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ESPEN Guideline

ESPEN guideline on clinical nutrition in acute and chronic pancreatitis

Marianna Arvanitakis [a, *], Johann Ockenga [b], Mihailo Bezmarevic [c], Luca Gianotti [d], Željko Krznarić [e], Dileep N. Lobo [f, g], Christian Löser [h], Christian Madl [i], Remy Meier [j], Mary Phillips [k], Henrik Højgaard Rasmussen [l], Jeanin E. Van Hooft [m], Stephan C. Bischoff [n]

[a] Department of Gastroenterology, Erasme University Hospital ULB, Brussels, Belgium
[b] Department of Gastroenterology, Endocrinology and Clinical Nutrition, Klinikum Bremen Mitte, Bremen, Germany
[c] Department of Hepatobiliary and Pancreatic Surgery, Clinic for General Surgery, Military Medical Academy, University of Defense, Belgrade, Serbia
[d] School of Medicine and Surgery, University of Milano-Bicocca and Department of Surgery, San Gerardo Hospital, Monza, Italy
[e] Department of Gastroenterology, Hepatology and Nutrition, Clinical Hospital Centre & School of Medicine, Zagreb, Croatia
[f] Gastrointestinal Surgery, Nottingham Digestive Diseases Centre, National Institute for Health Research. (NIHR) Nottingham Biomedical Research Centre, Nottingham University Hospitals NHS Trust, University of Nottingham, Queen's Medical Centre, Nottingham, NG7 2UH, UK
[g] MRC Versus Arthritis Centre for Musculoskeletal Ageing Research, School of Life Sciences, University of Nottingham, Queen's Medical Centre, Nottingham NG7 2UH, UK
[h] Medical Clinic, DRK-Kliniken Nordhessen, Kassel, Germany
[i] Division of Gastroenterology and Hepatology, Krankenanstalt Rudolfstiftung, Krankenanstaltenverbund Wien (KAV), Vienna, Austria
[j] AMB-Praxis-MagenDarm Basel, Basel, Switzerland
[k] Department of Nutrition and Dietetics, Royal Surrey County Hospital NHS Foundation Trust, Guildford, UK
[l] Centre for Nutrition and Bowel Disease, Department of Gastroenterology, Aalborg University Hospital, Faculty of Health, Aalborg University, Aalborg, Denmark
[m] Department of Gastroenterology & Hepatology, Amsterdam Gastroenterology and Metabolism, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands
[n] Institute of Nutritional Medicine, University of Hohenheim, Stuttgart, Germany

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SUMMARY

Both acute and chronic pancreatitis are frequent diseases of the pancreas, which, despite being of benign nature, are related to a significant risk of malnutrition and may require nutritional support. Acute necrotizing pancreatitis is encountered in 20% of patients with acute pancreatitis, is associated with increased morbidity and mortality, and may require artificial nutrition by enteral or parenteral route, as well as additional endoscopic, radiological or surgical interventions. Chronic pancreatitis represents a chronic inflammation of the pancreatic gland with development of fibrosis. Abdominal pain leading to decreased oral intake, as well as exocrine and endocrine failure are frequent complications of the disease. All of the above represent risk factors related to malnutrition. Therefore, patients with chronic pancreatitis should be considered at risk, screened and supplemented accordingly. Moreover, osteoporosis and increased facture risk should be acknowledged in patients with chronic pancreatitis, and preventive measures should be considered.

1. Introduction

Acute pancreatitis (AP) is the most common acute gastrointestinal disease requiring hospital admission [1], with the outcome being favorable in most cases (80%) [2]. However, acute necrotizing pancreatitis (ANP) may develop in up to 20% of patients and is associated with significant rates of early organ failure (38%), need for intervention (38%), and death (15%) [2]. Catabolism is very high in this setting; therefore, nutritional support is one of the cornerstones of management [3]. A significant amount of research has shown the superiority of enteral over parenteral nutrition in ANP, creating a paradigm shift a decade ago and modifying the management strategy [3]. Nevertheless, additional questions regarding the timing, route and type of enteral nutrition (EN), as well as the place of oral refeeding, are still the objects of clinical investigations.

Chronic pancreatitis (CP) is a disease in which recurrent inflammatory episodes lead to replacement of the pancreatic parenchyma by fibrous connective tissue [4]. The major consequence of CP is the loss of functional exocrine and endocrine pancreatic

* Corresponding author.
E-mail address: Marianna.arvanitaki@erasme.ulb.ac.be (M. Arvanitakis).

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Abbreviations

ACS	Abdominal Compartment Syndrome
ANP	Acute Necrotizing Pancreatitis
AP	Acute Pancreatitis
BMI	Body Mass Index
CP	Chronic Pancreatitis
DPEJ	Direct Percutaneous Endoscopic Jejunostomy
DXA	Dual-energy X-ray Absorptiometry
EN	Enteral Nutrition
IAH	Intra-abdominal Hypertension
IAP	Intra-abdominal Pressure
MCT	Medium Chain Triglycerides
MUST	Malnutrition Universal Screening Tool
NAFLD	Non Alcoholic Fatty Liver Disease
ONS	Oral Nutritional Supplements
PEG-J	Percutaneous Endoscopic Gastrostomy with Jejunal Extension
PEI	Pancreatic Exocrine Insufficiency
PERT	Pancreatic Enzyme Replacement Therapy
PN	Parenteral Nutrition
PPI	Proton Pump Inhibitor
RCT	Randomized Controlled Trial
SIBO	Small Intestinal Bacterial Overgrowth
VARD	Video-assisted Retroperitoneal Debridement

tissue, thus resulting in both exocrine and endocrine insufficiency [4]. Pain is also frequently encountered in patients with CP, and seems to be related to a multitude of factors such as pancreatic neural remodeling and neuropathy, increased intraductal and parenchymal pressure, pancreatic ischemia and acute inflammation during an acute relapse [5]. Both pain and loss of pancreatic function can lead to malnutrition in patients with CP [4]. Moreover, other long-term consequences such as osteoporosis are frequently overlooked, despite their potential impact on quality of life in patients with CP. Therefore, screening for malnutrition and nutritional support play a crucial part in the multimodal management required in this setting.

Although recent guidelines for AP [2] and CP [4] have been published, a dedicated consensus on nutritional support in pancreatic diseases is lacking.

2. Methods

The present guideline was developed according to the standard operating procedure for ESPEN guidelines [6]. The guideline was developed by an expert group of 13 authors from eleven European countries.

2.1. Methodology of guideline development

Based on the standard operating procedures for ESPEN guidelines and consensus papers, the first step of the guideline development was the formulation of so-called PICO questions which address specific **p**atient groups or **p**roblems, **i**nterventions, **c**ompare different therapies and are **o**utcome-related [6]. In total, 31 PICO questions were created and split into two main chapters, “Acute pancreatitis” and “Chronic Pancreatitis”. To answer these PICO questions, a literature search was performed to identify suitable meta-analyses, systematic reviews and primary studies, published from 1977 up to December 2018. The PICO questions were allocated to subgroups/experts for the different subjects who created 42 recommendations and seven statements. For grading the literature, the grading system of the Scottish Intercollegiate Guidelines Network (SIGN) was used [7]. Allocation of studies to the different levels of evidence is shown in Table 1. Supportive of the recommendations, the working group added commentaries to the recommendations where the bases of the recommendations are explained.

The recommendations were graded according to the levels of evidence assigned (Table 2). The wording of the recommendations reflect the grades of recommendations, level A is indicated by “shall”, level B by “should” and level 0 by “can/may”. The good practice point (GPP) is based on experts' opinions due to the lack of studies, here, the wording can be chosen deliberately.

Online voting on the recommendations was performed on the guideline-services.com platform. All ESPEN members were invited to agree or disagree with the recommendations and to comment on them. A first draft of the guideline was also made available to the participants; on that occasion 36 recommendations and all seven statements reached an agreement of >90%, six recommendations reached an agreement of 75–90% and no recommendation an agreement of <75%. Those recommendations with an agreement of >90%, which means a strong consensus (Table 3) were passed directly; all others were revised according to the comments and voted on again during a consensus conference, which took place on 29th April 2019. All recommendations received an agreement of >90%. During the consensus conference, one of the original recommendations was considered redundant and one statement was transformed into a recommendation. Therefore, the guideline comprises 42 recommendations and six statements. To support the recommendations and the assigned grades of recommendation, the ESPEN guideline office created evidence tables of relevant meta-analyses, systematic reviews and randomized controlled trials (RCTs). These evidence tables are available online as supplemental material to this guideline.

2.2. Search strategy

A comprehensive literature research including systematic reviews, controlled clinical trials and cohort studies, with the keywords and filters presented in Table 4 was performed. We initially searched Pubmed, Cochrane Library and EMBASE for recent, rigorous systematic reviews and meta-analyses that answered our clinical questions. In the absence of these, we looked for comparative studies, whether randomized or not. The search phrases included the following terms: (acute pancreatitis OR acute necrotizing pancreatitis OR chronic pancreatitis OR pancreatitis OR hypertriglyceridemic pancreatitis OR hyperlipidemic pancreatitis) AND (nutritional status OR nutritional assessment OR nutritional screening OR malnutrition OR oral feeding OR enteral nutrition OR tube feeding OR parenteral nutrition OR intravenous nutrition OR timing OR formula OR formulation OR nasogastric tube OR nasojejunal tube OR digestive intolerance OR necrosectomy OR minimally invasive OR increased intra-abdominal pressure OR abdominal compartment syndrome OR open abdomen OR immunonutrition OR glutamine OR antioxidants OR probiotics OR enzyme supplementation OR enzyme replacement therapy OR micronutrients OR macronutrients OR nutrient deficiency OR diet OR fat OR nitrogen OR dietary protein OR carbohydrates oral

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Table 1
Levels of evidence.

1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++	High quality systematic reviews of case control or cohort studies. High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

According to the Scottish Intercollegiate Guidelines Network (SIGN) grading system. Source: SIGN 50: A guideline developer's handbook. Quick reference guide October 2014 [SIGN 50]. RCT = randomized controlled trial.

Table 2
Grades of recommendation [6].

A	At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population; or A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
0	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2++ or 2+
GPP	Good practice points/expert consensus: Recommended best practice based on the clinical experience of the guideline development group

RCT = randomized controlled trial.

Table 3
Classification of the strength of consensus.

Strong consensus	Agreement of >90% of the participants
Consensus	Agreement of >75–90% of the participants
Majority agreement	Agreement of 50–75% of the participants
No consensus	Agreement of <50% of the participants

According to the AWMF (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften, Association of the Scientific Medical Societies in Germany) methodology [8].

Table 4
Criteria for systematic search for literature – databases, filters and keywords.

Publication date	From 1977 to December 2018
Language	English
Databases	Pubmed, EMBASE, Cochrane library
Filters	human
Publication type	Cohort study, controlled trial, systematic review
Keywords	Acute pancreatitis, chronic pancreatitis, nutrition

supplementation OR medium chained triglycerides OR osteoporosis OR osteopenia).

Finally, 88 articles were selected for the AP chapter, and 111 articles for the CP chapter.

3. Results

3.1. Acute pancreatitis

1. Which patients with AP are considered at nutritional risk?

Statement 1

Patients with AP should be considered at moderate to high nutritional risk, because of the catabolic nature of the disease and because of the impact of the nutritional status for disease development.

Strong consensus (97% agreement).

Recommendation 1

All patients with predicted mild to moderate AP should be screened using validated screening methods such as the Nutritional Risk Screening – 2002 (NRS-2002); however, the patients with predicted severe AP should always be considered at nutritional risk.

Grade of Recommendation B – Strong consensus (100% agreement).

Commentary

Fortunately, the majority of patients with AP have predicted mild or moderately severe forms of the disease that are self-limited with fully recovery in less than a week, in whom oral feeding can be started within few days after the onset of AP [9]. Gut-barrier dysfunction may occur in up to 60% of patients with AP; mostly in severe AP and it is thought to lead to bacterial translocation and infection of necrosis [10]. Along with the increased catabolic state related to the disease, patients with predicted severe AP are considered at nutritional risk [11]. Nevertheless, malnourished patients should also be considered at nutritional risk, even if they have predicted mild AP, because of their pre-existing condition. Similarly, patients with increased alcohol consumption are frequently malnourished [12]. Scoring systems such as the NRS 2002 [13], can be helpful in identifying these patients [14–17]. These scores have been validated in hospitalized, as well as critically ill patients. Nevertheless, no studies have validated these scoring systems in a specific population of patients with AP [18].

A low body mass index (BMI) may also identify patients who are at nutritional risk. Nevertheless, obesity is a known risk factor for severe AP and is, therefore, a disease severity-related nutritional risk [19].

2. Is early oral feeding feasible in patients with predicted mild AP?

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Recommendation 2

Oral feeding shall be offered as soon as clinically tolerated and independent of serum lipase concentrations in patients with predicted mild AP.

Grade of Recommendation A – Strong consensus (100% agreement).

Recommendation 3

Low-fat, soft oral diet shall be used when reinitiating oral feeding in patients with mild AP.

Grade of Recommendation A – Strong consensus (100% agreement).

Commentary

Most patients with AP suffer from disease of a mild to moderate severity, non-necrotizing type with an uncomplicated clinical course. Four RCTs have shown that patients with mild to moderate AP can tolerate early oral feeding and this strategy is related with a shorter length of stay compared with conventional oral feeding (introduced after enzyme decrease, pain resolution and bowel movement) [9,20–23]. Furthermore, one of these trials revealed that oral food intake is safe and well-tolerated independently of the course and normalization of serum lipase [20]. Immediate oral feeding with a soft diet seems to be more beneficial regarding caloric intake and equally tolerated compared with clear liquid diets [23–25]. A meta-analysis confirmed that early oral feeding was feasible in patients with predicted mild AP and reduced length of stay [26]. A recent meta-analysis including 17 studies identified that 16.3% of patients with AP will subsequently have intolerance to oral feeding [27]. Predictive factors included the presence of pleural effusions and/or collections and severity (higher Ranson/Glasgow and Balthazar scores).

Hyperlipidemia is the third most common cause of AP and accounts for 4–10% of cases [28]. It was reported that hyperlipidemia is associated with a worse prognosis of AP than other etiological factors [28–30]. The initial management of hyperlipidemic AP is the same as for all other causes of the disease, but subsequent management in addition to generalized supportive measures may include etiology-specific targeted therapies. These include initially putting patients on a nil by mouth regimen for 24–48 h, subsequent dietary modifications, medical management with the different classes of anti-hyperlipidemic agents, in-hospital pharmacological treatment with insulin and/or heparin and plasmapheresis. Whilst these measures are effective in lowering triglyceride concentrations, they do not appear to affect the outcome of AP [28,29]. However, tight regulation of triglyceride concentration after presentation with AP was found to reduce the risk of recurrence. These include a low fat diet, encouragement of weight loss and treatment with a fibrate, with the addition of a statin if hypercholesterolemia is present in addition to hypertriglyceridemia [28].

3. If required, what type of medical nutrition (enteral or parenteral) is preferable in patients with AP?

Recommendation 4

In patients with AP and inability to feed orally, EN shall be preferred to parenteral nutrition (PN).

Grade of Recommendation A – Strong consensus (97% agreement).

Commentary

EN is supposed to preserve the integrity of the gut mucosa, stimulate intestinal motility, prevent bacterial overgrowth, and increase the splanchnic blood flow [10]. Currently there are twelve RCTs and eleven systematic reviews/meta-analyses including a Cochrane-standard meta-analysis which clearly prove that in patients with severe AP, EN is safe and well-tolerated, with significant decreases in complication rates, multi-organ failure, and mortality, compared with PN [31–41]. The meta-analysis by Al-Omran et al. was performed to Cochrane-standards on the basis of eight RCTs with 348 patients and clearly shows that early EN when compared with initial total PN, significantly decreases mortality by 50% (OR 0.50 [95% CI 0.28 to 0.91]), rate of infection (OR 0.39 [95% CI 0.23 to 0.65]), multi-organ failure (0.55 [95% CI 0.37 to 0.81]) as well as the necessity for operation (OR 0.44 [95% CI 0.29 to 0.67]) [35]. Furthermore if only patients with severe AP were included in this meta-analysis, mortality further decreased by more than 80% [0.18 [95% CI 0.006 to 0.58]) [35]. These results were confirmed by more recent meta-analyses, including a latest publication including only critically ill patients with AP [39]. Compared with PN, EN was associated with a significant reduction in overall mortality (RR 0.36, 95% CI 0.20 to 0.65, $p = 0.001$) and the rate of multiple organ failure (RR 0.39, 95% CI 0.21 to 0.73, $p = 0.003$).

4. What is the optimal timing for initiating EN in patients with AP?

Recommendation 5

EN should be started early, within 24–72 h of admission, in case of intolerance to oral feeding.

Grade of Recommendation B – Strong consensus (92% agreement).

Commentary

Several meta-analyses have investigated the clinical effects and tolerance of early EN in patients with AP either within 24 h [42–44] or 48 h [45–47] of admission. All these meta-analyses clearly reveal that early EN is feasible, safe and well-tolerated and associated with substantial clinical benefits regarding mortality, organ failure and infectious complications for both time-points compared with delayed EN. Nevertheless, a potential bias could be that five of these meta-analysis included studies which had patients receiving PN in their control groups [42–46]. One meta-analysis, compared early (within 24 h) with late enteral nutrition (after 72 h), but no comparison was made between 24 and 48 h [44].

In contrast to these data from the aforementioned meta-analyses that provided strong evidence for early EN within

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24–48 h, a multicenter RCT (208 patients with predicted severe AP) found no difference in the rate of major infection or death between early EN, started within 24 h after admission, and an oral diet initiated 72 h after admission [48]. A second RCT (214 patients with AP) confirmed these results, showing no significant reduction in persistent organ failure and mortality in patients receiving early EN compared with patients receiving no nutritional support [49]. A plausible explanation could be that these trials included mostly patients with mild or moderate AP (in the Bakker trial there were only 63% of cases with necrotizing AP [48]); therefore, the beneficial effect of early EN could be less pronounced.

Finally, a prospective cohort study including 105 patients with AP concluded that the third day after hospital admission was the best cut-off time for early EN (with an area under the curve of 0.744), by reducing the risk of secondary infection and improving the nutritional status of patients, with a better tolerance [50].

5. What type of EN is indicated?
Recommendation 6

In patients with AP a standard polymeric diet shall be used.

Grade of Recommendation A – Strong consensus (97% agreement).

Commentary

Most studies that evaluated the clinical benefits of early EN in comparison with total PN used semi-elemental formulas while the recent studies were performed with polymeric formulas. In all studies both types of formulas were proven to be feasible, safe and well-tolerated. One small RCT in 30 patients found that both formulas were safe and well-tolerated (based on a visual analog scale and number of stools per day) with some clinical benefits for semielemental diets, including length of stay (23 ± 2 *vs.* 27 ± 1 days, $p = 0.006$) and weight maintenance [51]. On the other hand an indirect adjusted meta-analysis of Petrov et al. on 428 patients using PN as a reference treatment showed no differences regarding tolerance, rate of infection and mortality between both formulas [52]. Finally, a second, more recent meta-analysis, including 15 trials (1376 participants), showed no evidence to support a specific enteral formula [53]. Nevertheless, a subgroup of patients with severe AP may have malabsorption and therefore, semi-elemental diets could be of interest.

6. What route should be used for EN in patients with AP?
Recommendation 7

If EN is required in patients with AP, it should be administered via a nasogastric tube. Administration via a nasojejunal tube should be preferred in case of digestive intolerance.

Grade of Recommendation B – Strong consensus (95% agreement).

Commentary

Three RCTs compared nasojejunal with nasogastric support route in patients with severe AP [54–56] showed no differences regarding tolerance, complications rates and mortality. Four meta-analyses [57–60] conclude that nasogastric tube feeding is feasible, safe and well-tolerated and, compared with nasojejunal tube feeding, does not increase complication rate, mortality, refeeding pain recurrence or prolong hospital stay in patients with severe AP. Compared with nasojejunal tubes, nasogastric tubes are much easier to place, more convenient and cheaper. Nevertheless, about 15% of patients will experience digestive intolerance, mostly because of delayed gastric emptying and gastric outlet syndrome [57,58] and in this situation, nasojejunal tube feeding is required. Furthermore, potential bias arises from the small number of patients included in the aforementioned trials and the use of different criteria to define severe AP.

7. In patients with AP, when should PN be initiated?
Recommendation 8

PN should be administered in patients with AP who do not tolerate EN or who are unable to tolerate targeted nutritional requirements, or if contraindications for EN exist.

Grade of Recommendation GPP – Strong consensus (97% agreement).

Commentary

The primary nutritional route in all patients with severe AP should be enteral, as this route has been shown to have benefits over other regimens. However, PN is indicated in patients with severe AP who do not tolerate EN or who are unable to tolerate targeted requirements, or if there exists contraindication for EN overall. Complications of severe AP, which may occur and represent a contraindication for EN, include bowel obstruction, abdominal compartment syndrome, prolonged paralytic ileus and mesenteric ischemia [61]. Similar to critically ill patients with other diseases, approximately 20% of patients with severe AP have complications, which are associated with absolute or relative contraindications for EN (Fig. 1) [17].

8. How should medical nutrition be provided in case of necrosectomy (endoscopically or by minimally invasive surgery) in patients with severe AP?
Recommendation 9

Oral food intake in patients undergoing minimally invasive necrosectomy is safe and feasible and should be initiated in the first 24 h after the procedure, if the clinical state (hemodynamic stability, septic parameters, gastric emptying) of the patient allows it.

Grade of Recommendation GPP – Strong consensus (95% agreement).

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Recommendation 10

In patients undergoing minimally invasive necrosectomy who are unable to be fed orally, EN is indicated via nasojejunal as preferred route.

Grade of Recommendation B – Strong consensus (91% agreement).

Recommendation 11

PN is indicated in patients undergoing minimally invasive necrosectomy who do not tolerate EN or who are unable to tolerate targeted nutritional requirements, or if there exist contraindications for EN.

Grade of Recommendation GPP – Strong consensus (94% agreement).

Commentary

Approximately 10–20% of patients with AP will develop necrosis of the pancreas and/or peripancreatic tissue (ANP) [1,2]. These patients with ANP have moderate or severe forms of AP, and a higher risk for development of multiple organ failure, secondary infection of the necrosis, and death [62]. After proven benefits of the "step-up" (minimally invasive approach) over the open approach for the treatment of ANP [63], minimally invasive techniques have been used extensively [64]. Furthermore, the Dutch Pancreatitis Study Group recently showed a lower rate of pancreatic fistula and better cost benefits of endoscopic over surgical step-up approach for infected necrotizing pancreatitis [65]. Unfortunately, to date there are no published data on nutritional support in patients with AP treated by the minimally invasive approach. In the aforementioned trial [65], all patients received oral nutrition, if tolerated. If this was not tolerated, a nasojejunal feeding tube was introduced and EN was started. If gastrointestinal feeding was contraindicated, the patient received PN. No specific data were reported regarding nutrition-related outcomes.

In the RCT by Bakker et al. [48], there was no superiority of early (first 24 h) nasojejunal tube feeding when compared with an oral diet after 72 h in reducing the rate of infection or death in patients with predicted severe AP. In this trial interventional procedures due to necrotizing pancreatitis included percutaneous catheter drainage, endoscopic transgastric drainage or necrosectomy and surgical necrosectomy (without information on the type of surgery performed – minimally invasive or open approach). The authors did not find any difference in the number of patients who underwent interventions between groups (24 percutaneous drainages in early EN group *vs.* 46 in the on demand feeding group, $p = 0.13$; eight endoscopic transgastric drainage or necrosectomy in the early EN group *vs.* six in the on-demand feeding group, $p = 0.53$; and three surgical necrosectomy in the early EN group *vs.* seven in the on-demand feeding group, $p = 0.49$). In this trial PN was not used, as it was not mentioned in the feeding protocol of the study. In a retrospective series of 37 patients undergoing laparoscopic transgastric necrosectomy, an oral food intake 24–48 h after the procedure was feasible and safe [66]. In one prospective study on video-assisted retroperitoneal debridement (VARD) the feeding regimen was reported but without specified time of initiation and reasons for shifting oral nutrition to EN or PN [67]. Forty patients in that study were fed by nasojejunal tube as the preferred route when tolerated; otherwise, PN was given [67]. Therefore, based on small series, nasojejunal feeding seems safe in patients having undergone minimally invasive necrosectomy. Nevertheless, definitive data are missing.

9. How should medical nutrition (EN and PN) be provided in critically patients with severe AP (intra-abdominal hypertension (IAH), abdominal compartment syndrome (ACS) with need for open abdomen)?

Recommendation 12

In patients with severe AP and intraabdominal pressure (IAP) < 15 mmHg early EN shall be initiated via nasojejunal, as the preferred route, or nasogastric tube. IAP and the clinical condition of patients during EN shall be monitored continuously.

Grade of Recommendation A – Strong consensus (91% agreement).

Recommendation 13

In patients with severe AP and IAP > 15 mmHg EN should be initiated via nasojejunal route starting at 20 mL/h, increasing the rate according to the tolerance. Temporary reduction or discontinuation of EN should be considered when IAP values further increase under EN.

Grade of Recommendation B – Strong consensus (94% agreement).

Recommendation 14

In patients with severe AP and IAP > 20 mmHg or in the presence of ACS, EN should be (temporarily) stopped and PN should be initiated.

Grade of Recommendation GPP – Strong consensus (94% agreement).

Recommendation 15

In patients with severe AP and open abdomen EN should be administered, at least in a small amount. If required for achievement of nutritional requirements, supplementary or total PN should be added.

Grade of Recommendation B – Strong consensus (97% agreement).

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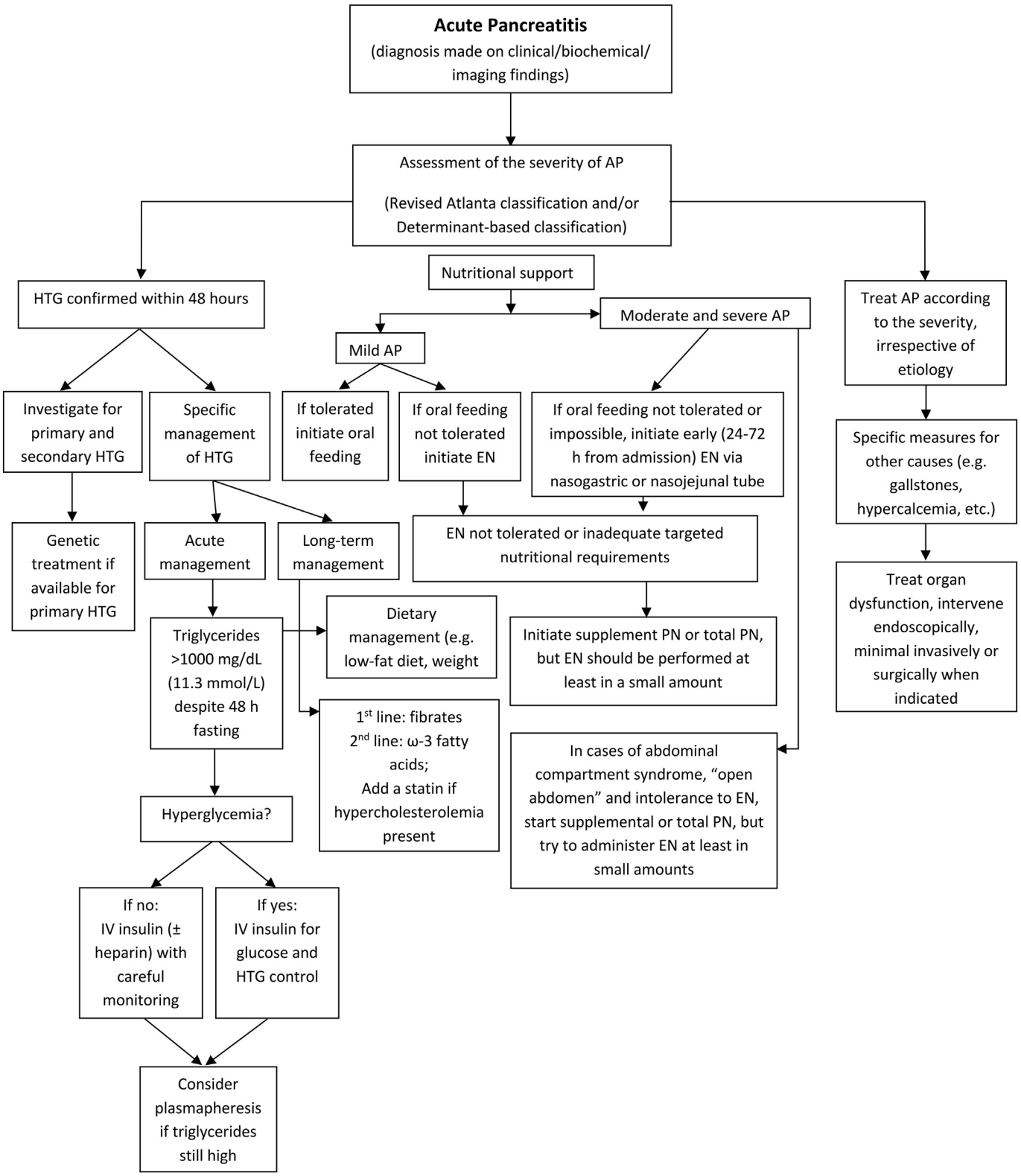

Fig. 1. Algorithm suggesting nutritional management in acute pancreatitis. HTG: hypertriglyceridemia; EN: enteral nutrition; PN: parenteral nutrition. Adapted from Adiamah et al. [28].

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Commentary

The mortality of patients with severe AP who develop IAH/ACS during the course of the disease rises from 25% up to 66% [68,69]. Energy expenditure in patients with AP is increased by 1.49 (1.08–1.78) × the predicted resting energy expenditure; 58% of patients with severe AP have an increase in energy expenditure, approximate net nitrogen loses are 20–40 g per day, and proteolysis can be increased by 80% [70,71]. There are no data available regarding energy requirements in patients with both AP and IAH/ACS, however, energy expenditure in such patients may be increased due to several reasons (decreased splanchnic blood flow, acidosis and bacterial translocation) [17,72].

It has been clearly demonstrated that EN in patients with severe AP reduces mortality and infectious complications, decreases organ failure and surgical intervention rate, has a trend towards reduction of hospital stay, and is safer and more effective than PN [17]. Nevertheless, it has been reported that EN may increase intraluminal pressure with subsequent elevation of IAP and development of severe complications [73,74]. Therefore, it is recommended that EN should be administered with caution when IAP reaches 15 mmHg and over [74]. In an observational study, 274 patients with AP had IAH and 103 developed ACS. The intolerance of EN was more frequent in patients with grade III and IV IAH ($n = 105$) and 62/105 (59%) required PN [75]. In only one RCT including 60 patients, comparing early with delayed EN in patients with IAH and severe AP, it was found that early EN had benefits in patients with IAP <15 mmHg preventing development of IAH. In patients with IAP above 15 mmHg abdominal distension was more frequent in the early EN group. The group of patients with early EN experienced feeding intolerance more often than patients in delayed EN group. However, early EN did not increase IAP and was able to ameliorate clinical course of the disease [76]. Because the majority of patients with IAH have gastrointestinal symptoms and signs (absence of bowel movements, abdominal distension, high gastric residual volume, etc.), EN should be initiated via nasojejunal tube [77]. From a practical point of view, in patients with severe AP and IAH the initiation of EN should be at 20 mL/h, increasing the rate according to the tolerance. The reduction of EN from higher rates to 20 mL/h should be considered when IAP increases between 15 and 20 mmHg. In patients with IAP above 20 mmHg or in the presence of ACS, EN should be (temporarily) stopped [74]. When it is impossible to meet nutritional goals with EN only, supplementary or total PN should be considered.

A decompressive laparotomy (laparostomy) may be necessary in up to 74% of patients who develop ACS during course of AP [72]. Patients with an open abdomen are in a hyper-catabolic state with high nitrogen losses and negative nitrogen balance. It has been estimated that such patients have nitrogen loss of almost 2 g/L of abdominal fluid output and, therefore, nutritional therapy in patients with an open abdomen is essential [78]. Several cohort studies reported that initiation and feeding by EN was feasible and safe despite a relatively high rate of digestive intolerance, ranging from 48 to 67% [78–83]. Two studies concluded that early EN in patients with an open abdomen resulted in higher fascial closure rates, lower fistula rates, reduced nosocomial infections and lower hospital costs [82,83]. In the multicenter analysis by Burlew et al., out of 597 with an open abdomen patients, EN was successfully initiated in 39% [81]. For the 307 patients without a bowel injury, logistic regression indicated that EN was associated with higher fascial closure rates (OR 5.3; $p < 0.01$) decreased complication rates (OR, 0.46; $p = 0.02$), and decreased mortality (OR 0.30; $p = 0.01$) [81].

10. Is there any role for immunonutrition (glutamine, antioxidants) in severe AP?

Recommendation 16

> When EN is not feasible or contraindicated and PN is indicated, parenteral glutamine should be supplemented at 0.20 g/kg per day of L-glutamine. Otherwise, there is no role for immunonutrition in severe AP.
>
> Grade of Recommendation B – Strong consensus (94% agreement).

Commentary

An initial meta-analysis including eleven RCTs assessed the effect of antioxidants (five RCTs on glutamine and six on various other antioxidants) on the outcome of patients with AP [84]. Among patients with AP, antioxidant therapy resulted in a borderline significant reduction in hospital stay (mean difference 1.74; 95% CI 3.56 to 0.08), a significant decrease in complications (RR 0.66; 95% CI 0.46 to 0.95) and a non-significant decrease in mortality rate (RR 0.66; 95% CI 0.30 to 1.46). Nevertheless, these results were mostly attributed to the effect of glutamine. Recently, a Cochrane Review assessed the effects of different pharmacological interventions including antioxidants in patients with AP [85]. Very low-quality evidence suggested that none of the pharmacological treatments decreased short-term mortality in patients with AP.

Regarding glutamine, four meta-analyses have been published. A meta-analysis of ten RCTs including 433 patients with severe AP revealed a significant decrease in the incidence of infectious complications and mortality in the patient group with glutamine-enriched nutrition [86]. Another meta-analysis of twelve RCTs (including 505 patients) demonstrated a significantly reduced infection rate and mortality after glutamine supplementation in patients with AP [87]. In the subgroup analyses, only patients who received total PN demonstrated a significant benefit in terms of study outcomes. Two recently published meta-analyses showed beneficial effects of glutamine supplementation in patients with AP in the terms of elevation of serum albumin concentrations, decrease in serum concentrations of C-reactive protein, and reductions in infectious complications, mortality and hospital stay [84,88]. Nevertheless, the risk of bias of the included studies is important due to many reasons: (i) small sample size in most of the studies, (ii) possible heterogeneity in disease severity and (iii) confounding factors such as other interventions that may change outcome (drainage, debridement or surgery).

11. Is there any role for probiotic use in severe AP?

Recommendation 17

> Probiotics cannot be recommended in patients with severe AP.
>
> Grade of Recommendation 0 – Consensus (89% agreement).

Commentary

A meta-analysis of six RCTs including 536 patients revealed no significant benefit of probiotics on pancreatic infection rate, overall infection rate, operation rate, length of hospital stay and mortality [89]. Significant heterogeneity was observed in the type, dose and treatment duration of probiotics in these trials. In one of these RCTs the patient group assigned to a particular combination of probiotic strains showed similar pancreatic infection rate but increased mortality when compared with the placebo group [90].

12. Is there any role for the use of oral enzyme supplementation in AP?

Recommendation 18

Pancreatic enzymes should not be supplemented generally except in patients with obvious pancreatic exocrine insufficiency (PEI).

Grade of Recommendation B – Strong consensus (97% agreement).

Commentary

There are only two RCTs with a total of 78 patients randomized to pancreatic enzyme supplementation or placebo [91,92]. In the study by Kahl et al. 20 of the 56 patients showed low fecal elastase values indicating PEI. Although the pancreatic enzyme supplement group showed a tendency for better outcome this did not reach statistical significance [91]. In the second small study by Patankar et al. there was also no significant difference in laboratory or clinical outcomes [92]. Therefore, no conclusion can be drawn, but enzyme supplementation should be considered in patients with proven or obvious exocrine insufficiency and malabsorption with steatorrhea.

3.2. Chronic pancreatitis

13. What are the risks of developing malnutrition in patients with CP?

Statement 2

Risk of malnutrition in CP is high and malnutrition is common in patients with CP.

Strong consensus (100% agreement).

Commentary

CP is a disease with progressive and irreversible inflammatory changes in the pancreas that result in permanent structural damage with fibrosis, which can lead to abdominal pain and to impairment of exocrine (pancreatic insufficiency) and often endocrine function [4,93–95].

Malnutrition is often a late, but important manifestation in the course of CP and depends on the intensity and duration of the underlying disease. There are differences in the onset of pancreatic insufficiency and malnutrition between patients with alcoholic and idiopathic CP. The latency between onset of first symptoms and signs of CP, including pain and malabsorption/malnutrition is between five to ten years in alcoholic, but delayed in non-alcoholic pancreatitis [94].

Despite the inconsistency of the data there is an evident risk of malnutrition in patients with CP [95–97]. According to a recent study medium or higher risk for malnutrition based on Malnutrition Universal Screening Tool (MUST) score of one or higher was found in 31.5% patients [98]. Similarly, 26% underweight patients with a nutritional risk were identified in a study of outpatients with CP [99].

At the same time a recent prospective cohort study on 62 patients with CP and 66 controls showed that over half of the patients with CP were overweight or obese [100]. Nevertheless, significant differences in handgrip strength were shown in patients with CP when compared with controls.

In patients with CP with moderate to severe weight loss, decreased lean body mass and sarcopenia may lead to decreased functional capacity, which may have an impact on quality of life [101,102]. In addition, PEI leads to the increased risk of developing significant bone loss and severe osteoporosis [103,104]. A recent prospective study [102] including 182 patients with CP showed that sarcopenia was present in 17% (74% of patients with CP had a BMI > 18.5 kg/m^2). During follow-up, sarcopenia was associated with an increased risk of hospitalization (OR 2.2; 95% CI 0.9 to 5.0; $p = 0.07$), increased number of in-hospital days ($p < 0.001$), and reduced survival (HR 6.7; 95% CI 1.8 to 25.0; $p = 0.005$).

14. What are the causes of malnutrition in patients with CP?

Statement 3

Pancreatic insufficiency, abdominal pain, alcohol abuse, lower food intake, diabetes mellitus and smoking are the main causes of malnutrition in CP.

Strong consensus (97% agreement).

Commentary

Multiple risk factors for developing nutrient deficiencies and malnutrition co-exist in patients with CP. First of all, pancreatic insufficiency (exocrine but also often endocrine) can lead to maldigestion and malabsorption. Clinical signs of PEI include steatorrhea, abdominal pain, weight loss and malnutrition [4]. Recent data showed endocrine insufficiency and/or clinical steatorrhea in 41% and 36% of 809 patients [93]. Moreover, increased resting energy expenditure can be seen in up to 50% of patients with CP, thus leading to a negative energy balance and malnutrition [105]. Furthermore, abdominal pain, which is frequent in patients with CP, can lead to suboptimal dietary intake and also contribute to malnutrition [4].

Tobacco is an independent risk factor for CP, and can also be a disease modifier, acting in synergy with alcohol intake, and therefore, adds to the nutritional risk factors [93].

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15. Which diagnostic tests are preferred to assess nutritional status in patients with CP?

Recommendation 19

Nutritional status should be assessed according to symptoms, organic functions, anthropometry, and biochemical values. Solely BMI should not be used, because it does not register sarcopenia in the obese patient with CP.

Grade of Recommendation GPP – Strong consensus (97% agreement).

Commentary

Studies assessing malnutrition have identified many biochemical factors that are associated with malnutrition [106,107] and prevalence studies show a diverse presentation of malnutrition. Olesen et al. identified that 26% of patients with CP were underweight in a cross-sectional study of 166 patients with CP [99], whereas Duggan et al. highlighted that over half of the patients in their prospective controlled cohort study (n = 128) fell into the overweight/obese category using BMI [100]. However, patients had lower muscle stores and reduced functional status assessed using hand-grip strength than healthy controls. Consequently, BMI alone is not considered an adequate method of assessing nutritional status. Percentage weight loss is considered a more reliable indicator of the onset of malnutrition and is associated with an increased risk in the surgical setting [108].

Consequently, nutritional assessment should allow for detection of simple malnutrition, sarcopenia and micronutrient deficiencies in addition to identifying symptoms that may predispose patients to worsening malnutrition (Table 5).

Table 5
Nutritional assessment in the patient with chronic pancreatitis.

Anthropometric assessment	Biochemical assessment	Symptom assessment	Body composition
• Change in body weight • Functional assessment: Hand-grip strength dynamometry/6-min walk tests/sit to stand tests. • Skin fold thickness, waist circumference and mid arm muscle circumference. • Presence of ascites/edema	• Fat soluble vitamins (A, D, E, K) • Bone health (Parathyroid hormone) • Trace elements (magnesium, selenium, zinc) • Anemia screen (iron studies, B12, folate, ferritin and CRP) • Glycemic control: HbA1c and random glucose	• Change in dietary intake • Appetite • Presence of symptoms that impact on oral intake (nausea/pain/indigestion/early satiety) • Presence of exocrine/endocrine dysfunction	• CT/US imaging of muscle stores (muscle mass) • DXA scanning (bone mineral density)

CRP = C-reactive protein, HbA1c = hemoglobin A1c, CT = computed tomography, US = ultrasound, DXA = dual-energy X-ray absorptiometry.

16. What is the frequency of screening for micro- and macronutrient deficiencies in patients with CP?

Recommendation 20

Patients should undergo screening for micro- and macronutrient deficiencies at least every twelve months; screening may need to occur more frequently in those with severe disease or uncontrolled malabsorption.

Grade of Recommendation GPP – Strong consensus (100% agreement).

Commentary

Patients with CP are at high risk of malnutrition, both in terms of body weight and altered body composition [100]. This has an impact on quality of life [99] and survival after surgery [109,110]. Nutritional intervention can improve nutritional markers and is associated with reduced pain [111] and, therefore, routine screening to trigger nutritional intervention should be undertaken. Deficiencies in micronutrients (vitamin B12, folic acid, vitamin A, D and E, zinc, selenium, iron) are well documented in patients with exocrine insufficiency, these are diverse in presentation with some studies reporting biochemical deficiencies [100,103,112] and case reports document clinical manifestations including night blindness [113,114]. However, there are no data recommending the frequency of assessment or the likely timing of progression to micronutrient deficiency. As clinical manifestation of deficiency represents a late presentation, routine screening should be implemented to detect early signs of deficiency.

17. What recommendations regarding diet and intake of fat, carbohydrates and proteins should be given in patients with CP?

Statement 4

Patients with CP do not need to follow a restrictive diet.

Strong consensus (94% agreement).

Recommendation 21

CP patients with a normal nutritional status should adhere to a well-balanced diet.

Grade of Recommendation GPP – Strong consensus (94% agreement).

Recommendation 22

Malnourished patients with CP should be advised to consume high protein, high-energy food in five to six small meals per day.

Grade of Recommendation GPP – Strong consensus (94% agreement).

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Recommendation 23

In patients with CP, diets very high in fiber should be avoided.

Grade of Recommendation B – Strong consensus (91% agreement).

Statement 5

In patients with CP, there is no need for dietary fat restriction unless symptoms of steatorrhea cannot be controlled.

Strong consensus (100% agreement).

Commentary

There are very little data to suggest the optimal dietary management for patients with CP. Historically, patients were encouraged to have a low-fat diet, and studies in the Netherlands suggest 48–58% of patients still restrict dietary fat [104,115]. International guidelines are consistent in their recommendation that patients should have a balanced diet and avoid fat restriction [4,116–119].

The role of dietary fat has been examined in small studies, suggesting an improvement in dyspeptic symptoms in patients with very mild pancreatic disease who did not consume alcohol regularly when a very low fat diet was consumed (<20 g fat per day) [120] and patients who consumed a higher fat diet were thought to be diagnosed at a younger age, and had an increased probability of continuous abdominal pain [121] suggesting a potential role in the initial development of CP. However once CP was diagnosed, there was no difference in severity or complications of disease. An RCT comparing dietary counseling and nutritional supplements in a cohort of 60 malnourished patients with CP found that nutritional intervention in which 33% of energy was derived from fat was well tolerated [111]. Improvements in nutritional status and pain control were observed in patients receiving nutritional intervention and the authors did not report any adverse events [111].

Patients consuming very high fiber diets reported increased flatulence, and increased fecal weight and fat losses were observed in a small trial (n = 12) in patients with CP. This study suggested that very high fiber diets may inhibit pancreatic enzyme replacement therapy, thus resulting in malabsorption. Thus, very high fiber diets are not recommended in this patient group [122].

18. Are oral supplements, with or without medium-chain triglycerides (MCTs), indicated in patients with CP?

Recommendation 24

Oral nutritional supplements (ONS) should be prescribed to undernourished patients only if oral nutrition is insufficient for reaching the calorie and protein goals.

Grade of Recommendation GPP – Strong consensus (100% agreement).

Recommendation 25

If adequate enzyme supplementation and exclusion of bacterial overgrowth has not led to relief of malabsorption and its accompanying symptoms, ONS with MCT can be administered.

Grade of Recommendation 0 – Strong consensus (97% agreement).

Commentary

Very few studies have investigated the benefit of ONS in patients with CP. Eighty percent of patients can be treated with diet and enzyme supplementation, the rest need oral supplementation [96].

ONS can be of benefit in undernourished patients with CP, especially if the caloric and protein goals cannot be reached with normal meals and counseling. ONS are a simple way to improve oral intake, but long-term compliance may be a problem.

There are no RCTs investigating the relative efficacy of different formulas (e.g. standard or peptide-based with MCT). However, in the presence of PEI, enteral formulas consisting of pre-digested products and a mixture of long chain fatty acids and MCT would seem, theoretically, to have potential advantage. MCTs are less dependent on lipase activity for their absorption [123].

A reduction in oral fat intake or the replacement of dietary fat with MCT risks a reduction in energy intake and, therefore, a negative energy balance. MCTs have an unpleasant taste and are associated with adverse effects like cramps, nausea, and diarrhea. Up to now, studies have not shown any clear benefit of MCTs over standard long-chain triglycerides when used in combination with enzyme supplementation [123,124]. One RCT investigated the efficacy of ONS in patients with CP and severe malnutrition [111]. Dietary counseling achieved equal results compared with the use of a commercial supplement enriched with MCTs. Both groups also received enzyme supplementation and so it is not possible to explain the additional gain from dietary MCTs over enzyme supplementation.

If MCTs are being considered, their dose should be increased slowly depending on the patient's tolerance.

19. When is micronutrient supplementation indicated in patients with CP (not including osteoporosis prevention)?

Recommendation 26

Fat-soluble (A, D, E, K) and water-soluble (vitamin B12, folic acid, thiamine) vitamins as well as minerals such as magnesium, iron, selenium and zinc should be monitored (if available) and administered if low concentrations are detected or if clinical signs of deficiency occur. Supplementation should be proposed to patients with known malabsorption.

Grade of Recommendation GPP – Strong consensus (95% agreement).

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Commentary

The reported prevalence of deficiency of fat-soluble vitamins is 3–14.5% for vitamin A deficiency [100,103,125], 58–77.9% for vitamin D deficiency [100,103,125,126], 9–24% for vitamin E deficiency [100,103,106,125,126] and 13–63% for vitamin K deficiency [100,103,125,126]. In a prospective controlled cohort study of 128 subjects and 66 age/gender-matched controls, 14.5% and 24.2% were deficient in vitamins A and E, respectively, with a significant difference compared with controls. Nineteen percent of patients had excess serum vitamin A concentrations [100]. This must be taken in account and a blind supplementation of all fat-soluble vitamins for all patients with CPs is not advised.

Deficiencies of water-soluble vitamins in patients with CP are less frequent. A recent study with 301 patients with CP and 266 controls showed that patients with CP had significantly lower concentrations of vitamins A, D and E, but no difference regarding vitamin B12 [103]. Similarly, another cohort study of 114 patients with CP (33% with exocrine failure) did not show any significant deficiencies of vitamin B12 (0%) and folic acid (2.2%) [127].

Thiamine deficiency secondary to concomitant alcoholism must be considered [106].

Minerals and trace elements deficiencies have been reported in patients with CP in some case-control studies. The results are conflicting. Lower concentrations of zinc, selenium [106] and magnesium [127] have been observed. Furthermore, low magnesium concentrations seemed to correlate with exocrine failure [127].

20. When is EN indicated in patients with CP and how should it be administered?

Recommendation 27

EN should be administered in patients with malnutrition who are not responding to oral nutritional support.

Grade of Recommendation GPP – Strong consensus (100% agreement).

Recommendation 28

EN should be administered via the nasojejunal route in patients with pain, delayed gastric emptying, persistent nausea or vomiting and gastric outlet syndrome.

Grade of Recommendation GPP – Strong consensus (100% agreement).

Recommendation 29

Long-term jejunostomy access (percutaneous endoscopic gastrostomy with jejunal extension (PEG-J) or direct percutaneous endoscopic jejunostomy (DPEJ) or surgical jejunostomy) can be used in those requiring EN for more than 30 days.

Grade of Recommendation GPP – Strong consensus (97% agreement).

Recommendation 30

Semi-elemental formulas with medium chain triglycerides can be used if standard formulas are not tolerated.

Grade of Recommendation GPP – Strong consensus (94% agreement).

Recommendation 31

Pancreatic enzymes should be supplemented in patients requiring EN, if signs of exocrine failure manifest.

Grade of Recommendation GPP – Strong consensus (100% agreement).

Commentary

Oral nutritional support with dietary counseling is usually sufficient to improve nutritional status in patients with CP [111]. EN is indicated in approximately 5% of patients with CP [97]. Regarding indications and outcomes of EN in these patients, evidence is based on few cohort studies and RCTs are generally lacking [4].

Four retrospective series have shown the benefits of EN in patients with CP regarding weight gain and pain control [128–131]. Two of them included 58 [129] and 50 patients [131] respectively, in whom a naso-jejunal tube was placed. Long-term access with PEG-J or DPEJ was used in 57 [128] and 58 patients [130]. All studies showed that this type of nutritional support was safe and effective in patients with CP, even in case of gastric outlet syndrome [130,131].

There is limited high quality evidence for the composition of enteral formulas in patients with CP. However, there is a rationale that semi-elemental enteral formulas with MCTs are more adapted for jejunal nutrition, compared with polymeric formulas [132]. In two of the aforementioned studies [129,131], semi-elemental formulas were used with good digestive tolerance. Nevertheless, the cost of these feeds is higher and data on cost-effectiveness are also lacking.

In patients with exocrine failure, who do not improve with semi-elemental formulae, pancreatic enzymes can be administered with the formula [133]. This involves opening the capsules and suspending the enzyme microspheres in thickened acidic fluid (such as the mildly thickened or “nectar-thick” fruit juice used for dysphagia) for delivery via the feeding tube.

21. When is PN indicated in patients with CP and how should it be administered?

Recommendation 32

PN may be indicated in patients with gastric outlet obstruction and in those with complex fistulating disease, or in case of intolerance of EN.

Grade of Recommendation GPP – Strong consensus (100% agreement).

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Recommendation 33

For PN the preferable route is central venous access.

Grade of Recommendation GPP – Strong consensus (100% agreement).

Commentary

PN is infrequently uses in patients with CP [4,97]. EN preserves immune function and mucosal architecture and decreases the possibility for hyperglycemia while PN also increases the risk of catheter-related infections and septic complications [96,119]. PN is, therefore, only indicated when it is impossible to use EN (e.g. presence of gastric outlet obstruction, the need for gastric decompression, when it is impossible to introduce a tube into the jejunum, or a complicated fistula is present) or if requirements are only partly reached by EN. PN is mainly administered over a short-term period and long-term studies are lacking. In this case, a standard nutritional solution should be administered via central venous access such as a peripherally inserted central catheter. Contraindications to PN do not differ from general contraindications to medical nutrition.

22. What are the indicators for starting pancreatic enzyme replacement therapy (PERT) in patients with CP?

Recommendation 34

When PEI is diagnosed through clinical signs and symptoms and/or laboratory tests of malabsorption, PERT shall be initiated. An accurate nutritional assessment is mandatory to detect signs of malabsorption.

Grade of Recommendation A – Strong consensus (100% agreement).

Commentary

PEI is defined as an insufficient secretion of pancreatic enzymes (acinar function) and/or sodium bicarbonate (ductal function) [4]. Diagnosis of PEI can be challenging in practice because pancreatic function and secretion are not solely reliant on the quantity or quality of pancreatic tissue [134] but also depend on complex pancreatic stimulatory mechanisms [135]. Moreover, different PEI biomarkers and their threshold values have been used in the current literature [136]. For these reasons a wide range (from 22% to 94%) of prevalence rates for PEI among patients with CP has been reported [98,106,137–146].

The most frequent clinical sign of PEI is steatorrhea [147], defined as presence of fat in the stool, and associated generally with flatulence, bloating, dyspepsia, urgency to pass stools, and cramping abdominal pain. In a recent systematic review, including 14 studies on pancreatic enzyme supplementation in patients with CP, the criteria for the diagnosis of PEI were the measurement of the coefficient of fat absorption with a threshold <80% or the fecal fat absorption less than 7–15 g of fat per day [136].

Overt steatorrhea is not expected unless there is severe or decompensated PEI (i.e. when secretion of pancreatic lipase is less than <10% of normal). However, the absence of overt steatorrhea is not always an indicator of adequate absorption and nutritional status. PEI is consistently associated with biochemical and clinical signs of malnutrition [148]. Management of PEI involves replacing the inadequate pancreatic enzymes, which should be used to maintain weight and improve the symptoms of maldigestion [149].

Awareness of PEI among many physicians is poor outside of referral centers and especially among physicians in primary care [115]. Consequentially, patients who present with symptoms of PEI may be overlooked or advised to adopt inappropriate dietary restrictions in an attempt to control the symptoms. A study identified that the primary unmet patient need was the difficulty in managing gastrointestinal symptoms, diet, and digestion; indeed, many of these patients and caregivers cited delays in dietary assessment and initiation of PERT causing additional distress that could have been prevented [150]. Untreated PEI has also a deleterious impact on the quality of life of patients [151]. As the quantitative measurement of fecal fat is often omitted, it is recommended that enzyme replacement is started when clinical signs of malabsorption, or anthropometric and/or biochemical signs of malnutrition are present [96,127,152–154]. Symptoms include weight loss, alteration of body compartments at bioimpedance analysis, and low nutritional markers (albumin, cholinesterase, prealbumin, retinol-binding protein, and magnesium) [127]. Although it is assumed that steatorrhea is the most important clinical manifestation of PEI, several studies have shown reduced absorption of fat-soluble vitamins even in patients with mild to moderate PEI [155–158].

Non-alcoholic fatty liver disease (NAFLD) is also a poorly recognized complication of PEI. The mechanisms underlying NAFLD in PEI is different from NAFLD associated with metabolic syndrome, because it is mainly due to malabsorption of essential amino acids such as choline which leads to a decrease in plasma concentrations of apoprotein B [159], a major component of very-low-density lipoprotein.

23. What are the enzyme preparations of choice for PERT?

Recommendation 35

pH-sensitive, enteric-coated microspheres pancreatic enzyme replacement preparations shall be used for treating PEI.

Grade of Recommendation A – Strong consensus (100% agreement).

Commentary

There are multiple pancreatic enzyme replacement preparations that are now licensed around the world. All are of porcine origin and contain, with varying concentrations and mixtures, pancreatic lipase, amylase, protease, and other pancreas-derived proteins and nucleic acids. Several factors affect the efficacy of pancreatic enzyme supplementation: (a) mixture with meal; (b) gastric emptying with meal; (c) mixing with chyme and bile acids and rapid release of enzymes in duodenum [160].

Nowadays, most of the pancreatic enzyme preparations are formulated as pH-sensitive, enteric-coated, capsules containing microspheres or tablets that protect the enzymes from gastric acidity and allow them to disintegrate rapidly at pH > 5.5 in the

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duodenum [160,161]. Non enteric-coated, conventional powder or tablet formulations have been abandoned because they are less effective in treating PEI as pancreatic enzymes are partially inactivated by pepsin and gastric acidity [162].

The efficacy of these more recent formulations has been demonstrated in several recent studies [163–166] and in a recent meta-analysis [136]. A Cochrane review on the efficacy of pancreatic enzyme preparations in patients with pancreatic insufficiency demonstrated a higher efficacy for enteric-coated microspheres compared with enteric-coated tablets [167]. Mini-microspheres 1.0–1.2 mm in diameter seem to be associated with higher therapeutic efficacy compared with 1.8–2.0 mm microspheres that still have an optimal therapeutic action [168]. Another trial compared two enteric-coated pancreatic enzyme preparations. One moisture-resistant, formulated to contain between 90% and 110% labeled lipase content over the shelf life of the product and the other potentially unstable in the presence of moisture and degradable over time. The characteristics of the moisture-resistant formulation should have allowed more accurate dosing, both providing more predictable therapeutic effects and reducing the risk of overdose, which is assumed as a potential risk factor for fibrosing colonopathy. The results suggested a comparable efficacy and safety in patients with cystic fibrosis for the treatment of PEI [169].

24. How should enzyme supplementation be administered?

Recommendation 36

Oral pancreatic enzymes should be distributed along with meals and snacks.

Grade of Recommendation B – Strong consensus (100% agreement).

Commentary

The efficacy of pancreatic enzyme supplements presupposes the mixing of enzymes and chyme [161]. While one study evaluating the impact of the scheduling of PERT administration on fat malabsorption suggested the optimal timing of administration was during or after meals, no significant difference was observed when patients took PERT immediately before meals [170]. In practice, although many patients prefer to take PERT at the beginning of meals, they should be encouraged to spread the capsules out over a meal when using multiple capsules or with larger meals [162,170]. If the patient is taking the older preparations of pancreas powder, they should take about a third of the dose immediately before, one third during, and one third immediately after the meal. This concerns only meals and snacks that contain fat (e.g. not for fruit).

25. What is the optimal dosage of enzyme supplementation?

Recommendation 37

The posology aims at individual needs and depends on the severity of the disease and the composition of the meal. In practice, a minimum lipase dose of 20,000–50,000 PhU (based on the preparation) shall be taken together with main meals, and half that dose with snacks.

Grade of Recommendation A – Strong consensus (100% agreement).

Commentary

The dosage recommended depends on the patient's clinical response, but the dosage and dosing will need to be monitored carefully, as well as altered, depending on patient's food intake/pattern of eating, method of cooking, portion sizes, and disease evolution.

For the digestion of a normal meal a minimum activity of 30,000 IU of naturally secreted pancreatic lipase is required. The recommended initial dose is about 10% of the physiologically secreted dose of lipase after a normal meal [171]. Since 1 IU of naturally secreted lipase equals 3 PhU in commercial preparations, the minimum amount of lipase needed for digestion of a normal meal is 90,000 PhU (endogenous plus orally administered lipase).

The results of several RCTs have proven the efficacy of pancreatic enzyme replacement therapy with enteric-coated mini-microspheres at a dose ranging from 40,000–80,000 PhU of lipase per main meal, and half dose per snack [165,166,170,172–174]. Studies evaluating enteric-coated microspheres have shown a similar efficacy for doses ranging from 10,000–40,000 PhU of lipase per meal, indicating the lack of a dose-response relationship with these preparations [175,176].

Dose escalation may be warranted according to response. In adults there is no upper limit to dosing, as there is no risk of overdose because pancreatic enzymes exceeding the needs are eliminated through stools. Caution for dosage should be placed in children in whom colonic strictures have been described after high dose of the enteric coated, delayed release preparations [177].

26. How should the efficacy of enzyme supplementation be evaluated?

The efficacy of PERT should be evaluated by the relief of gastrointestinal symptoms and the improvement of nutritional parameters (anthropometric and biochemical). In patients who do not respond, the evaluation should be extended to pancreatic function tests (fecal fat excretion or ^{13}C-MTG-breath test).

Grade of Recommendation B – Strong consensus (97% agreement).

Recommendation 38

Commentary

The aforementioned recent meta-analysis including 14 RCTs [136] showed that PERT increased the coefficient of fat absorption, as well as improved gastrointestinal symptoms, compared with baseline or placebo. Two open label extensions up to one year from RCTs included in the meta-analysis demonstrated significant improvement in nutritional parameters and weight [164,178]. A review of reported data [106] as well as the recent guidelines on the therapy for CP [4] support the use of nutritional parameters as an optimal way to assess the efficacy of PERT. Dietary intake and nutritional status should be monitored regularly to maximize patient compliance and specialist dietetic assessment sought in patients with underlying malnutrition [179].

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In patients who do not respond, pancreatic function tests [136] while on PERT can monitor effectiveness. ^{13}C-MTG-breath test is a useful method that can replace the somewhat cumbersome fecal fat excretion tests and can be used for patients on PERT [180].

27. What should be done in cases of unsatisfactory clinical response?

Recommendation 39

In case of unsatisfactory clinical response, PERT dosage should be increased or a protein pump inhibitor (PPI) should be added. If these methods fail, other causes of malabsorption such as small intestinal bacterial overgrowth (SIBO) should be excluded.

Grade of Recommendation B – Strong consensus (97% agreement).

Commentary

The recommended dose of 20,000–50,000 PhU with main meals has been shown to improve symptoms in more than half the patients [136]. Dose escalation may be warranted according to response. In adults there is no upper limit to dosing, as there is no risk of overdose because pancreatic enzymes exceeding the needs are eliminated in the stool. Caution for high PERT dosage should be exercised in children, in whom colonic strictures have been described after high dose of the enteric coated, delayed release preparations [177].

The inhibition of gastric acid secretion by PPIs can lead to a significant improvement and even normalization of fat digestion in patients with an incomplete response to PERT, as shown in a prospective cohort study of 21 patients with CP (43% had an initial incomplete response to PERT, and 29% normalized their function after addition of a PPI) [181]. Nevertheless, a review including 34 clinical trials failed to show improvement in the efficacy of PERT with PPI or histamine-2 receptor antagonists [182]. It is noteworthy that the populations included and the therapeutic schemes were very heterogeneous, therefore, suggesting significant bias.

SIBO can also explain persistent symptoms. A recent prospective case-control study revealed that SIBO was present in 15% of patients with CP whereas no healthy control was tested positive by means of a fasting glucose hydrogen breath test [183].

28. Does the surgical technique for treating CP affect PERT and nutritional status?

Recommendation 40

Long-term PERT and nutritional status are similarly affected by all surgical procedures. Tissue-preserving procedures shall be preferred.

Grade of Recommendation A – Strong consensus (100% agreement).

Commentary

Surgical intervention is effective in carefully selected patients. Common indications for surgical intervention in CP include poorly controlled pain, duodenal, biliary and pancreatic duct obstruction, and suspicion of cancer [184].

Surgery for CP can be broadly classified into three categories: drainage procedures, partial pancreatic resection including or not the duodenum, and total pancreatectomy. Recently, Kamper et al. [185], reviewed all the available techniques in detail. In drainage procedures a dilated pancreatic duct is cut open and anastomosed to the proximal jejunum. The most common drainage procedures are the modified Puestow procedure, also known as lateral pancreatico-jejunostomy, and the Frey procedure, which in addition to a pancreaticojejunostomy includes coring of the pancreatic head. In patients with persistent inflammation of the pancreatic head without upstream ductal dilatation, a resective surgery such as a classic pancreaticoduodenectomy or a duodenum-preserving head resection (Beger procedure) can be performed.

Theoretically, the type of procedure may deeply affect short- and long-term nutritional outcomes, since the extension of the parenchyma resection, as well as the preservation of the duodenum and bile natural transit, and pancreatic secretion may represent key factors for endocrine and exocrine functions [186,187].

Meta-analyses showed better postoperative pain relief and improved quality of life with the Beger procedure compared with conventional pancreaticoduodenectomy [188,189]. However, the studies included had a high grade of heterogeneity and a recent large prospective large RCT showed no significant difference between procedures in the long-term nutritional status, quality of life, and preservation of the exocrine pancreatic function [190].

A 2015 meta-analysis of 23 studies compared outcomes of the Frey procedure with pancreaticoduodenectomy and the Berger procedure [191]. Short-term quality of life and pancreatic function outcomes were more favorable in patients who had the Frey procedure than in those who had pancreaticoduodenectomy. Long-term follow-up data from an RCT comparing the Frey and Berger procedures for CP showed no significant difference in endocrine or exocrine insufficiency more than a decade after surgery [192].

29. What is the risk of developing osteoporosis or osteopenia in patients with CP?

Statement 6

Patients with CP are at risk for osteoporosis (almost one out of four) and at high risk (about two out of three), for osteopathy (either osteoporosis or osteopenia).

Strong consensus (97% agreement).

Commentary

Osteoporosis is characterized by structural deterioration of bone tissue and low bone mass, leading to bone fragility and increased risk of fracture [193]. Osteoporosis and osteopenia are defined by the World Health Organization according to T-scores (a T-score between −1.0 and −2.5 standard deviations is defined as osteopenia; a T-score below 2.5 standard deviations is defined as osteoporosis), T-scores compare bone density values with those of young adults (peak bone mass) [194]. Osteoporosis and osteopenia can also be defined according to Z-score (Z-score < −1 defined as osteopenia, Z-score < −2 defined as osteoporosis). The Z-scores represents gender- and age-matched controls for the evaluation of secondary osteoporosis, they are usually used in premenopausal women, men under the age of 50, and in children [195].

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A systematic review and meta-analysis including ten studies applied the definition in accordance with the T-scores in eight and the Z-scores in two studies. It revealed that, based on the random-effects model of the total 513 patients with CP included, a pooled prevalence rate of osteoporosis of 24.3% (95% CI 16.6–32.0%) and osteopathy (either osteoporosis or osteopenia) of 65% (95% CI 54.7–74.0%) [196]. Two of the included studies revealed osteoporosis rate for controls respectively 8.6 and 10.2%. All the included studies had relatively small sample sizes (<100) and considerable heterogeneity; therefore, subgroup analyses were not acquiescent. Certain patterns were, however, evident from the studies included, like an association between pancreatic enzyme insufficiency and lower bone mineral density. On the contrary, the available data failed to show direct associations between serum vitamin D concentrations and low bone mineral density. These data suggest that vitamin D deficiency is not the sole driver of bone demineralization, other factors that may be of importance for premature bone demineralization in CP are heavy smoking, low physical activity, and chronic inflammation [197].

The important clinical endpoint of osteoporosis is bone fracture. Two large retrospective studies shed light on this regarding patients with CP. The first is a cohort database study, examining patients with CP at a single tertiary care center. A total of 3192 patients with CP and 1,436,699 controls were included in the study. The fracture prevalence (patients with fracture per total patients) was 1.1% in controls (16,208/1,436,699) and 4.8% in patients with CP (154/3192); in comparison Crohn's disease revealed a risk of 3.0% (182/6057); liver cirrhosis 4.8% (805/16,658) and celiac disease 5.0% (74/1480) [198].

The second, a Danish retrospective cohort study including 2594 patients with CP revealed an adjusted hazard ratio for any fracture of 1.7 (95% CI 1.6 to 1.8) [199]. Patients with CP receiving PERT for fat malabsorption had a lower risk of fractures than other CP patients (HR 0.8; 95% CI 0.7 to 0.9).

30. What methods should be used to identify patients who are at risk?

Recommendation 41

Dual-energy X-ray absorptiometry (DXA) shall be used to identify patients with CP with osteopathy.

Grade of Recommendation A – Strong consensus (100% agreement).

Commentary

The American College of Radiology aims to rate the appropriateness of several radiological modalities for specific patient populations. Although they do not mention CP explicitly, they do state that in premenopausal females and males 20–50 years of age with malabsorption, DXA of the lumbar spine and hip(s) or distal forearm is usually an appropriate diagnostic modality to identify low bone mineral density [200]. It is not yet well defined when and to whom these tests should be offered in patients with CP. However, there are recommendations from the American Gastroenterological Association on the detection of osteoporosis in other gastrointestinal diseases: recommending that patients with at least one additional osteoporosis risk factor should undergo initial screening with DXA [201]. This recommendation was specifically for inflammatory bowel disease, celiac disease, and post-gastrectomy patients. The recently published HaPanEU guidelines on CP argued that bone density testing by DXA should be extended to patients with CP with an additional risk; post-menopausal women, those with previous low-trauma fractures, men over 50 years and those with malabsorption [4]. They further stated that considering the associated morbidity and cost of bone fractures when prevention is within range [202], a baseline bone density assessment for all patients with CP may be worth considering.

31. What is the recommended management for the prevention and treatment of these conditions?

Recommendation 42

Basic preventive measures should be advised to all patients with CP including adequate calcium/vitamin D intake and, if indicated, pancreatic enzyme supplementation, regular weight-bearing exercise and smoking and alcohol avoidance. Additional pharmacologic treatment should be reserved for patients with osteopathy and, in particular, osteoporosis.

Grade of Recommendation GPP – Strong consensus (97% agreement).

Commentary

The reasons for osteopathy in CP are multifactorial; (i) low serum vitamin D concentrations due to impaired absorption of fat-soluble vitamin D, poor dietary intake (including calcium) and/or sunshine exposure, (ii) smoking and alcohol intake, (iii) low physical activity, and (iv) chronic inflammation, all contribute. Therefore, basic preventive measures should be advised to all patients with CP including adequate calcium/vitamin D intake and PERT if indicated, regular weight-bearing exercise and avoidance of smoking and alcohol [4]. Research on pharmaceutical supplementation of vitamin D and calcium in patients with osteopenia and adding bisphosphonates in osteoporosis has mainly been performed in post-menopausal women and elderly patients. Based on these findings, and bearing in mind that the cost and side effects are limited, one could consider in patients with osteopathy to supplement vitamin D (800 IU) and calcium (500–1000 mg) daily [149]. In patients with osteopenia it is recommended to repeat the DXA every two years, whereby in patients with osteoporosis there are no specific recommendations beside appropriate medication, screening for other causes and/or referral to a bone specialist [4].

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Author contributions

All authors contributed: literature research, PICO questions and writing the corresponding recommendation and comments; MA: overall manuscript writing and editing; DNL and SCB: critical revision of the final manuscript; all authors approved the final submitted version of the manuscript.

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Conflict of interest

The expert members of the working group were accredited by the ESPEN Guidelines Group, the ESPEN Education and Clinical Practice Committee, and the ESPEN executive. All expert members have declared their individual conflicts of interest according to the rules of the International Committee of Medical Journal Editors (ICMJE). If potential conflicts were indicated, they were reviewed by the ESPEN guideline officers and, in cases of doubts, by the ESPEN executive. None of the expert panel had to be excluded from the working group or from co-authorship because of serious conflicts. The conflict of interest forms are stored at the ESPEN guideline office and can be reviewed by ESPEN members with legitimate interest upon request to the ESPEN executive.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2020.01.004.

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