for acute pancreatitis
Has a relative or friend, doctor or other health worker been concerned about your drinking or suggested you cut down?	No		Yes, but not since my admission for acute pancreatitis		Yes, also since my admission for acute pancreatitis

Additional file 6. Participating Dutch centers

1. Admiraal de Ruyter Hospital, Goes
2. Alrijne Hospital, Leiderdorp
3. Amsterdam University Medical Centers, Amsterdam
4. Bravis Hospital, Roosendaal
5. Canisius Wilhelmina Hospital, Nijmegen
6. Catharina Hospital, Eindhoven
7. Deventer Hospital, Deventer
8. Dijklander Hospital, Hoorn
9. Erasmus MC, Rotterdam
10. Flevo Hospital, Almere
11. Franciscus Gasthuis and Vlietland, Rotterdam
12. Gelre Hospitals, Apeldoorn
13. Haga Hospital, The Hague
14. Hospital Gelderse Vallei, Ede
15. Ikazia Hospital, Rotterdam
16. Isala, Zwolle
17. Leiden University Medical Center
18. Maastad Hospital, Rotterdam
19. Meander MC, Amersfoort
20. Medical Center Leeuwarden, Leeuwarden
21. Medical Spectrum Twente, Enschede
22. Maastricht UMC+, Maastricht
23. NoordWest Ziekenhuisgroep, Alkmaar
24. OLVG, Amsterdam
25. Radboud University Medical Center, Nijmegen
26. Reinier de Graaf Gasthuis, Delft
27. Sint Antonius Hospital, Nieuwegein
28. Spaarne Gasthuis, Hoofddorp
29. TerGooi, Hilversum
30. Treant Zorggroep, Emmen
31. University Medical Center Utrecht, Utrecht
32. Ziekenhuisgroep Twente, Hengelo
33. Zuyderland MC, Sittard