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Structured alcohol cessation support program versus current practice in acute alcoholic pancreatitis (PANDA): Study protocol for a multicentre cluster randomised 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 randomised superiority trial. Participating hospitals are randomised 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 multicentre trial with a cluster randomised 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.

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1. 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-centre randomised 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 favour 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 multicentre cluster randomised 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.

2. Methods

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

2.1. Design

PANDA is a multicentre two-level cluster randomised 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.

2.2. 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 aetiologies 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 aetiology 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.

2.3. 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-centred intervention following the principles of motivational interviewing: listen with empathy, develop discrepancy between patient's drinking behaviour 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 behaviour 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 behaviour of drinking and his or her motivation to change this behaviour.
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.

2.4. 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.

2.5. Primary endpoint

The primary endpoint is recurrence of acute pancreatitis (irrespective of aetiology) 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].

2.6. 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 behaviour 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).

2.7. 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 favour 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.

2.8. 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).

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

2.9. 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 Anaesthesiologist'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 of 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 compromise 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.

3. 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 randomised 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 behaviour 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 behaviour change, while maintaining the patient's autonomy. In MI, patients are encouraged to explore the cons of continuing current behaviour and the pros of behaviour 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 6–12 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 acknowledge 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 aetiology 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 enrol. In patients with harmful drinking behaviour 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 trans-abdominal ultrasound [18]. Because pancreatitis recurrence is the primary endpoint, we have chosen not to include patients with two or more potential aetiologies.

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 randomised 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 randomised 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 randomised 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 aetiology, 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 10–20 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.

In conclusion, the PANDA trial is a multicentre, cluster randomised 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.

Trial status

The trial was registered on the 26th of August 2020 in the Netherlands Trial Registry. The first patient was included on the 7th of January 2021. To date, 13th of June 2023, 68 patients have been included.

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Appendix A. Supplementary data

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References

[1] Roberts SE, Morrison-Rees S, John A, Williams JG, Brown TH, Samuel DG. The incidence and aetiology of acute pancreatitis across Europe. Pancreatology 2017 Mar;17(2):155–65.
[2] Ahmed Ali U, Issa Y, Hagenaars JC, Bakker OJ, van Goor H, Nieuwenhuijs VB, et al. Risk of recurrent pancreatitis and progression to chronic pancreatitis after a first episode of acute pancreatitis. Clin Gastroenterol Hepatol 2016;14(5):738–46.
[3] Magnusdottir BA, Baldursdottir MB, Kalaitzakis E, Björnsson ES. Risk factors for chronic and recurrent pancreatitis after first attack of acute pancreatitis. Scand J Gastroenterol 2019 Jan;54(1):87–94.
[4] Lankisch PG, Breuer N, Bruns A, Weber-Dany B, Lowenfels AB, Maisonneuve P. Natural history of acute pancreatitis: a long-term population-based study. Am J Gastroenterol 2009 Nov;104(11):2797–805. quiz 2806.
[5] Takeyama Y. Long-term prognosis of acute pancreatitis in Japan. Clin Gastroenterol Hepatol 2009 Nov;7(11 Suppl):S15-S17.
[6] Bertilsson S, Swärd P, Kalaitzakis E. Factors that affect disease progression after first attack of acute pancreatitis. Clin Gastroenterol Hepatol 2015 Sep;13(9):1662-9.e3.
[7] Yu B, Li J, Li N, Zhu Y, Chen Y, He W, et al. Progression to recurrent acute pancreatitis after a first attack of acute pancreatitis in adults. Pancreatology 2020 Oct;20(7):1340–6.
[8] Cho JH, Jeong YH, Kim KH, Kim TN. Risk factors of recurrent pancreatitis after first acute pancreatitis attack: a retrospective cohort study. Scand J Gastroenterol 2020 Jan;55(1):90–4.
[9] Pelli H, Lappalainen-Lehto R, Piironen A, Sand J, Nordback I. Risk factors for recurrent acute alcohol-associated pancreatitis: a prospective analysis. Scand J Gastroenterol 2008;43(5):614–21.
[10] Pelli HSJ, Laippala P, Nordback I. Long-term follow-up after the first episode of acute alcoholic pancreatitis: time course and risk factors for recurrence. Scand J Gastroenterol 2000 May;35(5):552–5.
[11] Nikkola J, Raty S, Laukkarinen J, Seppanen H, Lappalainen-Lehto R, Jarvinen S, et al. Abstinence after first acute alcohol-associated pancreatitis protects against recurrent pancreatitis and minimizes the risk of pancreatic dysfunction. Alcohol Alcohol 2013;48(4):483–6.
[12] Bertilsson S, Sward P, Kalaitzakis E. Factors that affect disease progression after first attack of acute pancreatitis. Clin Gastroenterol Hepatol 2015;13(9). 1662-9 e3.
[13] Lankisch PGBN, Bruns A, Weber-Dany B, Lowenfels AB, Maisonneuve P. Natural history of acute pancreatitis: a long-term population-based study. Am J Gastroenterol 2009 Nov;104(11):2797–805.
[14] Andersson B, Appelgren B, Sjodin V, Ansari D, Nilsson J, Persson U, et al. Acute pancreatitis–costs for healthcare and loss of production. Scand J Gastroenterol 2013;48(12):1459–65.
[15] Peery AF, Crockett SD, Murphy CC, Lund JL, Dellon ES, Williams JL, et al. Burden and cost of gastrointestinal, liver, and pancreatic diseases in the United States: update 2018. Gastroenterology 2019 Jan;156(1):254–72. e11.
[16] Alaja R, Seppa K. Six-month outcomes of hospital-based psychiatric substance use consultations. Gen Hosp Psychiatr 2003;25(2):103–7.
[17] McQueen J, Howe TE, Allan L, Mains D, Hardy V. Brief interventions for heavy alcohol users admitted to general hospital wards. Cochrane Database Syst Rev 2011;8:CD005191.
[18] Working Group IAPAPAAPG. IAP/APA evidence-based guidelines for the management of acute pancreatitis. Pancreatology 2013;13(4 Suppl 2):e1-15.
[19] Sissingh NJ, Umans DS, Goudriaan AE, Sijbom M, Verdonk RC, van Hooft JE. Dutch pancreatitis study group. Alcohol reduction to reduce relapse in acute alcoholic pancreatitis-missed opportunities. Alcohol Alcohol 2021 Oct 29;56(6):678–82.
[20] Nordback I, Pelli H, Lappalainen-Lehto R, Jarvinen S, Raty S, Sand J. The recurrence of acute alcohol-associated pancreatitis can be reduced: a randomized controlled trial. Gastroenterology 2009;136(3):848–55.
[21] Lannuzzi Jp KJ, Leong JH, Quan J, Windsor JW, Tanyingoh D, Coward S, et al. Global incidence of acute pancreatitis is increasing over time: a systematic review and meta-analysis. Gastroenterology 2022 Jan;162(1):122–34.
[22] Spanier BWM, Bruno M, Dijkgraaf M. An update on hospital admissions for acute pancreatitis in The Netherlands (2013-2019). Eur J Gastroenterol Hepatol 2022 Jun 1;34(6):726–7.
[23] Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin JA, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. BMJ Br Med J (Clin Res Ed) 2013;346:e7586.
[24] Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, et al. Classification of acute pancreatitis–2012: revision of the Atlanta classification and definitions by international consensus. Gut 2013;62(1):102–11.
[25] Reinert DF, Allen JP. The alcohol use Disorders identification test: an update of research findings. Alcohol Clin Exp Res 2007;31(2):185–99.
[26] Schneider A, Lohr JM, Singer MV. The M-ANNHEIM classification of chronic pancreatitis: introduction of a unifying classification system based on a review of previous classifications of the disease. J Gastroenterol 2007;42(2):101–19.
[27] Boomsma LJ, Drost IM, Larsen IM, Luijkx JJHM, Meerkerk GJ, Valken N, et al. NHG-Standaard Problematisch alcoholgebruik (Derde herziening) Huisarts Wet 2014;57(12):638–46.
[28] CBO. Multidisciplinaire Richtlijn Stoornissen in het gebruik van alcohol. 2009.
[29] Borsari BHL, Manuel JK, Apodaca TR, Mastroleo NR, Jackson KM, et al. Improvement in therapist skills over sessions in brief motivational interventions predicts client language and alcohol use outcomes. Psychol Addict Behav 2019;33(5):484–94.
[30] Trimbos Institute. https://www.trimbos.nl/docs/pfg79055-folder-wat-iedereen-over-alcohol-zou-moeten-weten-bundel-van-50-stuks.pdf; May 2019.
[31] Besselink MG, van Santvoort HC, Buskens E, Boermeester MA, van Goor H, Timmerman HM, et al. Probiotic prophylaxis in predicted severe acute pancreatitis: a randomised, double-blind, placebo-controlled trial. Lancet 2008;371(9613):651–9.
[32] van Santvoort HC, Besselink MG, Bakker OJ, Hofker HS, Boermeester MA, Dejong CH, et al. A step-up approach or open necrosectomy for necrotizing pancreatitis. N Engl J Med 2010;362(16):1491–502.
[33] Bakker OJ, van Brunschot S, van Santvoort HC, Besselink MG, Bollen TL, Boermeester MA, et al. Early versus on-demand nasoenteric tube feeding in acute pancreatitis. N Engl J Med 2014;371(21):1983–93.
[34] Bakker OJ, van Santvoort HC, van Brunschot S, Geskus RB, Besselink MG, Bollen TL, et al. Endoscopic transgastric vs surgical necrosectomy for infected necrotizing pancreatitis: a randomized trial. JAMA 2012;307(10):1053–61.
[35] da Costa DW, Bouwense SA, Schepers NJ, Besselink MG, van Santvoort HC, van Brunschot S, et al. Same-admission versus interval cholecystectomy for mild gallstone pancreatitis (PONCHO): a multicentre randomised controlled trial. Lancet 2015;386(10000):1261–8.
[36] van Brunschot S, van Grinsven J, van Santvoort HC, Bakker OJ, Besselink MG, Boermeester MA, et al. Endoscopic or surgical step-up approach for infected necrotising pancreatitis: a multicentre randomised trial. Lancet 2018;391(10115):51–8.
[37] Doepel MEJ, Halme L, Kumpulainen T, Höckerstedt K. Good long-term results in patients surviving severe acute pancreatitis. Br J Surg 1993 Dec;80(12):1583–6.
[38] Romano MPL. Understanding the process of motivational interviewing: a review of the relational and technical hypotheses. Psychother Res 2016;26(2):220–40.
[39] Miller WRRS. Motivational interviewing, preparing people to change addictive behavior. New York: The Guildford Press; 1991.
[40] Chan DNSSW. Effectiveness of motivational interviewing in enhancing cancer screening uptake amongst average-risk individuals: a systematic review. Int J Nurs Stud 2021 Jan;113:103786.
[41] Lindson-Hawley NTT, Begh R. Motivational interviewing for smoking cessation. Cochrane Database Syst Rev 2015 Mar 2;(3):CD006936.
[42] Soderlund P. Effectiveness of motivational interviewing for improving physical activity self-management for adults with type 2 diabetes: a review. Chron Illness 2018 Mar;14(1):54–68.
[43] Havard A, Shakeshaft A, Sanson-Fisher R. Systematic review and meta-analyses of strategies targeting alcohol problems in emergency departments: interventions reduce alcohol-related injuries. Addiction 2008;103(3):368–76.
[44] Reus VI, Fochtmann LJ, Bukstein O, Eyler AE, Hilty DM, Horvitz-Lennon M, et al. The American psychiatric association practice guideline for the pharmacological treatment of patients with alcohol use disorder. Am J Psychiatr 2018 Jan 1;175(1):86–90.
[45] Broers S, Smets E, Bindels P, Evertsz FB, Calff M, de Haes H. Training general practitioners in behavior change counseling to improve asthma medication adherence. Patient Educ Counsel 2005;58(3):279–87.
[46] Daeppen J, Fortini C, Gaume J, Faouzi M, Bonvin R, Layat C, et al. Teaching motivational interviewing to medical students to improve behavior change counseling skills-results of a pilot test. J Gen Intern Med 2009;24:177–8.
[47] Sobell LCSM. Timeline Followback: a technique for assessing self-reported alcohol consumption. In: Litten RZ, Allen JP, editors. Measuring alcohol consumption: psychosocial and biochemical methods. Totowa, NJ: Humana Press; 1992. p. 41–72.
[48] Nordback ISJ, Andrén-Sandberg A. Criteria for alcoholic pancreatitis. Results of an international workshop in Tampere, Finland, June 2006. Pancreatology 2007;7(2–3):100–4.
[49] Juliusson SJ, Nielsen JK, Runarsdottir V, Hansdottir I, Sigurdardottir R, Björnsson ES. Lifetime alcohol intake and pattern of alcohol consumption in patients with alcohol-induced pancreatitis in comparison with patients with alcohol use disorder. Scand J Gastroenterol 2018 Jun;53(6):748–54.
[50] Kristiansen L, Grønbaek M, Becker U, Tolstrup JS. Risk of pancreatitis according to alcohol drinking habits: a population-based cohort study. Am J Epidemiol 2008 Oct 15;168(8):932–7.
[51] Ren Z, Yang F, Wang X, Wang Y, Xu M, Frank JA, et al. Chronic plus binge

ethanol exposure causes more severe pancreatic injury and inflammation. Toxicol Appl Pharmacol 2016 Oct 1;308:11–9.
[52] Samokhvalov AV, Rehm J, Roerecke M. Alcohol consumption as a risk factor for acute and chronic pancreatitis: a systematic review and a series of meta-analyses. EBioMedicine 2015 Nov 14;2(12):1996–2002.
[53] Stigendal L, Olsson R. Alcohol consumption pattern and serum lipids in alcoholic cirrhosis and pancreatitis. A comparative study. Scand J Gastroenterol 1984 Jul;19(5):582–7.
[54] Yadav D, Hawes RH, Brand RE, Anderson MA, Money ME, Banks PA, et al. North American Pancreatic Study Group. Alcohol consumption, cigarette smoking, and the risk of recurrent acute and chronic pancreatitis. Arch Intern Med 2009 Jun 8;169(11):1035–45.
[55] Becker U, Timmermann A, Ekholm O, Grønbæk M, Drewes AM, Novovic S, et al. Alcohol drinking patterns and risk of developing acute and chronic pancreatitis. Alcohol Alcohol 2023 Mar 1:agad012.
[56] Umans DS, Timmerhuis HC, Hallensleben ND, Bouwense SA, Anten MG, Bhalla A, et al. Dutch Pancreatitis Study Group. Role of endoscopic ultrasonography in the diagnostic work-up of idiopathic acute pancreatitis (PICUS): study protocol for a nationwide prospective cohort study. BMJ Open 2020 Aug 20;10(8):e035504.
[57] Schepers NJ, Hallensleben NDL, Besselink MG, Anten MGF, Bollen TL, da Costa DW, et al. Dutch Pancreatitis Study Group. Urgent endoscopic retrograde cholangiopancreatography with sphincterotomy versus conservative treatment in predicted severe acute gallstone pancreatitis (APEC): a multicentre randomised controlled trial. Lancet 2020 Jul 18;396(10245):167–76.
[58] Whitcomb DC. Gene-environment factors that contribute to alcoholic pancreatitis in humans. J Gastroenterol Hepatol 2006 Oct;21(Suppl 3):S52–5.
[59] Berglund L, Brunzell JD, Goldberg AC, Goldberg IJ, Sacks F, Murad MH, et al. Evaluation and treatment of hypertriglyceridemia: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2012;97(9):2969–89.
[60] Schwarz ASNB, Søgaard J, Søgaard Nielsen A. Making a bridge between general hospital and specialised community-based treatment for alcohol use disorder-A pragmatic randomised controlled trial. Drug Alcohol Depend 2019 Mar 1;196:51–6.