ESPEN guideline on clinical nutrition in acute and chronic pancreatitis

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Abbreviations:

ACS, Acute Compartmental 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;

Abstract

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 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.

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.

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 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

I. 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?

<u>Recommendation 2</u>

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)

<u>Recommendation 3</u>

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 hours, 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 hours 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 hours (42-44) or 48 hours (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 hours) with late enteral nutrition (after 72 hours), but no comparison was made between 24 and 48 hours (44).

In contrast to these data from the aforementioned meta-analyses that provided strong evidence for early EN within 24-48 hours, 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 hours after admission, and an oral diet initiated 72 hours 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?

<u>Recommendation 6</u>

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 formulae while the recent studies were performed with polymeric formulae. In all studies both types of formulae were proven to be feasible, safe and well-tolerated. One small RCT in 30 patients found that both formulae were safe and well-tolerated (based on a visual analogue 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 formulae (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 (Figure 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 hours 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)

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 hours) nasojejunal tube feeding when compared with an oral diet after 72 hours 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 hours 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)?

<u>Recommendation 12</u>

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/hour, 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)

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 to 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 grams 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/hour, increasing

458 the rate according to the tolerance. The reduction of EN from higher rates to 20 mL/h
459 should be considered when IAP increases between 15 and 20 mmHg. In patients with
460 IAP above 20 mmHg or in the presence of ACS, EN should be (temporarily) stopped (74).
461 When it is impossible to meet nutritional goals with EN only, supplementary or total PN
462 should be considered.
463 A decompressive laparotomy (laparostomy) may be necessary in up to 74% of patients
464 who develop ACS during course of AP (72). Patients with an open abdomen are in a
465 hyper-catabolic state with high nitrogen losses and negative nitrogen balance. It has
466 been estimated that such patients have nitrogen loss of almost 2 g/L of abdominal fluid
467 output and, therefore, nutritional therapy in patients with an open abdomen is essential
468 (78). Several cohort studies reported that initiation and feeding by EN was feasible and
469 safe despite a relatively high rate of digestive intolerance, ranging from 48-67% (78-83).
470 Two studies concluded that that early EN in patients with an open abdomen resulted in
471 higher fascial closure rates, lower fistula rates, reduced nosocomial infections and lower
472 hospital costs (82, 83). In the multicenter analysis by Burlew *et al.*, out of 597 with an
473 open abdomen patients, EN was successfully initiated in 39% (81). For the 307 patients
474 without a bowel injury, logistic regression indicated that EN was associated with higher
475 fascial closure rates (OR 5.3; $p < 0.01$) decreased complication rates (OR, 0.46; $p = 0.02$),
476 and decreased mortality (OR 0.30; $p = 0.01$) (81).
477
478 *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.

II. 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).

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

<u>Recommendation 19</u>

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 (**Error! Reference source not found.**5).

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

<u>Recommendation 20</u>

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)

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 counselling 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?

<u>Recommendation 24</u>

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)

<u>Recommendation 25</u>

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 counselling. 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 formulae (e.g. standard or peptide-based with MCT). However, in the presence of PEI, enteral formulae 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 counselling 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)

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 formulae with medium chain triglycerides can be used if standard formulae 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 counselling 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 formulae in patients with CP. However, there is a rationale that semi-elemental enteral formulae with MCTs are more adapted for jejunal nutrition, compared with polymeric formulae (132). In two of the aforementioned studies (129, 131), semi-elemental formulae 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)

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 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% to 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?

Recommendation 38

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)

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).

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?

<u>Recommendation 40</u>

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).

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 to 32.0%) and osteopathy (either osteoporosis or osteopenia) of 65% (95% CI 54.7 to 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 3,192 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 - 1,000 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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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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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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Figure legends

Figure 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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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

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-minute 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

Figure

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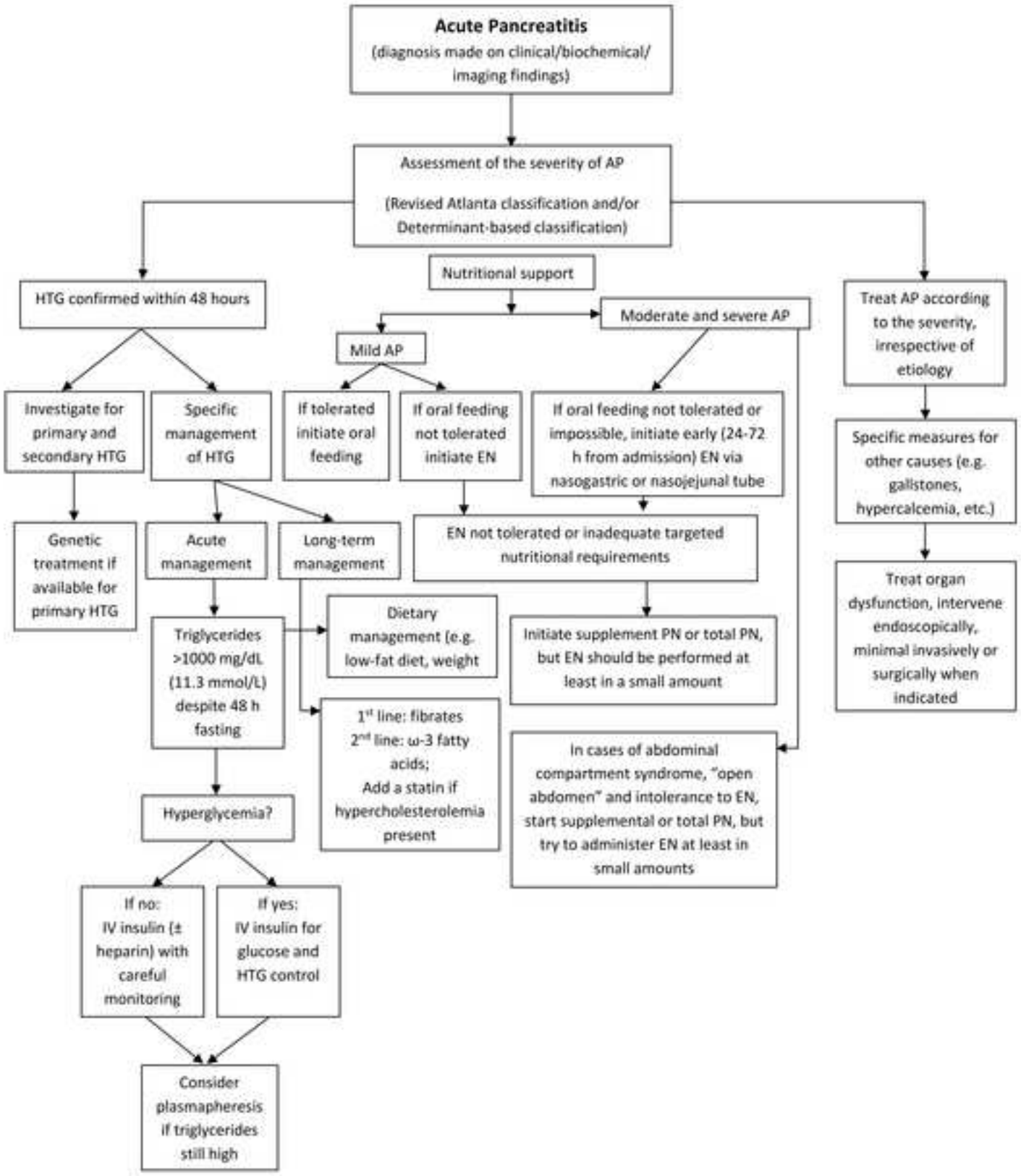

I. Acute pancreatitis

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

Recommendation 2

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

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

1. Teich N, Aghdassi A, Fischer J, Walz B, Caca K, Wallochny T, et al. Optimal timing of oral refeeding in mild acute pancreatitis: results of an open randomized multicenter trial. Pancreas. 2010;39:1088-92.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1-	***Countries:*** Germany ***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** n/a ***Dropout rates:*** 32% of the LIP group; 10% of the PAT group ***Study limitations:*** required sample size to detect the predetermined effect size was not enrolled; sample could be biased owing to inhomogeneous regional provenance; primary outcome LOHS was based on the subjective	**Total no. Patients:** 143 **Inclusion criteria:** acute upper abdominal pain of < 48 hours duration; serum lipase surpasses the 3-fold upper limit of the reference range; peripancreatic edema **Exclusion criteria:** invasive and noninvasive respiratory support; catecholamine therapy; renal support therapy (dialysis, hemofiltration); continuous analgesic therapy before the onset of acute pancreatitis; severe malnutrition	- lipase directed group: n= 74; serum lipase had to normalize before eating; if the daily measured lipase level declined below the 2-fold upper limit of the reference range: white bread with jam and tea - self selected PAT group: n= 69; patients restarted eating through self-selection; if opioid analgesics were necessary not later than 8 a.m.: low-fat diet (only white bread with jam) and tea for dinner

	discretion of the medical teams		
Notes	**Author's Conclusion:** normalization of serum lipase is not obligatory for enteral nutrition in mild acute pancreatitis		
Outcome measures/results	primary outcomes: pain after first ingestion of oral food after the onset of acute pancreatitis; length of hospital stay secondary outcomes: earlier decline of CRP and leucocytes		- mean time between admission and oral nutrition was 2 days in the PAT group and 3 days in the LIP group - before and after the first meal the mean visual analogue scale was +3.14 mm (± 11.5 mm) in the PAT group and +2.85 mm (± 16.4) in the LIP group (P = 0.597) - the length of hospital stay was 7 days in the PAT group and 8 days in the LIP group (P = 0.315) - median lipase decrease after the first meal was 57% in the PAT group and 49% in the LIP group - CRP decreased by 15.9 (median; IQR, -55.6 to 0) in the PAT group and 16.4 (median; IQR, -35.9 to 0) in the LIP group (P = 0.3) - leucocytes decreased by 0.92 (median; IQR, -3.31 to 0.01) in the PAT group and 0.86 (median; IQR, -2.4 to 0) in the LIP group (P = 0.64)

2. Zhao XL, Zhu SF, Xue GJ, Li J, Liu YL, Wan MH, et al. Early oral refeeding based on hunger in moderate and severe acute pancreatitis: a prospective controlled, randomized clinical trial. Nutrition. 2015;31:171-5.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+	***Countries:*** China ***Centers:*** single-center; Department of Integrative Medicine, West China Hospital, Sichuan University ***Setting:*** n/a ***Funding Sources:*** n/a ***Dropout rates:*** 5% ***Study limitations:*** single center study – caution	**Total no. Patients:** 146 **Inclusion criteria:** elevated serum amylase and/or lipase levels (≥ 3-fold above the upper reference limit); unequivocal evidence of AP **Exclusion criteria:** abdominal pain lasting > 72 h before admission; mild AP; pancreatic neoplasm, endoscopic retrograde	- early oral refeeding (EORF) group (n= 70): restarted oral diet when they felt hungry, regardless of laboratory parameters - conventional oral refeeding (CORF) group (n= 76): restarted oral diet only when clinical and laboratory symptoms had resolved

	with generalizing the results; difficult to calculate the energy in the food accurately	cholangiopancreatography, or trauma etiology; gastroparesis or surgical intervention; intubation; infected pancreatic necrosis or pancreatic hemorrhage	
Notes	**Author's Conclusion:** EORF could shorten the length of hospitalization in patients		
Outcome measures/results	primary outcome: hospital length of stay secondary outcomes: duration of fasting; subjective tolerance of food		- the total length of hospitalization (13.7 ± 5.4 d versus 15.7 ± 6.2 d; P= 0.0398) and duration of fasting (8.3 ± 3.9 d versus 10.5 ± 5.1 d; P= 0.0047) were shorter in the EORF group than in the CORF group - mean blood glucose level after oral refeeding was higher in the EORF group than in the CORF group (P= 0.0030)

3. Li J, Xue GJ, Liu YL, Javed MA, Zhao XL, Wan MH, et al. Early oral refeeding wisdom in patients with mild acute pancreatitis. Pancreas. 2013;42:88-91.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+	***Countries:*** China ***Centers:*** Pancreatic Research Group, Department of Integrated Traditional and Western Medicine at West China Hospital, Sichuan University, China ***Setting:*** n/a ***Funding Sources:*** n/a ***Dropout rates:*** none ***Study limitations:*** single center; no blinding	**Total no. Patients:** 149 **Inclusion criteria:** onset of acute abdominal pain accompanied with elevated serum levels of amylase and/or lipase, overall at least 3-fold higher than the upper limit measure of the reference range **Exclusion criteria:** diseases before hospital admission; pancreatic neoplasm or endoscopic retrograde cholangiopancreatograph; Ranson score of 3 or higher or the severe type according to Balthazar CT criteria; poor oral intake	- early oral refeeding (EORF) group (n= 75): started oral feeding once they subjectively felt hungry - routine oral refeeding (RORF) group (n= 74): started refeeding if there was: absence of abdominal discomfort; decrease of serum amylase and lipase to less than 2-fold of the ULM; normal bowel sounds; subjective feeling of hunger

Notes	**Author's Conclusion:** commencing oral refeeding as soon as patients have sensation of hunger is safe, feasible, and could be cost-effective	
Outcome measures/results	primary outcome: time interval between disease onset and initiation of oral refeeding, total LOH, and post refeeding LOH secondary outcomes: relapse abdominal pain; transitional abdominal distension; elevation of serum amylase or lipase; hyperglycemia after oral refeeding	- patients in the EORF group started refeeding significantly earlier than those in the RORF group (4.56 ± 1.53 vs 6.75 ± 2.29 days; P < 0.05) - patients in the EORF group had significantly shorter total (6.8 ± 2.1 vs 10.40 ± 4.1 days; P < 0.01) and post refeeding LOH (2.24 ± 0.52 vs 3.27 ± 0.61days; P < 0.01) - no significant difference in adverse gastrointestinal events

4. Larino-Noia J, Lindkvist B, Iglesias-Garcia J, Seijo-Rios S, Iglesias-Canle J, Dominguez-Munoz JE. Early and/or immediately full caloric diet versus standard refeeding in mild acute pancreatitis: a randomized open-label trial. Pancreatology. 2014;14:167-73.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1-	***Countries:*** Spain ***Centers:*** Department of Gastroenterology, University Hospital of Santiago de Compostela ***Setting:*** n/a ***Funding Sources:*** none ***Dropout rates:*** 10% ***Study limitations:*** no blinding; moderate number of patients; proportion of severe cases was low	**Total no. Patients:** 80 **Inclusion criteria:** acute upper abdominal pain and serum amylase or lipase levels higher than three times the upper limit of normal **Exclusion criteria:** decreased ability of oral intake; factors affecting normal pancreatic exocrine function; diseases affecting diet tolerance	- four different refeeding protocols: group 1 (n= 17) and 2 (n= 20): a stepwise increasing diet during three days; group 3 (n= 18) and 4 (n= 17): an immediately full caloric, low fat diet - group 2 and 4: early refeeding; group 1 and 3: started at standard time - stepwise increasing caloric intake from 1207, to 1470, to 1767 kcal over three days - immediate full caloric intake started with the 1767 kcal diet
Notes	**Author's Conclusion:** Refeeding after AP when bowel sounds are present with immediately full caloric diet is safe and well tolerated. Early refeeding shortens LOHS		
Outcome measures/results	primary outcome: length of hospital stay (LOHS) secondary outcome: tolerance to oral refeeding		- LOHS was significantly reduced after early refeeding (median 5 versus 7 days (p= 0.001)) but not in patients receiving immediately full caloric diet, compared to standard management (6 versus 6 days(p= 0.12))

		- no difference in refeeding tolerance comparing immediately full caloric diet versus stepwise increasing diet (31/35 (89%) versus 33/37 (89%) patients tolerating the treatment, p= 1.00) or early versus standard time for refeeding (33/37 (89%) versus 31/35 (89%), (p= 1.00))

5. Horibe M, Nishizawa T, Suzuki H, Minami K, Yahagi N, Iwasaki E, et al. Timing of oral refeeding in acute pancreatitis: A systematic review and meta-analysis. United European Gastroenterol J. 2016;4:725-32.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Systematic review and Meta-Analysis 1+	***Countries:*** Sweden, Germany, China, Spain, ***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** none ***Dropout rates:*** n/a ***Study limitations:*** n/a	**Total no. Patients:** n/a **Inclusion criteria:** RCTs that compared the length of hospital stay and rates of adverse events between early and standard oral refeeding in cases of acute pancreatitis **Exclusion criteria:** Duplicate publications and reviews	comparing early oral refeeding with standard oral refeeding in acute pancreatitis
Notes	**Author's Conclusion:** early oral refeeding in acute pancreatitis reduces length of hospital stay with no significant differences in the adverse events		
Outcome measures/results	primary and secondary outcome: length of hospital stay, adverse events		- compared with standard oral refeeding, early oral refeeding significantly decreased the length of hospital stay - no significant difference between the early refeeding group and standard refeeding groups with respect abdominal pain and distension

6. Bevan MG, Asrani VM, Bharmal S, Wu LM, Windsor JA, Petrov MS. Incidence and predictors of oral feeding intolerance in acute pancreatitis: A systematic review, meta-analysis, and meta-regression. Clin Nutr. 2017;36:722-9.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Systematic review and Meta-Analysis 1-	***Countries:*** The Netherlands; Brazil; Poland; Sweden; Spain; USA; France; China; India; New Zealand; Latvia; Germany ***Centers:*** n/a ***Funding Sources:*** the HealthResearch Council of New Zealand ***Study limitations:*** meta-analyses for serum lipase, (peri) pancreatic collections, and pleural effusions were based on data from 2 or 3 studies only, and hence the results should be interpreted with caution	**Total no. Patients:** n/a **Inclusion criteria:** prospective or retrospective observational, or interventional study **Exclusion criteria:** studies without the incidence of oral feeding intolerance (OFI)	- this study aimed to quantify the incidence of oral feeding intolerance, the effect of confounders, and determine the best predictors of oral feeding intolerance
Notes	**Author's Conclusion:** Oral feeding intolerance affects approximately 1 in 6 patients with acute pancreatitis. Serum lipase levels of more than 2.5 times the upper limit of normal prior to refeeding is a potentially useful threshold to identify patients at high risk of developing oral feeding intolerance.		
Outcome measures/results	incidence of oral feeding intolerance		- the incidence of oral feeding intolerance was 16.3 %, and was not affected by WHO region, age, sex, or etiology of acute pancreatitis - serum lipase level prior to refeeding, pleural effusions, (peri)pancreatic collections, Ranson score, and Balthazar score were found to be statistically significant in meta-analyses

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

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)

7.	**Larino-Noia J, Lindkvist B, Iglesias-Garcia J, Seijo-Rios S, Iglesias-Canle J, Dominguez-Munoz JE. Early and/or immediately full caloric diet versus standard refeeding in mild acute pancreatitis: a randomized open-label trial. Pancreatology. 2014;14:167-73.**
→ See No. 4	

8.	**Sathiaraj E, Murthy S, Mansard MJ, Rao GV, Mahukar S, Reddy DN. Clinical trial: oral feeding with a soft diet compared with clear liquid diet as initial meal in mild acute pancreatitis. Aliment Pharmacol Ther. 2008;28:777-81.**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+	***Countries:*** ***Centers:*** Asian Institute of Gastroenterology ***Setting:*** n/a ***Funding Sources:*** none ***Dropout rates:*** 4.9% ***Study limitations:*** the timing of discharge was left to the medical team without inputs from the study coordinators	**Total no. Patients:** 101 **Inclusion criteria:** Amylase and / or lipase greater than three times the upper limit of normal or greater than two times the upper limit; mild acute pancreatitis **Exclusion criteria:** organ dysfunction and neoplasms; acute pancreatitis with enteral support via tube feeding or parenteral nutrition; acute on chronic pancreatitis with enzyme supplementation	- clear liquid diet group: n= 52 - soft diet group: n= 49 - all patients: standardized diets and not permitted to consume anything else on study day 1 and 2

Notes	**Author's Conclusion:** Oral refeeding with a soft diet can be considered safe and can result in shorter length of hospitalization	
Outcome measures/results	primary outcome: length of hospitalization from the time of refeeding until discharge secondary outcomes: frequency that the subjects discontinued oral feeding because of intolerance such as pain, nausea and vomiting	- statistically significant decrease in the length of hospitalization (total and post refeeding) of a median of 2 days was seen in patients receiving a soft diet (P< 0.001) - no significant difference in the need for cessation of diet because of pain - Patients initiated on a soft diet consumed significantly more calories and fats on study day 1 (P< 0.001)

9.	**Moraes JM, Felga GE, Chebli LA, Franco MB, Gomes CA, Gaburri PD, et al. A full solid diet as the initial meal in mild acute pancreatitis is safe and result in a shorter length of hospitalization: results from a prospective, randomized, controlled, double-blind clinical trial. J Clin Gastroenterol. 2010;44:517-22.**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1++	***Countries:*** Brazil ***Centers:*** n/a ***Setting:*** Gastroenterology and General Surgery wards of the Hospital Universita´ rio of the Universidade Federal de Juiz de For a ***Funding Sources:*** n/a ***Dropout rates:*** 5 % ***Study limitations:*** n/a	**Total no. Patients:** 221 **Inclusion criteria:** upper abdominal pain lasting at least 24 hours associated with elevated serum levels of amylase and/or lipase above 3 times the upper limit of normal; mild AP defined by absence or <30 % of pancreatic necrosis **Exclusion criteria:** more than 30% of pancreatic necrosis; evidence of organ failure; AP complications requiring surgical intervention; received any nutritional support before randomization; severe comorbidities; received parenteral analgesic; pancreatic neoplasm	- three different groups for the initial meal for refeeding: clear liquid, soft, or full solid - n = 70 in each arm - diet A: hypocaloric clear liquid diet containing low proportion of fat and with gradual increase in the amounts of solid calories, proteins, and fat during the subsequent days - diet B: hypocaloric soft diet, containing an average proportion of fat and with gradual increase in the amounts of solid calories during the subsequent days - diet C: full solid diet, with average amounts of fat and calories throughout the refeeding period

Notes	**Author's Conclusion:** Oral refeeding with a full solid diet in mild AP was well tolerated and resulted in a shorter LOH in patients without abdominal pain relapse.	
Outcome measures/results	primary endpoint: relapse of pain secondary endpoint: dietary intake, length of hospital stay	- no difference in pain relapse rates during refeeding between the 3 diet arms (P=0.80) - shorter LOH (median of –1.5 d) was observed among patients receiving a full solid diet without abdominal pain relapse (P=0.000)

3. If required, what type of medical nutrition (enteral vs 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)

10. Marik PE, Zaloga GP. Meta-analysis of parenteral nutrition versus enteral nutrition in patients with acute pancreatitis. BMJ. 2004;328:1407.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-Analysis 1-	***Countries:*** n/a ***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** n/a ***Dropout rates:*** n/a ***Study limitations:*** Studies are of poor quality; None of the studies were blinded; small number of patients; different inclusion and exclusion criteria between the studies	**Total no. Patients:** 263 **Inclusion criteria:** patients admitted to hospital with acute pancreatitis characterized by abdominal pain with raised serum amylase and lipase activity. **Exclusion criteria:** n/a	- enteral versus parenteral nutrition - enteral nutrition was delivered through a nasojejunal tube that had been placed endoscopically or radiographically
Notes	**Author's Conclusion:** Enteral nutrition should be the preferred route of nutritional support in patients with acute pancreatitis		
Outcome measures/results	infections, complications other than infections, operative interventions, length of hospital stay and mortality		- enteral nutrition was associated with a significantly lower incidence of infections, reduced surgical interventions to control pancreatitis, and a reduced length of hospital stay - no significant differences in mortality or non-infectious complications between the two groups of patients

11. Petrov MS, van Santvoort HC, Besselink MG, van der Heijden GJ, Windsor JA, Gooszen HG. Enteral nutrition and the risk of mortality and infectious complications in patients with severe acute pancreatitis: a meta-analysis of randomized trials. Arch Surg. 2008;143:1111-7.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-Analysis 1 +	***Countries:*** Greece, UK, Canada, Sweden, Russia ***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** n/a ***Dropout rates:*** n/a ***Study limitations:*** n/a	**Total no. Patients:** 202 **Inclusion criteria:** RCT; severe acute pancreatitis; no immune enhancing ingredients in EN nutritional formula **Exclusion criteria:** n/a	- comparison of the effect of enteral vs. parenteral nutrition in patients with severe acute pancreatitis - 95 patients were randomly allocated to the EN group and 107 to the PN group
Notes	**Author's Conclusion:** EN, compared with PN, has important beneficial effects in patients with predicted severe acute pancreatitis		
Outcome measures/results	total infectious complications, pancreatic infections, need for surgery, nonpancreatic infections, organ failure, and in-hospital mortality		- enteral nutrition reduced the risk of infectious complications, pancreatic infections and mortality - no statistically significant risk reduction for organ failure.

12. Petrov MS, Pylypchuk RD, Emelyanov NV. Systematic review: nutritional support in acute pancreatitis. Aliment Pharmacol Ther. 2008;28:704-12.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Systematic review 1+	***Countries:*** US, Spain, Sweden, UK, Greece, Canada, Hungary, China ***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** none ***Dropout rates:*** n/a ***Study limitations:*** moderate heterogeneity between the study results in some comparisons; inclusion of unpublished	**Total no. Patients:** EN vs. PN: 453 patients; PN vs. no supplementary nutrition: 113; EN vs. no supplementary nutrition: 27 **Inclusion criteria:** RCTs comparing EN with no supplementary nutrition, or PN with no supplementary nutrition, or EN with PN in acute pancreatitis	- data from RCTs in acute pancreatitis that compares enteral nutrition (EN) with no supplementary nutrition, parenteral nutrition (PN) with no supplementary nutrition and enteral nutrition with parenteral nutrition - EN and PN were defined as a delivery of standard nutrition formula not supplemented with any immune enhancing ingredients

	studies into the systematic review		
Notes	**Author's Conclusion:** this systematic review demonstrates the benefits of artificial nutrition (either enteral or parenteral) over no nutrition management in patients with acute pancreatitis.		
Outcome measures/results	total infectious complications and ⁄or in-hospital mortality		- EN, when compared with no supplementary nutrition, was associated with no significant change in infectious complications but a significant reduction in mortality - PN, when compared with no supplementary nutrition, was associated with no significant change in infectious complications but a significant reduction in mortality - EN, when compared with parenteral nutrition, was associated with a significant reduction in infectious complications but no significant change in mortality

13. Cao Y, Xu Y, Lu T, Gao F, Mo Z. Meta-analysis of enteral nutrition versus total parenteral nutrition in patients with severe acute pancreatitis. Ann Nutr Metab. 2008;53:268-75.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-Analysis 1+	***Countries:*** Greece, UK, Sweden, Russia, Spain **Centers:** n/a **Setting:** n/a ***Funding Sources:*** n/a ***Dropout rates:*** n/a ***Study limitations:*** number of patients was limited; not all trials were blinded; possible that studies with negative results may remain unpublished	**Total no. Patients:** 224 **Inclusion criteria:** RCT; patients with SAP; EN versus TPN; SAP was diagnosed in patients with at least 2 of the following criteria in the first 96 h of the process: (a) an Acute Physiology and Chronic Health Evaluation II score of 8 or higher; (b) a serum C-reactive protein of 150 mg/l or higher, and (c) a Balthazar D or E grade in the abdominal computed tomography scan.	- 106 were randomly assigned to the EN group and 118 to the TPN group - TPN was delivered through a peripheral or central venous catheter, while EN was delivered through a nasojejunal tube

		Exclusion criteria: pregnancy, subjects younger than 18 years old, and exacerbation of chronic pancreatitis	
Notes	**Author's Conclusion:** Enteral nutrition appears safer than total parenteral nutrition in nutrition support of patients with severe acute pancreatitis		
Outcome measures/results	Infections, artificial nutrition-related complications, pancreatitis-related complications, non-pancreatitis-related complications, organ failure and mortality.		- compared with total parenteral nutrition, enteral nutrition was associated with a significantly lower risk of infections, pancreatitis-related complications, organ failure, multiple organ dysfunction syndrome and mortality - no significant differences in artificial nutrition-related complications and non-pancreatitis related complications between the two groups.

14. Al-Omran M, Albalawi ZH, Tashkandi MF, Al-Ansary LA. Enteral versus parenteral nutrition for acute pancreatitis. Cochrane Database Syst Rev. 2010:CD002837.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Systematic Review 1++	***Countries:*** n/a ***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** n/a ***Dropout rates:*** 45% ***Study limitations:*** All included studies had a small sample size. Two of the included studies were underpowered. Not all studies provided the standard deviations and their funding sources. None of the included	**Total no. Patients:** n=348 **Inclusion criteria:** Patients with a diagnosis of acute pancreatitis established by clinical presentation and elevated serum amylase **Exclusion criteria:** n/a	Total parenteral nutrition (TPN) delivered through a central or peripheral venous line. Enteral nutrition (EN) delivered through a nasoenteric feeding tube placed endoscopically or under fluoroscopy down into the jejunum at or below the level of ligament of Treitz, or confirmed radiologically after placement.

	studies had a conflict of interest statement.		
Notes	**Author's Conclusion:** The findings of this review support the use of EN in patients with acute pancreatitis requiring nutritional support over TPN. Patients receiving EN are less likely to suffer from MOF, systemic infections, operative interventions and, more importantly, death. The quality of evidence for these outcomes are of moderate quality (as shown in Summary of findings for the main comparison) except for death being of low quality. The best available evidence is in favor of EN.		
Outcome measures/results	Death; Length of hospital stay; Systemic inflammatory response syndrome (SIRS); Multiple organ failure (MOF); Operative intervention; Systemic infection (septicemia, urinary tract infection (UTI), pneumonia, line infection); Local septic complications (pancreatic abscess formation, infected necrosis); Other local complications (fluid collection, pseudocyst, sterile pancreatic necrosis, fistula); Protection of gut mucosal barrier as estimated, indirectly, by changes in the serum level of IgM anti-endotoxin core antibody (Endo CAb), total antioxidant capacity (TAC), Tumor Necrosis Factor (TNF), or Interlukin-6 (IL-6)		The relative risk (RR) for death was 0.50 (95% CI 0.28 to 0.91) in favor for EN. The mean difference for length of hospital stay with EN was 2.37 (95% CI -7.18 to 2.44). The RR for SIRS was 1.00 (95% CI 0.17 to 5.89). The RR for MOF was 0.55 (95% CI 0.37 to 0.81) in favor for EN. Operative interventions showed a RR of 0.44 (95% CI 0.29 to 0.67) in favor for EN. Systemic infections showed a RR of 0.39 (95% CI 0.23 to 0.65) in favor for EN. The RR for local septic complications with EN vs. TPN was 0.74 (95% CI 0.40 to 1.35). The RR for other local complications with EN vs TPN was 0.70 (95% CI 0.43 to 1.13). For TNF-α, the change in means from baseline was 59.3% for the EN group and -1.2% for the TPN group. On the other hand, IL-6 showed 83.6% reduction from the baseline value compared to 58.7% for TPN. There were no significant differences observed between the two groups with a P value >0.05.

15. Petrov MS, Whelan K. Comparison of complications attributable to enteral and parenteral nutrition in predicted severe acute pancreatitis: a systematic review and meta-analysis. Br J Nutr. 2010;103:1287-95.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-Analysis 1-	***Countries:*** n/a ***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** n/a ***Dropout rates:*** n/a ***Study limitations:*** the observed results might be influenced by the quality	**Total no. Patients:** 174 **Inclusion criteria:** reported in English; studied adults with predicted severe acute pancreatitis defined on the basis of generally accepted criteria; evaluated the efficacy of exclusive PN via central venous	to review the complications related to the use of nutrition in patients with predicted severe acute pancreatitis receiving EN vs. PN

	of nutritional practice and adherence to nutrition protocols rather than whether EN or PN were used; the meta-analysis focuses only on the nutrition-related complications; many included primary trials did not provide a definition	catheter v. exclusive EN via nasojejunal tube; assessed the incidence of at least one complication of nutrition, including diarrhea, abdominal bloating or hyperglycemia	
Notes	**Author's Conclusion**: significant reduction in infectious complications and mortality associated with the use of EN over PN		
Outcome measures/results	diarrhea, hyperglycemia		- diarrhea occurred in six of ninety-two (7%) patients receiving PN and twenty-four of eighty-two (29%) patients receiving EN - hyperglycemia developed in twenty-one of ninety-two (23%) patients receiving PN and nine of eighty-two (11%) receiving EN

16. Quan H, Wang X, Guo C. A meta-analysis of enteral nutrition and total parenteral nutrition in patients with acute pancreatitis. Gastroenterol Res Pract. 2011;2011:698248.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-Analysis 1+	***Countries:*** UK, Russia, Sweden, Spain, India, China ***Centers:*** n/a ***Setting:*** n/a ***Funding Sources***: grants from Shanghai Shen Kang Hospital Management Center—municipal hospital joint research projects leading-edge technology	**Total no. Patients:** 335 **Inclusion criteria:** RCTs; adults; acute pancreatitis; **Exclusion criteria:** comparison not between EN and TPN	RCTs of total parenteral nutrition and enteral nutrition in patients with acute pancreatitis

	Dropout rates: n/a ***Study limitations:*** retrospective; small sample size		
Notes	**Author's Conclusion:** Enteral nutrition could be the preferred nutrition feeding method in patients with acute pancreatitis		
Outcome measures/results	At least one of the following: pancreatitis-related complications, non-pancreatitis related complications, non-infection-related complications, multiple-organ failure, surgery intervention, hospital stay and mortality.		- enteral nutrition is associated with significantly lower incidence of pancreatic infection complications, MOF, surgical interventions and mortality - no statistic significance in non-pancreatitis-related complications - enteral nutrition had a significantly higher incidence of non-infection-related complications

17. Yi F, Ge L, Zhao J, Lei Y, Zhou F, Chen Z, et al. Meta-analysis: total parenteral nutrition versus total enteral nutrition in predicted severe acute pancreatitis. Intern Med. 2012;51:523-30.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-Analysis 1+	***Countries:*** n/a ***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** n/a ***Dropout rates:*** n/a ***Study limitations:*** n/a	**Total no. Patients:** 381 **Inclusion criteria:** patients with predicted severe acute pancreatitis **Exclusion criteria:** n/a	- total enteral or parenteral nutrition - n= 184 use total enteral nutrition, others use total parenteral nutrition
Notes	**Author's Conclusion:** total enteral nutrition was superior to total parenteral nutrition		
Outcome measures/results	primary outcome is the mortality, hospital length of stay (LOS), infectious complications, organ failure and need for surgical intervention		Total enteral nutritional support is associated with lower mortality, fewer infectious complications, decreased organ failure and surgical intervention rate compared to parenteral nutritional support

18. Yao H, He C, Deng L, Liao G. Enteral versus parenteral nutrition in critically ill patients with severe pancreatitis: a meta-analysis. Eur J Clin Nutr. 2018;72:66-8.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-Analysis and systematic review 1-	***Countries:*** n/a ***Centers:*** n/a ***Setting:*** ICU ***Funding Sources:*** n/a ***Dropout rates:*** n/a ***Study limitations:*** not all full texts were available, small sample sizes, differences between calorie and protein intake in the underlying studies	**Total no. Patients:** n=348 **Inclusion criteria:** RCT with available data; critically ill adult patients with severe pancreatitis that were enrolled to the ICU; EN versus PN; the relevant outcomes were reported **Exclusion criteria:** n/a	Enteral nutrition vs. parenteral nutrition
Notes	**Author's Conclusion:** In conclusion, EN can help reduce overall mortality and the rate of multiple organ failure, and should be recommended as the preferred nutritional support for critically ill patients with severe pancreatitis.		
Outcome measures/results	mortality, multiple organ failure, nutrition routine and the amount of nutrition received by either group		There was a significant difference in overall mortality (fixed-effect model: RR = 0.36, 95% CI 0.20–0.65, P = 0.001) between the EN and PN groups in favor for the EN group. EN support reduced the frequency of multiple organ failure (random-effect model: RR = 0.39, 95% CI 0.21–0.73, P = 0.003).

19. Wu P, Li L, Sun W. Efficacy comparisons of enteral nutrition and parenteral nutrition in patients with severe acute pancreatitis: a meta-analysis from randomized controlled trials. Biosci Rep. 2018;38.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-Analysis 1-	***Countries:*** n/a ***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** none ***Dropout rates:*** n/a	**Total no. Patients:** 562 **Inclusion criteria:** design type: RCT or cohort studies; Children or adults with SAP who required enteral or PN for at	n= 281 in the EN group and n= 281 in the PN group

	Study limitations: small sample sizes, therefore low statistical power; patients were not blinded	least 48h; Comparison: EN with PN **Exclusion criteria:** experimentation studies, comments, reviews, letters, and conferences abstracts; studies with very small sample sizes	
Notes	**Author's Conclusion:** EN is recommended as an initial treatment option for patients with SAP		
Outcome measures/results	mortality, infection, multiple organ failure, hospitalization time		- EN can significantly decrease the mortality rate and lowers the risk of infection and complications more than does PN - EN group had a similar risk of multiple organ failure compared with the PN group - use of EN was also found to significantly reduce mean hospitalization time

20.	**Li W, Liu J, Zhao S, Li J. Safety and efficacy of total parenteral nutrition versus total enteral nutrition for patients with severe acute pancreatitis: a meta-analysis. J Int Med Res. 2018;46:3948-58.**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-Analysis 1+	***Countries:*** Sweden, Russia, Spain, China, India, Canada, UK, Greece ***Funding Sources:*** none ***Dropout rates:*** n/a ***Study limitations:*** low quality of some studies; heterogeneity among the studies (differences in clinical samples); the P value was not stable because of one study	**Total no. Patients:** 500 **Inclusion criteria:** RCTs; patients with SAP; the study compared the efficacy and safety of TEN versus TPN for SAP; at least one of the outcome measures **Exclusion criteria:** patient age of <18 years; studies that did not include participants; non-English language literature	- comparing the safety and efficacy of total enteral nutrition (TEN) and total parenteral nutrition (TPN) for patients with severe acute pancreatitis (SAP). - n= 244 in the TEN group and n= 256 in the TPN group
Notes	**Author's Conclusion:** TEN is safer and more effective than TPN for patients with SAP and TEN is the preferred option.		

Outcome measures/results	mortality, length of hospital stay, infectious complications, organ failure, and surgical interventions	- significantly lower mortality rate in the TEN than TPN group - the duration of hospitalization was significantly shorter in the TEN than TPN group - TEN had a lower risk of pancreatic infection and related complications, organ failure and surgical intervention

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

Recommendation 5

EN should start early, within 24-72 hours of admission, in case of intolerance of oral feeding

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

21. Qi D, Yu B, Huang J, Peng M. Meta-Analysis of Early Enteral Nutrition Provided Within 24 Hours of Admission on Clinical Outcomes in Acute Pancreatitis. JPEN J Parenter Enteral Nutr. 2018;42:1139-47.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-Analysis 1-	***Countries:*** n/a ***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** n/a ***Dropout rates:*** n/a ***Study limitations:*** 6 of the included RCTs were small and of poor quality. None of the RCTs was blinded. Four studies with inadequate concealment of allocation may have overestimated the intervention effect	**Total no. Patients:** 727 **Inclusion criteria:** acute pancreatitis; any type of EN initiated within 24 hours of admission controlled with PN or EN outside 24 hours; randomized clinical trials (RCT) **Exclusion criteria:** duplicate publications; not RCT; patients <18 years of age; undefined timing of EN initiated within 24 hours of admission; not reporting clinically relevant outcomes	Early EN within 24 hours of admission in patients with AP, especially in predicted severe or severe acute pancreatitis (SAP)
Notes	**Author's Conclusion:** Early EN within 24 hours of admission is safe and provides benefits for predicted severe or SAP, but not for mild to moderate pancreatitis		
Outcome measures/results	primary outcome: mortality; multiple organ failure; adverse events, including nausea, vomiting, bloating, diarrhea, pain relapse, hyperglycemia.		Enteral nutrition is more beneficial than parenteral nutrition in reducing organ failure, infectious complications, and mortality of acute pancreatitis

	secondary outcomes: all the infections as a whole; pancreatic infection	

22. Bakker OJ, van Brunschot S, Farre A, Johnson CD, Kalfarentzos F, Louie BE, et al. Timing of enteral nutrition in acute pancreatitis: meta-analysis of individuals using a single-arm of randomised trials. Pancreatology. 2014;14:340-6.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-Analysis 1-	***Countries:*** Greece, UK, USA, Hungary, Canada, Spain, New Zealand ***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** the Netherlands Organization for Health Research and Development ***Dropout rates:*** n/a ***Study limitations:*** the composite primary outcome of this study was not the primary outcome in the included trials; different inclusion criteria between the trials	**Total no. Patients:** 165 **Inclusion criteria:** use of a validated classification system; initiation of EN according to a prespecified protocol **Exclusion criteria:** n/a	- the cohort of patients with EN was divided into patients receiving EN within 24 h or after 24 h of admission - EN within 24 h: n=100 - EN after 24 h of admission: n=65
Notes	**Author's Conclusion:** EN within 24 h after hospital admission, compared with after 24 h, was associated with a reduction in complications.		
Outcome measures/results	infected pancreatic necrosis, organ failure, mortality		EN within 24 h after hospital admission reduced the risk of infected pancreatic necrosis, organ failure and mortality

23.	**Li X, Ma F, Jia K. Early enteral nutrition within 24 hours or between 24 and 72 hours for acute pancreatitis: evidence based on 12 RCTs. Med Sci Monit. 2014;20:2327-35.**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-Analysis 1+	***Countries:*** n/a ***Centers:*** *n/a* ***Setting:*** n/a ***Funding Sources:*** n/a ***Dropout rates:*** n/a ***Study limitations:*** no clear definition of early EN; no clear interval between onset of symptoms and patient admission; intervention of control group was not consistent	**Total no. Patients:** 625 **Inclusion criteria:** RCTs; consecutive patients with acute pancreatitis; patients were randomized assigned to experimental EEN group initiated within 72 h of admission or control group with TPN or DEN (beyond 72 h) **Exclusion criteria:** Studies without detailed information for required clinical outcomes	- 12 studies included - 4 provided EEN to patients within 24 h after admission and 8 studies provided EEN to patients at 24–72 h after admission - Except one study, all of the others used the nasojejunal feeding route - n=301 in the EEN group and n= 324 in the control group
Notes	**Author's Conclusion:** If the patients are reasonably expected to have high compliance to EN therapy, it could be considered as early as possible		
Outcome measures/results	cases of pancreatic infection, mortality, hyperglycemia, organ failure, and catheter-related septic complications		- EEN, but not TPN or delayed enteral nutrition (DEN), is associated with reduced risk of pancreatic infection, mortality, organ failure, hyperglycemia, and catheter-related septic complications - EEN within 24 h of admission presented significantly better outcome in morality than EEN between 24 and 72 h - no significant heterogeneity in the risk of pancreatic infection, organ failure, hyperglycemia, and catheter-related septic complications between the 2 subgroups

24.	**Song J, Zhong Y, Lu X, Kang X, Wang Y, Guo W, et al. Enteral nutrition provided within 48 hours after admission in severe acute pancreatitis: A systematic review and meta-analysis. Medicine (Baltimore). 2018;97:e11871.**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Systematic review and Meta-Analysis 1 -	***Countries:*** China, Netherlands, Sweden, UK, Greece, Russia, Poland, Croatia ***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** n/a ***Dropout rates:*** n/a ***Study limitations:*** some studies were small in size and single center; different feeding routes of EN; intervention of the control group not consistent in all studies	**Total no. Patients:** n/a **Inclusion criteria:** Enteral nutrition within 48 hours after admission, controlled by enteral nutrition outside 48 hours or parenteral nutrition **Exclusion criteria:** undefined timing of enteral nutrition within 48 hours after admission	evaluating the efficacy and safety of enteral nutrition within 48 hours after admission in patients with severe acute pancreatitis (SAP) or predicted severe acute pancreatitis (pSAP)
Notes	**Author's Conclusion:** enteral nutrition within 48 hours after admission is efficient and safe for patients with SAP or pSAP		
Outcome measures/results	mortality; multiple organ failure; systemic inflammatory response syndrome; operative intervention; systemic infection; local septic complications; gastrointestinal symptoms		- significant reduction of mortality in early EN group compared to late EN or PN group - early EN associated with significant reduction in the rate of multiple organ failure - not significant reduction of systemic inflammatory response syndrome in early EN - significant reduction of operative intervention, local septic complications and gastrointestinal symptoms in early EN group - reduced rate of systemic infection in early EN group

25. Petrov MS, Pylypchuk RD, Uchugina AF. A systematic review on the timing of artificial nutrition in acute pancreatitis. Br J Nutr. 2009;101:787-93.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Systematic review 1 -	***Countries:*** n/a ***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** none ***Dropout rates:*** n/a ***Study limitations:*** no uniformity in the definition of „early“ EN; 8/11 RCTs did not provide the data on timing between the onset of symptoms and admission; patients who died early in the course of disease were excluded	**Total no. Patients:** 451 **Inclusion criteria:** enteral nutrition v. parenteral nutrition in acute pancreatitis; studies that reported the timing of the initiation of the nutrition protocol **Exclusion criteria:** n/a	11 RCTs comparing the effect of enteral vs. parenteral nutrition with regard to the time points when they were administered in the RCTs
Notes	**Author's Conclusion:** The magnitude of these benefits from EN within 48h may depend on the timing of the commencement of nutrition.		
Outcome measures/results	multiple organ failure, pancreatic infectious complications and mortality		- started within 48h of admission: EN in comparison with PN, resulted in a statistically significant reduction in the risks of multiple organ failure, pancreatic infectious complications and mortality - after 48h of admission, EN, in comparison with PN, did not result in a statistically significant reduction in the risks of multiple organ failure, pancreatic infectious complications and mortality

26.	**Feng P, He C, Liao G, Chen Y. Early enteral nutrition versus delayed enteral nutrition in acute pancreatitis: A PRISMA-compliant systematic review and meta-analysis. Medicine (Baltimore). 2017;96:e8648.**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Systematic review and Meta-Analysis 1-	***Countries:*** n/a **Centers:** n/a **Setting:** n/a ***Funding Sources:*** none ***Dropout rates:*** n/a ***Study limitations:*** not all included studies were RCTs; different feeding routes and timing; not every included study reported every item	**Total no. Patients:** n/a **Inclusion criteria:** RCTs or retrospective trails; consecutive patients with acute pancreatitis; EEN within 48 hours and DEN beyond 48 hours **Exclusion criteria:** duplicate publications; containing no available data for this meta-analysis	to evaluate the effect of early enteral nutrition (EEN) within 48 hours versus delayed enteral nutrition (DEN) beyond 48 hours
Notes	**Author's Conclusion:** EEN within 48 hours is superior to DEN beyond 48 hours for patients with acute pancreatitis		
Outcome measures/results	multiple organ failure; systemic inflammatory response syndrome; mortality		- EEN was related to a reduced risk of multiple organ failure but not for necrotizing pancreatitis - tendency for decreased systemic inflammatory response syndrome in the EEN group, but it was not significant - for mortality, there was no significant difference between the two groups.

27.	**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;371:1983-93.**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1-	***Countries:*** The Netherlands ***Centers:*** 19 Dutch hospitals	**Total no. Patients:** 208 **Inclusion criteria:** APACHE II score was 8 or higher; Imrie or modified Glasgow score was 3 or	- early group (n=102): nasoenteric tube feeding within 24 hours after randomization with Nutrison Protein Plus (Nutricia) - on-demand group (n=106): oral diet initiated 72 hours after presentation

	Setting: six university medical centers and 13 large teaching hospitals of the Dutch Pancreatitis Study Group ***Funding Sources:*** the Netherlands Organization for Health Research and Development and others ***Dropout rates:*** 1 % ***Study limitations:*** tube feeding in the early group should have been started even earlier; the study was too small to detect a difference between the two groups	higher; serum CRP level was more than 150 mg per liter **Exclusion criteria:** recurrent acute or chronic pancreatitis; patients with enteral or parenteral nutrition at home	- in both groups: full nutrition was defined as an energy target of 25 kcal per kilogram of body weight per day for patients in the ICU and 30 kcal per kilogram per day for patients in the ward
Notes	**Author's Conclusion:** This trial did not show the superiority of early nasoenteric tube feeding, as compared with an oral diet after 72 hours.		
Outcome measures/results	primary outcome: composite of major infection (infected pancreatic necrosis, bacteremia, or pneumonia) or death during 6 months of follow-up secondary endpoints: development of necrotizing pancreatitis and development of organ failure after randomization		- primary endpoint: in 30 of 101 patients (30%) in the early group and in 28 of 104 (27%) in the on-demand group - no significant differences between early group and on-demand group in the rate of major infection (25% and 26%) or death (11% and 7%) - in the on-demand group, 72 patients (69%) tolerated an oral diet and did not require tube feeding - secondary endpoint: necrotizing pancreatitis in 63% of the patients in the early group and in 62% of those in the on-demand group - in the on-demand group, 32 patients (31%) required nasoenteric tube feeding

28. Stimac D, Poropat G, Hauser G, Licul V, Franjic N, Valkovic Zujic P, et al. Early nasojejunal tube feeding versus nil-by-mouth in acute pancreatitis: A randomized clinical trial. Pancreatology. 2016;16:523-8.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+	***Countries:*** Rijeka, Croatia ***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** Grant from the Ministry of Science, Education and Sports of the Republic of Croatia ***Dropout rates:*** n/a ***Study limitations:*** mortality initially defined as primary outcome- since the observed mortality rate and disease severity were lower than expected, this was changed to SIRS, and required sample size was calculated accordingly	**Total no. Patients:** 214 **Inclusion criteria:** the onset of symptoms consistent with AP within 72 h before admission to the hospital; a 3-fold increase in serum amylase (normal value less than90 U/L) or lipase (normal value less than 160 U/L) concentrations; a predicted disease severity defined as an APACHE II score ≥ 6, calculated within the first 24 h from admission **Exclusion criteria:** patients younger than 18 years	- Patients with AP were randomized to receive either EN via a nasojejunal tube initiated within 24 h of admission or no nutritional support - n=107 in each group - EN was started at a median of 4 h after admission (range 30 min to 14 h), and at a median of 11 h after symptom onset (range 6- 36 h) - ingestion of small amounts of clear liquids was started in both groups on the third day
Notes	**Author's Conclusion:** no significant reduction of persistent organ failure and mortality in patients with AP receiving early EN compared to patients treated with no nutritional support		
Outcome measures/results	Primary outcome: systemic inflammatory response syndrome (SIRS) Secondary outcomes: mortality, organ failure, local complications, infected pancreatic necrosis, surgical interventions, length of hospital stay, adverse events and inflammatory response intensity		- SIRS occurrence was similar between the two groups - no significant reduction of persistent organ failure and mortality in the EN group - there were no significant differences in other outcomes between the groups

5. What type of enteral nutrition is indicated?

Recommendation 6

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

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

29.	**Tiengou LE, Gloro R, Pouzoulet J, Bouhier K, Read MH, Arnaud-Battandier F, et al. Semi-elemental formula or polymeric formula: is there a better choice for enteral nutrition in acute pancreatitis? Randomized comparative study. JPEN J Parenter Enteral Nutr. 2006;30:1-5.**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+	***Countries:*** France ***Centers:*** Gastroenterology and Nutrition Department of Caen Teaching Hospital ***Setting:*** n/a ***Funding Sources:*** n/a ***Dropout rates:*** n/a ***Study limitations:*** small sample size	**Total no. Patients:** 30 **Inclusion criteria:** over the age of 18; acute pancreatitis requiring jejunal nutrition **Exclusion criteria:** edematous acute pancreatitis with a Balthazar score < B, not justifying treatment by enteral nutrition; hypertriglyceridemia > 10 mmol/L on the day of inclusion (D0); failure of insertion of the nasojejunal tube; and life-threatening intercurrent diseases	- the semi-elemental group received 35 kcal/kg/d of Peptamen (n = 15), and the polymeric group received the same quantity of Sondalis-Iso (n = 15) - all patients received symptomatic treatment comprising suspension of oral feeding, gastric aspiration in the case of ileus, IV fluids (40 mL/kg/d compensation of gastric aspiration), vitamin B1 and B6 supplements (in alcoholic patients), and analgesics
Notes	**Author's Conclusion:** Semi-elemental and polymeric nutrition are very well tolerated in patients with acute pancreatitis. Nutrition with a semi-elemental formula supports the hypothesis of a more favorable clinical course than nutrition with a polymeric formula		
Outcome measures/results	weight loss, length of hospital stay, and infection rate		- in semi-elemental group, the length of hospital stay was shorter and weight loss was less marked

		- one patient in semi-elemental group and 3 patients in polymeric group developed an infection

30. Petrov MS, Loveday BP, Pylypchuk RD, McIlroy K, Phillips AR, Windsor JA. Systematic review and meta-analysis of enteral nutrition formulations in acute pancreatitis. Br J Surg. 2009;96:1243-52.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Systematic review and Meta-Analysis 1-	***Countries:*** n/a ***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** n/a ***Dropout rates:*** n/a ***Study limitations:*** small sample size; poor methodological quality of some of the studies	**Total no. Patients:** n/a **Inclusion criteria:** RCT; compare two different feeding regimens, at least one of which had to include enteral tube feeding; report on feeding intolerance (defined as an episode of temporary reduction, stoppage or withdrawal of feeding) and total infectious complications and/or in-hospital mortality **Exclusion criteria:** Studies investigating the tolerance of oral refeeding or combined enteral and parenteral nutrition or postoperative nutrition	- comparing the tolerance and safety of enteral nutrition formulations in patients with acute pancreatitis - Patients received (semi)elemental formulation in nine arms of the included trials, polymeric formulation in seven arms, fiber-enriched enteral formulation in six arms, enteral nutrition supplemented with probiotics in four arms and immunonutrition (glutamine, arginine and omega-3 fatty acids) in three arms
Notes	**Author's Conclusion:** Neither the supplementation of enteral nutrition with probiotics nor the use of immunonutrition significantly improves the clinical outcomes.		
Outcome measures/results	feeding intolerance, infectious complications and mortality		- Fiber enriched formulation may be safely administered in acute pancreatitis and its supplementation with immunonutrition or probiotics does not improve clinically meaningful outcomes - Polymeric, in comparison with (semi)elemental, enteral nutrition formulation is not associated with a statistically significant difference in tolerance of feeding, infectious complications and mortality

31. Poropat G, Giljaca V, Hauser G, Stimac D. Enteral nutrition formulations for acute pancreatitis. Cochrane Database Syst Rev. 2015:CD010605.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Systematic Review and Meta-Analysis 1++	***Countries:*** n/a ***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** n/a ***Dropout rates:*** 46% ***Study limitations:*** Diversity of interventions across the studied trials, the included trials were at high risk of bias.	**Total no. Patients:** n=1376 **Inclusion criteria: P**atients diagnosed with AP by any method according to, or compatible with, at least two of the three following criteria. • Abdominal pain consistent with AP. • Three-fold or greater elevation in serum amylase or lipase. Morphological (structural) changes consistent with AP detected on CT **Exclusion criteria:** n/a	Any type of EN regimen with a clearly specified type of nutritional formulation, irrespective of the route, start, rate or duration of administration versus a different type of EN formulation, placebo or no intervention for the treatment of patients with AP. Any additional interventions were allowed if they were received equally by all treatment groups within a trial.
Notes	**Author's Conclusion:** The findings of our systematic review are based on evidence of low to very low quality and show no beneficial effects of one specific enteral nutrition formulation over another. Immunonutrition seems generally well tolerated and safe on the basis of evidence of low to very low quality. Our results showed a reduction in all-cause mortality, which is based on evidence of low quality. Routine use of probiotic supplements to enteral nutrition should be avoided on the basis of current available evidence because of safety concerns. We have found evidence of low or very low quality for the effects of nutrition over no nutritional support in reduction of all-cause mortality.		
Outcome measures/results	Primary outcomes: All-cause mortality; systemic inflammatory response syndrome (SIRS); multiple organ dysfunction syndrome; adverse events Secondary outcomes: Local septic complications; other local complications; other infection; length of hospital stay; quality of life.		The use of immunonutrition significantly decreased mortality in participants with AP (RR 0.49, 95% CI 0.29 to 0.80, IS = 0%). Immunonutrition had no significant effect on SIRS development (RR 1.00, 95% CI 0.76 to 1.31, IS = 0%). Immunonutrition did not demonstrate any significant effect on the incidence of organ failure (RR 0.75, 95% CI 0.49 to 1.13, IS = 0%). The number of participants experiencing adverse events was not significantly different between groups (RR 1.32, 95% CI 0.78 to 2.24, IS = 50%). The secondary outcome parameters showed no differences between the groups. Subgroup analysis on specific formulas showed no differences between the groups either.

5. What type of enteral nutrition is indicated?

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)

32. Eatock FC, Chong P, Menezes N, Murray L, McKay CJ, Carter CR, et al. A randomized study of early nasogastric versus nasojejunal feeding in severe acute pancreatitis. Am J Gastroenterol. 2005;100:432-9.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1-	***Countries:*** United Kingdom ***Centers:*** Glasgow Royal Infirmary ***Setting:*** n/a ***Funding Sources:*** n/a ***Dropout rates:*** 2% ***Study limitations:*** no sample size calculation	**Total no. Patients:** n=50 **Inclusion criteria:** clinical and biochemical presentation of AP, Glasgow prognostic score ≥ 3 or APACHE II ≥6 or CRP ≥ 150 mg/L **Exclusion criteria:** 18 years, pregnancy	Nasogastric tubes vs. nasojejunal tubes
Notes	**Author's Conclusion:** The simpler, cheaper and more easily used nasogastric feeding is as good as the nasojejunal feeding in patients with objectively graded severe acute pancreatitis. This appears to be a useful and practical therapeutic approach to enteral nutrition in the early management of patients with severe acute pancreatitis.		
Outcome measures/results	APACHE II score, CRP levels, visual analogue scale (VAS) for pain, total analgesic requirement		There were no significant group differences regarding the outcome parameters.

33. Kumar A, Singh N, Prakash S, Saraya A, Joshi YK. Early enteral nutrition in severe acute pancreatitis: a prospective randomized controlled trial comparing nasojejunal and nasogastric routes. J Clin Gastroenterol. 2006;40:431-4.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+	***Countries:*** India ***Centers:*** n/a ***Setting:*** All India Institute of Medical Sciences in New Delhi ***Funding Sources:*** n/a ***Dropout rates:*** n/a ***Study limitations:*** n/a	**Total no. Patients:** 31 **Inclusion criteria:** CT severity score ≥ 7; Acute Physiology and Chronic Health Evaluation score of ≥ 8 **Exclusion criteria:** delay of more than 4 weeks between the onset of symptoms and presentation to the hospital; if they were already taking oral feeding at presentation; if there was acute exacerbation of chronic pancreatitis; if they where in shock	- N=15 in the nasogastric group - N=16 in the nasojejunal group - a semi-elemental formula was used through an enteral tube in both groups - nutritional parameters (anthropometry, serum prealbumin and albumin levels) were recorded at baseline and after 7 days - refeeding was started in all the patients 48 hours after admission - Peptamen (Nestle India Ltd, New Delhi, India), a commercially available semi-elemental enteral formula, was used - This was given as a slow infusion at a rate of 1 to 1.5 mL/min through the enteral tube in both groups - this was continued until day 7, when patients were given oral feedings and the tube was removed
Notes	**Author's Conclusion:** EN at a slow infusion is well tolerated by both NJ and NG routes. Neither NJ nor NG feeding leads to recurrence or worsening of pain		
Outcome measures/results	discharge, surgery, death		- recurrence of pain occurred in only 1 patient each in the 2 groups - diarrhea occurred in 3 and 4 patients in the NJ and NG groups - 4 deaths in the NJ group and 5 in the NG group - Two patients in the NJ group and 1 in the NG group underwent surgery - no difference in the outcome measures

34. Singh N, Sharma B, Sharma M, Sachdev V, Bhardwaj P, Mani K, et al. Evaluation of early enteral feeding through nasogastric and nasojejunal tube in severe acute pancreatitis: a noninferiority randomized controlled trial. Pancreas. 2012;41:153-9.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+	***Countries:*** India ***Center:*** tertiary care academic center **Setting:** n/a ***Funding Sources:*** n/a ***Dropout rates:*** 3 % ***Study limitations:*** delay in commencing EN. The reason for the delay in admission is mainly because of this center being a tertiary care center; patients are referred late when septic complications have already set in	**Total no. Patients:** 78 **Inclusion criteria:** patients with SAP admitted within 7 days of onset of pain **Exclusion criteria:** Patient already on oral feeds at the time of presentation; Patients in shock (i.e., systolic blood pressure < 90 mm Hg at the time of randomization	- patients with SAP were fed via NG (candidate) or NJ (comparative) route - comparative (control): nasojejunal feeding - candidate intervention: nasogastric feeding - an attempt was made to start refeeding in the included patients 48 hours after admission - Novasource (Nestle India Ltd, New Delhi, India), a commercially available semielemental enteral formula, was used to reach the nutrient goal (25 kcal/kg per day) in 3 to 4 days - the composition of feed was similar in both groups and was aimed to be of equal energy value in both groups
Notes	**Author's Conclusion:** Early enteral feeding through NG was not inferior to NJ in patients with SAP. Infectious complications were within the non-inferiority limit		
Outcome measures/results	- primary outcome: occurrence of any infectious complication in blood, pancreatic tissue, bile, or tracheal aspirate - secondary outcomes: pain in refeeding, duration of hospital stay, intestinal permeability assessed by lactulose/mannitol excretion, and endotoxemia assessed by endotoxin core antibody types immunoglobulin G and M		- the presence of any infectious complication in the NG and NJ groups was 23.1% and 35.9% - 8 patients should be treated with NG compared with the NJ group to prevent 1 patient from any of the infectious complications - pain in refeeding, intestinal permeability, and endotoxemia were comparable in both groups

35.	**Petrov MS, Correia MI, Windsor JA. Nasogastric tube feeding in predicted severe acute pancreatitis. A systematic review of the literature to determine safety and tolerance. JOP. 2008;9:440-8.**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Systematic review 1 -	***Countries:*** UK, Sweden, India ***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** n/a ***Dropout rates:*** 1 % ***Study limitations:*** n/a	**Total no. Patients:** 93 **Inclusion criteria:** cohort study or RCT; nasogastric tube feeding **Exclusion criteria:** n/a	- to review all available studies on nasogastric feeding in patients with severe acute pancreatitis to determine the safety and tolerance of this approach - nasogastric versus nasojejunal feeding
Notes	**Author's Conclusion:** Nasogastric feeding appears safe and well tolerated in patients with predicted severe acute pancreatitis		
Outcome measures/results	tolerance, organ failure, infectious complications, and mortality		- infected pancreatic necrosis developed in 11 patients and multiple organ failure in 10 out of 65 patients - exacerbation of pain after initiation of feeding occurred in 3 out of 69 patients - full tolerance was achieved in 73 patients who did not require temporary reduction, stoppage or withdrawal of nasogastric feeding - the results of nasogastric feeding as compared to nasojejunal feeding, were no worse in terms of mortality or intolerance of feeding

36.	**Nally DM, Kelly EG, Clarke M, Ridgway P. Nasogastric nutrition is efficacious in severe acute pancreatitis: a systematic review and meta-analysis. Br J Nutr. 2014;112:1769-78.**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Systematic review and Meta-Analysis 1-	***Countries:*** India, Scotland, Italy, Sweden ***Centers:*** n/a ***Funding Sources:*** n/a ***Study limitations:*** lack of high-quality level one	**Total no. Patients:** 258 **Inclusion criteria:** adult patients with a diagnosis of AP; Enteral nutrition delivered by NG tube (the intervention) compared with NJ nutrition	- evaluating the efficacy of nasogastric feeding and comparing the nasogastric and nasojejunal route - NG nutrition was received by 147 patients; exclusive NG feeding was achieved in 90 % - of the 147 patients, 129 (87 %) received 75 % of the target energy. In studies where all subjects received exclusive NG nutrition, 82 %

	trials pertaining to this subject; not all the secondary endpoints of this systematic review are reported in all studies	**Exclusion criteria:** n/a	(seventy-four of the ninety patients) received >75 % of the intended energy
Notes	**Author's Conclusion:** Nasogastric feeding is efficacious in 90 % of patients		
Outcome measures/results	- primary endpoint: exclusive NG feeding with delivery of 75 % of nutritional targets - secondary endpoints: change to total parenteral nutrition (TPN), increased pain or disease severity, vomiting, diarrhea, delivery rate reduction and tube displacement		- compared with NJ nutrition, there was no significant difference in the delivery of 75 % of nutritional targets or no increased risk of change to TPN, diarrhea, exacerbation of pain or tube displacement - vomiting and diarrhea were the most common side effects of NG feeding

37. Chang YS, Fu HQ, Xiao YM, Liu JC. Nasogastric or nasojejunal feeding in predicted severe acute pancreatitis: a meta-analysis. Crit Care. 2013;17:R118.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-Analysis 1 +	***Countries:*** Scotland, India ***Centers:*** Multicenter ***Setting:*** n/a ***Funding Sources:*** n/a ***Dropout rates:*** n/a ***Study limitations:*** small total sample size; blinding was not performed in any of the trials; differences in gender and etiology between the centers in Scotland and India	**Total no. Patients:** 157 **Inclusion criteria:** prospective randomized controlled trials; hospitalized patients with predicted SAP; **Exclusion criteria:** n/a	comparing nasogastric and nasojejunal feeding in patients with predicted severe acute pancreatitis
Notes	**Author's Conclusion:** Nasogastric feeding is safe and well tolerated compared with nasojejunal feeding		

Outcome measures/results	Primary outcome: mortality and at least one of the following variables: incidence of tracheal aspiration, diarrhea and exacerbation of pain Secondary outcome: achievement of energy balance	- the safety and tolerance were not significantly different between the NG and NJ feeding groups, with no increase in mortality or nutrition-associated adverse events - no significant difference between NG and NJ feeding with respect to tracheal aspiration

38. Zhu Y, Yin H, Zhang R, Ye X, Wei J. Nasogastric Nutrition versus Nasojejunal Nutrition in Patients with Severe Acute Pancreatitis: A Meta-Analysis of Randomized Controlled Trials. Gastroenterol Res Pract. 2016;2016:6430632.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-Analysis 1-	***Countries:*** UK, India, China ***Centers:*** Single center ***Setting:*** n/a ***Funding Sources:*** supported by Guangzhou Medical Science and Technology Project (20151A010025) and Academician Li Jieshou Special Research Foundation of the Intestinal Barrier ***Dropout rates:*** n/a ***Study limitations:*** small sample size; only single center studies; only four studies included	**Total no. Patients:** 237 **Inclusion criteria:** hospitalized patients with SAP **Exclusion criteria:** n/a	- comparing NG and NJ nutrition in patients with SAP - n=122 were randomly assigned to an NG group and n=115 to an NJ group
Notes	**Author's Conclusion:** NG nutrition was as safe and effective as NJ nutrition in patients with SAP		
Outcome measures/results	Primary outcome: mortality Secondary outcome: at least one of the following variables: incidence of complications (tracheal aspiration, infection,		no significant differences in the incidence of mortality, infectious complications, digestive complications, achievement of energy balance, or length of hospital stay between the NG and NJ nutrition groups

	diarrhea, or exacerbation of pain), achievement of energy balance, and length of hospital stay	

9. How should artificial nutrition (EN and PN) be provided in critically severe AP (increased intra-abdominal pressure (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 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/hour with 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 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)

39. Sun JK, Li WQ, Ke L, Tong ZH, Ni HB, Li G, et al. Early enteral nutrition prevents intra-abdominal hypertension and reduces the severity of severe acute pancreatitis compared with delayed enteral nutrition: a prospective pilot study. World J Surg. 2013;37:2053-60.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+	***Countries:*** China ***Centers:*** General Surgery Institute, Jinling Hospital ***Setting:*** n/a ***Funding Sources:*** Grants from the Key Project of the Eleventh Five-Year Plan Foundation of People's Liberation Army ***Dropout rates:*** 0 ***Study limitations:*** small sample size; single-center design; this study was not based on a pathophysiological model, the precise mechanisms of EEN in SAP should be verified by more basic experiments; the effects of EEN in the later stages of SAP should be confirmed	**Total no. Patients:** 60 **Inclusion criteria:** adult patients (aged 18–70 years) admitted within 3 days of onset of symptoms **Exclusion criteria:** n/a	- EN was started within 48 h after admission in the early enteral nutrition (EEN) group (n=30) and from the 8th day in the delayed enteral nutrition (DEN) group (n=30) - The intra-abdominal pressure (IAP) and intra-abdominal hypertension (IAH) incidence were recorded for 2 weeks - the caloric intake and feeding intolerance (FI) incidence were recorded daily after EN was started
Notes	**Author's Conclusion**: EEN did not increase IAP; in contrast, it might prevent the development of IAH		
Outcome measures/results	IAP, IAH		- no difference about IAP was found - the IAH incidence of the EEN group was significantly lower than that of the DEN group from the 9th day (8/30 versus 18/30) after admission - the FI incidence of the EEN group was higher than that of the DEN group during the initial 3 days of feeding

		- Patients with an IAP < 15 mmHg had lower FI incidence than those with an IAP ≥ 15 mmHg on the 1st day, the 3rd day and the 7th day of feeding - the severity markers and clinical outcome variables of the EEN group were significantly improved

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

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)

40. Jeurnink SM, Nijs MM, Prins HA, Greving JP, Siersema PD. Antioxidants as a treatment for acute pancreatitis: A meta-analysis. Pancreatology. 2015;15:203-8.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-Analysis 1+	***Countries:*** n/a ***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** none ***Dropout rates:*** n/a ***Study limitations:*** inclusion of patients with mild and severe AP; heterogeneity in various trials of antioxidants in terms of the large number of different antioxidants investigated, timing of administration, duration of intervention	**Total no. Patients:** 443 **Inclusion criteria:** use of anti-oxidant supplements compared with placebo or no treatment **Exclusion criteria:** animal studies	- to assess the efficacy of antioxidants in acute pancreatitis - subgroup analyses were performed on the use of the antioxidant glutamine
Notes	**Author's Conclusion:** There is a possible benefit of glutamine supplementation in patients with acute pancreatitis		

Outcome measures/results	hospital stay, mortality, and complications	- antioxidant therapy resulted in a borderline significant reduction in hospital stay - a significant decrease in complications - non-significant decrease in mortality rate - glutamine significantly reduced complications and mortality rate

41. Moggia E, Koti R, Belgaumkar AP, Fazio F, Pereira SP, Davidson BR, et al. Pharmacological interventions for acute pancreatitis. Cochrane Database Syst Rev. 2017;4:CD011384.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Systematic Review and Meta-Analysis 1++	***Countries:*** n/a ***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** n/a ***Dropout rates:*** 69% ***Study limitations:*** low quality of evidence	**Total no. Patients:** n=7366 **Inclusion criteria:** adults with acute pancreatitis irrespective of the severity (mild, moderately severe, or severe acute pancreatitis) or the type of acute pancreatitis (acute interstitial edematous pancreatitis or necrotizing pancreatitis) **Exclusion criteria:** n/a	Pharmacological interventions, among them antioxidants
Notes	**Author's Conclusion:** Very low-quality evidence suggests that no pharmacological treatment leads to a decrease in short-term mortality in people with acute pancreatitis. However, the confidence intervals were wide and consistent with an increase or decrease in short-term mortality. We did not find consistent clinical benefits with any intervention.		
Outcome measures/results	Primary outcomes: mortality, serious adverse events Secondary outcomes: adverse events, measures of decreased complications and earlier recovery, costs		There was no evidence of difference regarding mortality (both long- and short-term) in any of the comparisons. There was no difference regarding serious adverse events, organ failure, infected pancreatic necrosis and sepsis between patients with and without antioxidants. For the secondary outcomes, there were no differences regarding treatment with or without antioxidants neither.

42.	**Asrani V, Chang WK, Dong Z, Hardy G, Windsor JA, Petrov MS. Glutamine supplementation in acute pancreatitis: a meta-analysis of randomized controlled trials. Pancreatology. 2013;13:468-74.**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-Analysis 1-	***Countries:*** UK, Mexico, China, Hungary, China, Germany, Turkey ***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** n/a ***Study limitations:*** methodological quality was only moderate; the feed composition of patients receiving standard EN or PN was not analyzed; the dose, timing, duration, and chemical form varied considerably between the studies	**Total no. Patients:** n/a **Inclusion criteria:** RCT evaluating the effects of glutamine supplementation in AP, regardless of the route of nutrition **Exclusion criteria:** n/a	- the interventions were either with L-glutamine, alanyl-L-glutamine or glycyl-L-glutamine di-peptides, used either as a sole supplement or in combination with other nutrients
Notes	**Author's Conclusion:** clear advantage for glutamine supplementation in patients with acute pancreatitis who receive TPN. Patients with acute pancreatitis who receive enteral nutrition do not require glutamine supplementation		
Outcome measures/results	mortality, infectious complications, length of hospital stay		- glutamine supplementation resulted in a significantly reduced risk of mortality and total infectious complications but not length of hospital stay - only patients who received parenteral nutrition and those who received glutamine in combination with other immunonutrients demonstrated a statistically significant benefit in terms of all the studied outcomes

43. Yong L, Lu QP, Liu SH, Fan H. Efficacy of Glutamine-Enriched Nutrition Support for Patients With Severe Acute Pancreatitis: A Meta-Analysis. JPEN J Parenter Enteral Nutr. 2016;40:83-94.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-Analysis 1-	***Countries:*** China, Turkey, Mexico ***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** n/a ***Dropout rates:*** n/a ***Study limitations:*** methodological quality of the included studies was only moderate; the dose, timing, duration, and chemical form (L-glutamine or synthetic dipeptide such as alanyl-L-glutamine and glycyl-L-glutamine dipeptide) of Gln pharmaconutrition varied considerably between these studies	**Total no. Patients:** n/a **Inclusion criteria:** clinical RCTs of patients with SAP; RCTs that compared standard PN (or EN) with PN (or EN) supplemented with Gln **Exclusion criteria:** editorials and expert advice, reviews without original data, case reports, and studies lacking control groups	- comparison of conventional and Gln-enriched nutrition support - n=218 patients who received conventional methods (control group) and n=215 patients who received Gln-enriched nutrition support (experimental group)
Notes	**Author's Conclusion:** Gln-enriched nutrition support is superior to conventional methods for SAP, and intravenous infusion may be a better choice for drug administration		
Outcome measures/results	infectious complications, mortality, hospital stay		Gln is helpful in elevating the albumin level, decreasing C-reaction protein decreasing the incidence of infectious complication and mortality and shortening the hospital stay length

44. Jafari T, Feizi A, Askari G, Fallah AA. Parenteral immunonutrition in patients with acute pancreatitis: a systematic review and meta-analysis. Clin Nutr. 2015;34:35-43.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Systematic review and Meta-Analysis 1-	***Countries:*** n/a ***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** none ***Dropout rates:*** n/a ***Study limitations:*** small sample size; few number of studies on the subject specially about omega-3 FA; possible heterogeneity in the disease severity among the studies; absence of accurate data about antibiotic therapy which may influence the outcomes	**Total no. Patients:** n/a **Inclusion criteria:** RCTs which (a) used parenteral immunonutrition containing glutamine or glutamine dipeptide compared with standard parenteral nutrition; (b) used parenteral immunonutrition containing omega-3FAs or fish oil compared with standard parenteral nutrition; Both parenteral immunonutrition solution and standard form had to be iso-caloric and also iso-nitrogenus; Patients involved were females or males aged 16 or over, with acute pancreatitis whom needed PN therapy, and the parenteral feeding had begun within 72 h after admittance to ICU **Exclusion criteria:** RCTs evaluated EN, or compared EN with PN	A meta-analysis to evaluate the effects of parenteral immunonutrition on clinical outcomes in patients with acute pancreatitis
Notes	**Author's Conclusion:** Immunonutrients like glutamine and omega-3 FAs added to parenteral formulas can improve prognoses in patients with acute pancreatitis		
Outcome measures/results	infectious complications, length of hospital stay (LOS) and mortality		- parenteral immunonutrition significantly reduced the risk of infectious complications and mortality - LOS was also shorter in patients who received immunonutrition

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)

45. Kahl S, Schutte K, Glasbrenner B, Mayerle J, Simon P, Henniges F, et al. The effect of oral pancreatic enzyme supplementation on the course and outcome of acute pancreatitis: a randomized, double-blind parallel-group study. JOP. 2014;15:165-74.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+	***Countries:*** Germany ***Centers:*** three centers in Germany ***Funding Sources:*** n/a ***Dropout rates:*** 27 % ***Study limitations:*** low number of patients evaluable; no definitive data supporting the hypothesis regarding the primary endpoint	**Total no. Patients:** 56 **Inclusion criteria:** patients with moderate to severe acute pancreatitis (defined as patients CRP greater than 120 mg/L and APACHE II score greater than 4) **Exclusion criteria:** Patients with known chronic pancreatitis, pre-existing exocrine pancreatic insufficiency, earlier gastric or pancreatic resection, small bowel disease or known gastroparesis	- treatment group: pancreatic enzyme supplementation (Creon® 25,000 Minimicrospheres (mms) capsules; Abbott Laboratories GmbH (previously Solvay Pharmaceuticals GmbH), Hannover, Germany; lipase 25,000 European Pharmacopoeia (Ph. Eur.) Units; amylase 18,000 Ph. Eur. Units, protease 1,000 Ph. Eur. Units) orally - placebo group: placebo capsules - treatment period of 26-30 days - two capsules were taken per main meal (three main meals a day) and one capsule per snack (one to three snacks a day) - baseline: 20 out of 56 patients suffered from pancreatic exocrine insufficiency → these patients only were evaluable for the primary end-point of the study
Notes	**Author's Conclusion:** Enzyme supplementation positively effects the course of acute pancreatitis if administered during the early refeeding phase after acute pancreatitis		
Outcome measures/results	primary outcome: recovery from pancreatic exocrine insufficiency secondary outcomes: body weight, abdominal pain, course of APACHE II score, patient's symptoms and quality of life		- median time to recovery from exocrine pancreatic insufficiency was 14 days in the enzyme supplementation group and 23 days in the placebo group

		- overall differences for primary and all but one secondary endpoint did not reach statistical significance - a positive tendency in favor of enzyme supplementation was found for quality of life parameters (FACT-Pa) in all subscores - no relevant differences between placebo and oral pancreatic enzyme supplementation detected with respect to safety and tolerability

46. Patankar RV, Chand R, Johnson CD. Pancreatic enzyme supplementation in acute pancreatitis. HPB Surg. 1995;8:159-62.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1++	***Countries:*** UK ***Centers:*** n/a ***Setting:*** Southampton General Hospital ***Funding Sources:*** n/a ***Study limitations:*** n/a ***Dropout rates:*** 4 failed to complete the study	**Total no. Patients:** 23 **Inclusion criteria:** biochemically and radiologically proven acute pancreatitis as defined by a serum amylase level > 1000 IU/L and ultrasonographic or computerized tomography (CT) evidence of edematous/inflamed pancreas with or without a peripancreatic collection; mild and severe forms of acute pancreatitis **Exclusion criteria:** patients who were receiving pancreatic enzyme supplements or those allergic to porcine pancreatin	- active capsules contained pancreatic enzymes as enteric coated granules packaged in gelatine capsules (Creon, Duphar Laboratories, UK). Each capsule contained 210 units free protease, 440 units zymogen bound protease, 8000 BP units lipase and 9000 BP units amylase - Placebo capsules contained microcrystalline cellulose - Dosage was 3 capsules 4 times a day, providing 7800 units of protease per day - capsules were given orally and all patients had enzymes for a minimum of five days
Notes	**Author's Conclusion:** no beneficial effect of oral pancreatic enzyme supplements in the initial management of patients with acute pancreatitis		
Outcome measures/results	pain; analgesic requirement; incidence of complications		- no significant differences between the median (range) pain scores of patients who received placebo and those who received enzymes - hospital stay was 7 days in patients on placebo and 8 days in the enzyme group

		- no significant difference in analgesic requirements between the two groups

II. Chronic pancreatitis

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)

47. D'Haese JG, Ceyhan GO, Demir IE, Layer P, Uhl W, Lohr M, et al. Pancreatic enzyme replacement therapy in patients with exocrine pancreatic insufficiency due to chronic pancreatitis: a 1-year disease management study on symptom control and quality of life. Pancreas. 2014;43:834-41.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Cohort study 2+	***Countries:*** Germany ***Centers:*** selected medical practices in Germany ***Funding Sources:*** n/a ***Dropout rates:*** 1 % ***Study limitations:*** the actual dose was not recorded; compliance was assessed only by the overall impression of the physician;	**Total no. Patients:** 294 **Inclusion criteria:** patients with CP and EPI; patients who are already on pancreatin therapy or had agreed to start pancreatin therapy for the treatment of EPI; patients who are willing to complete a quality-of-life questionnaire **Exclusion criteria:** Patients with pancreatic cancer or cystic fibrosis	- cohort 1 (n=206): patients already taking pancreatin (Kreon; Abbott Arzneimittel GmbH, Hannover, Germany) - cohort 2 (n=88): patients with newly diagnosed EPI without prior pancreatic enzyme treatment - quality of life was assessed using the gastrointestinal quality of life index (GIQLI) at baseline, 6 months, and 1 year - the dosage prescribed was at the discretion of the treating physician according to the degree of severity of EPI
Notes	**Author's Conclusion:** Pancreatin demonstrated symptom relief and improvement in quality of life in patients with CP-related EPI in this disease management study		
Outcome measures/results	quality of life; body weight		- the proportion of patients experiencing gastrointestinal symptoms and recurrent pain after 1 year was significantly reduced in both cohorts

		- the alleviation of symptoms was reflected in GIQLI score improvements at 1 year in both cohorts - improvements in GIQLI score were more pronounced in cohort 2 - the recommended daily doses were consistently higher in cohort 1 than in cohort 2 throughout the entire observation period - at the time of enrollment, the mean daily dosage of pancreatin in cohort 1 (99,302 lipase units) was significantly increased compared with the mean daily dosage of pancreatin in cohort 2 (83,693 lipase units) - the mean daily dosages for both cohorts did not change significantly over time after 6 or 12 months - body weight: weight loss was significantly reduced in both cohorts; body weight was relatively stable throughout the observation period in both cohorts - quality of life: the mean total GIQLI score for the overall patient population showed a statistically significant increase from baseline to the end of the observation period

48.	**Ramesh H, Reddy N, Bhatia S, Rajkumar JS, Bapaye A, Kini D, et al. A 51-week, open-label clinical trial in India to assess the efficacy and safety of pancreatin 40000 enteric-coated minimicrospheres in patients with pancreatic exocrine insufficiency due to chronic pancreatitis. Pancreatology. 2013;13:133-9.**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1++	***Countries:*** India ***Centers:*** 9 centers in India ***Funding Sources:*** Abbott, Hannover, Germany ***Dropout rates:*** 21 % ***Study limitations:*** n/a	**Total no. Patients:** 61 **Inclusion criteria:** diagnosis of CP and PEI by a coefficient of fat absorption (CFA) ≤ 80% during the run-in period **Exclusion criteria:** Patients were prohibited from consuming additional PERT preparations concomitantly	- during open-label extension (OLE) period: all Patients received pancreatin (Creon® 40000 MMS™) at a dose of 80,000 Ph. Eur. lipase units with each of three main meals/day and 40,000 with each of up to three snacks/day

Notes	**Author's Conclusion:** Treatment with pancreatin for one year was associated with significant improvements in fat absorption, nitrogen absorption, and nutritional parameters, improvements in clinical symptoms, and a favorable safety and tolerability profile	
Outcome measures/results	coefficient of fat and nitrogen absorption; body weight; BMI; quality of life	- significant improvements from baseline to end of OLE in mean ± SD coefficient of fat absorption, coefficient of nitrogen absorption, body weight, BMI and most nutritional laboratory parameters tested - mean daily stool frequency was reduced from 2.8 to 1.6 - improvements in clinical symptoms, clinical global impression of disease symptoms, and quality of life

49.	**Thorat V, Reddy N, Bhatia S, Bapaye A, Rajkumar JS, Kini DD, et al. Randomised clinical trial: the efficacy and safety of pancreatin enteric-coated minimicrospheres (Creon 40000 MMS) in patients with pancreatic exocrine insufficiency due to chronic pancreatitis--a double-blind, placebo-controlled study. Aliment Pharmacol Ther. 2012;36:426-36.**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1++	***Countries:*** India ***Centers:*** multicenter (11 centers in India) ***Setting:*** n/a ***Funding Sources***: funded by Abbott ***Dropout rates:*** 1 % ***Study limitations:*** n/a	**Total no. Patients:** 62 **Inclusion criteria:** patients with pancreatic exocrine insufficiency as determined by a CFA < 80% during the run-in phase **Exclusion criteria:** medical conditions that could interfere with the study or study drug; endocrine disease other than diabetes; major surgery except gall bladder removal or appendectomy; ileus or acute abdomen; any type of malignancy involving the digestive tract in the past 5 years; investigational drugs within 30 days prior to study entry; current excessive intake of	- 1-week, double-blind, randomized, placebo-controlled, parallel-group, multicenter study - Men and women >18 years of age with proven CP and PEI [defined as a coefficient of fat absorption (CFA) < 80% during run-in phase] were randomized 1:1 to pancreatin or placebo (two capsules orally per main meal, one with snacks) - n= 34 in the pancreatin group, n=28 in the placebo group

		alcohol or drug abuse; and hypersensitivity to porcine proteins or pancreatin	
Notes	**Author's Conclusion:** pancreatin (Creon 40000 MMS) is well tolerated, with a good safety profile		
Outcome measures/results	- primary outcome measure: change in CFA from baseline to end of double-blind treatment (analysis of covariance) - Secondary efficacy endpoints: change from baseline to end of the double-blind phase in CNA, stool characteristics, clinical symptoms, clinical global impression (CGI) of disease symptoms, body weight and body mass index (BMI)		- Patients receiving pancreatin: statistically significant greater improvement in fat absorption from baseline to the end of double-blind treatment compared with those receiving placebo - Patients receiving pancreatin: also a statistically significant greater improvement in nitrogen absorption and greater reductions in mean stool fat, stool frequency and stool weight - Changes in body weight and BMI were similar in the pancreatin vs. the placebo groups

50. Whitcomb DC, Lehman GA, Vasileva G, Malecka-Panas E, Gubergrits N, Shen Y, et al. Pancrelipase delayed-release capsules (CREON) for exocrine pancreatic insufficiency due to chronic pancreatitis or pancreatic surgery: A double-blind randomized trial. Am J Gastroenterol. 2010;105:2276-86.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+	***Countries:*** Bulgaria, Poland, Russia, Serbia, Ukraine, and the United States of America ***Centers:*** 27 centers ***Setting:*** n/a ***Funding Sources:*** ***Dropout rates:*** 71 % ***Study limitations:*** slight imbalance in the number of pancreatic surgery patients between treatment groups	**Total no. Patients:** 52 **Inclusion criteria:** chronic pancreatitis or partial pancreactectomy >180 days before enrolment and confirmed exocrine pancreatic insufficiency **Exclusion criteria:** severe medical conditions that might limit participation in or completion of the study, or recent (as per investigator's judgment) major surgery with the exception of appendectomy, pancreatic surgery for chronic pancreatitis, abdominal surgery	Pancrelipase delayed-releasecapsules (72,000 lipase units per main meal (six 12,000-lipase unit capsules) and 36,000 lipase units per snack (three 12,000-lipase unit capsules) or placebo

		due to the underlying pancreatic disease that necessitated the surgery (e.g., pancreatectomy with additional abdominal surgery), or gall bladder removal; acute abdomen, any type of malignancy in the digestive tract other than pancreatic cancer in the past 5 years, any type of malignancy not in remission, HIV, celiac disease, Crohn ' s disease, presence of a pancreatic pseudocyst ≥ 4 cm, continued excessive intake of alcohol or drug abuse, known allergy to pancrelipase (pancreatin) or the inactive ingredients of pancrelipase delayed-release capsules, or exposure to an experimental drug within 4 weeks of the start of the study.	
Notes	**Author's Conclusion:** the results of this double-blind, randomized, placebo controlled study provide strong evidence for the efficacy and safety of pancrelipase delayed-release 12,000-lipase unit capsules in the treatment of EPI due to CP and PS, with significant improvements in fat absorption and protein absorption compared with placebo.		
Outcome measures/results	Primary outcome: Change in the coefficient of fat absorption (CFA) from baseline to the end of the double-blind treatment period Secondary outcomes: coefficient of nitrogen absorption (CNA), stool fat, stool nitrogen, and clinical symptomatology	The mean ± SD change from baseline CFA values was 32.1 ± 18.5 % for pancrelipase and 8.8 ± 12.5 % for placebo ($P < 0.0001$). A high proportion of patients in both groups had negative CAN values at baseline as indicated by the negative mean CNA values. The mean ± SD change from baseline in CNA was significantly greater in the pancrelipase group: 97.7 ± 82.3 % compared with placebo: 24.4 ± 101.0 %; $P = 0.0013$. The CNA value remained negative in the placebo group at the end of the double-blind period.	

51. Taylor CJ, Thieroff-Ekerdt R, Shiff S, Magnus L, Fleming R, Gommoll C. Comparison of two pancreatic enzyme products for exocrine insufficiency in patients with cystic fibrosis. J Cyst Fibros. 2016;15:675-80.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+	***Countries:*** Belgium, Bulgaria, Germany, Hungary, Italy, Poland, and the UK ***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** Aptalis Pharma US, Inc., an affiliate of Actavis, Inc ***Dropout rates:*** 10 % ***Study limitations:*** n/a	**Total no. Patients:** 96 patients and 83 completers **Inclusion criteria:** diagnosis of CF based on one clinical feature consistent with CF and either a genotype with two identifiable disease-causing CF mutations or a sweat chloride concentration > 60 mmol/L; pancreatic insufficiency documented by a monoclonal fecal elastase ≤ 100 µg/g stool; current treatment with pancreatic enzyme replacement therapy; BMI > 19 kg/m^2 **Exclusion criteria:** patients with clinically significant cardiac, renal, neurological, gastrointestinal (e.g., fibrosing colonopathy), hepatic, or endocrine disease	- Zenpep and Kreon, both containing 25,000 lipase units, were compared in a study for CF-associated EPI - two treatment sequences: Zenpep/Kreon or Kreon/Zenpep - 96 patients were randomized with 83 completers of both sequences comprising the efficacy population
Notes	**Author's Conclusion:** Zenpep is comparable with Kreon in efficacy and safety for the treatment of adolescents and adults with CF-associated EPI		
Outcome measures/results	Primary outcome: coefficient of fat absorption over 72 h (CFA-72 h) Secondary outcomes: change in body weight, coefficient of nitrogen absorption over 72 h (CNA-72 h), signs and symptoms of EPI as recorded inpatient diaries, and impact on overall health, daily life, perceived well-being, and CF		- Zenpep demonstrated non-inferiority and equivalence to Kreon in fat absorption - safety and tolerability were similar - efficacy results of Zenpep and Kreon also were similar for the secondary endpoint

	symptoms as evaluated by the Cystic Fibrosis Questionnaire-Revised (CFQ-R).	

52.	**de la Iglesia-Garcia D, Huang W, Szatmary P, Baston-Rey I, Gonzalez-Lopez J, Prada-Ramallal G, et al. Efficacy of pancreatic enzyme replacement therapy in chronic pancreatitis: systematic review and meta-analysis. Gut. 2017;66:1354-5.**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Systematic Review and Meta-Analysis 1++	***Countries:*** USA, Germany, Denmark, France, Belgium, South Africa, Spain, Netherlands, India ***Centers:*** n/a ***Setting:*** n/a ***Funding Sources***: work was funded by the University Hospital of Santiago de Compostela, Spain (DdlI-G, IB-R, JG-L, GP-R, JED-M), Royal College of Surgeons of England (PS) and the Biomedical Research Unit funding scheme of the National Institute for Health Research (WH, RM, QMN, RS). RS is an NIHR Senior Investigator ***Dropout rates:*** n/a ***Study limitations:*** n/a	**Total no. Patients:** n/a **Inclusion criteria:** in English peer-reviewed journals; prospective, randomized design, investigating efficacy and safety of PERT in EPI from CP in adults (age ≥ 18 years; including patients who had pancreatic resection for CP but no other indications); reporting clinical outcomes of interest; only the most recent study of multiple overlapping patient populations from the same institution unless a prior study had higher quality **Exclusion criteria:** Abstracts, case reports, letters, expert opinions, editorials, reviews and non-RCTs	- randomized controlled trials of pancreatic enzyme replacement therapy (PERT) to determine the efficacy of PERT in exocrine pancreatic insufficiency (EPI) from CP
Notes	**Author's Conclusion:** PERT is indicated to correct EPI and malnutrition in CP and may be improved by higher doses, enteric coating, administration during food and acid suppression.		

Outcome measures/results	Primary outcome: CFA Secondary outcome: CNA, FFE, FNE, fecal weight, fecal consistency (formed/normal or soft/watery), fecal frequency (stools per day), flatulence (none/mild/moderate/severe), abdominal pain (none/mild/moderate/severe) and adverse events. When available, serum nutritional markers, diarrhea, weight loss/gain and QoL were included.	- PERT improved CFA compared with baseline (83.7±6.0vs 63.1±15.0, $p<0.00001$; I^2= 89%) and placebo (83.2± 5.5 vs 67.4± 7.0, p= 0.0001; I^2= 86%) - PERT improved coefficient of nitrogen absorption, reduced fecal fat excretion, fecal nitrogen excretion, fecal weight and abdominal pain, without significant adverse events

53. Somaraju UR, Solis-Moya A. Pancreatic enzyme replacement therapy for people with cystic fibrosis. Cochrane Database Syst Rev. 2014:CD008227.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Systematic Review and Meta-Analysis 1++	***Countries:*** n/a ***Centers:*** n/a ***Setting:*** home or hospital setting ***Funding Sources:*** n/a ***Dropout rates:*** 33% ***Study limitations:*** trials with short treatment periods (< 4 weeks) were excluded, due to missing presentation of data cross-over trials had to be analyzed as parallel group trials	**Total no. studies:** 12 **Inclusion criteria:** RCTs and quasi-RCTs (using allocation methods such as alternate allocation to treatment and control groups; People of any age with cystic fibrosis, either diagnosed clinically and confirmed with sweat test, or by genetic testing or by newborn screening. **Exclusion criteria:** n/a	Any dose of PERT and in any formulation, in either home or hospital setting, for a period of not less than four weeks, compared either to placebo or other PERT preparations, commenced either at diagnosis of cystic fibrosis, at the onset of symptoms or at confirmation of abnormal pancreatic function.
Notes	**Author's Conclusion:** We found no evidence from any comparison of PERT to placebo. The available evidence suggests that enteric-coated microspheres are better at improving clinical symptoms in patients with cystic fibrosis compared to non-enteric- coated enzyme preparations. This evidence is, however, limited and is from a few small trials which are prone to bias. There is a lack of evidence on the long-term benefits and risks of treatment and the relative dosages of PERT required for patients with different severities of PI.		
Outcome measures/results	Primary outcomes: Changes in nutritional status (absolute or relative change) of weight, height and BMI		Weight/height/BMI: no (significant) data. Enteric-coated microspheres reduced stool frequency and abdominal pain. Days in hospital, quality of life,

	Secondary outcomes: Bowel symptoms, days in hospital, quality of life, number of times vitamin deficiency diagnosed, adverse events attributed to pancreatic enzyme replacement therapy, fecal fat excretion (FFE) or co-efficient of fat absorption (CFA), lung disease	number of times vitamin deficiency diagnosed, FFE, CFA, lung disease: no data / not enough reported / inconsistent results.

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)

54.	**Thorat V, Reddy N, Bhatia S, Bapaye A, Rajkumar JS, Kini DD, et al. Randomised clinical trial: the efficacy and safety of pancreatin enteric-coated minimicrospheres (Creon 40000 MMS) in patients with pancreatic exocrine insufficiency due to chronic pancreatitis--a double-blind, placebo-controlled study. Aliment Pharmacol Ther. 2012;36:426-36.**
→ See No. 49	

55.	**Whitcomb DC, Lehman GA, Vasileva G, Malecka-Panas E, Gubergrits N, Shen Y, et al. Pancrelipase delayed-release capsules (CREON) for exocrine pancreatic insufficiency due to chronic pancreatitis or pancreatic surgery: A double-blind randomized trial. Am J Gastroenterol. 2010;105:2276-86.**
→ See No. 50	

56.	**Dominguez-Munoz JE, Iglesias-Garcia J, Iglesias-Rey M, Figueiras A, Vilarino-Insua M. Effect of the administration schedule on the therapeutic efficacy of oral pancreatic enzyme supplements in patients with exocrine pancreatic insufficiency: a randomized, three-way crossover study. Aliment Pharmacol Ther. 2005;21:993-1000.**		
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+	***Countries:*** Spain ***Centers:*** n/a ***Setting:*** Pancreas Section of the Department of Gastroenterology of the	**Total no. Patients:** 24 **Inclusion criteria:** final diagnosis of severe chronic pancreatitis and exocrine pancreatic insufficiency with steatorrhea	- consecutive chronic pancreatitis patients with maldigestion secondary to exocrine pancreatic insufficiency were treated with 40 000 U lipase in the form of capsules containing enteric-coated mini-microspheres - capsules were taken just before meals (schedule A: 4–0–0), just after meals (schedule B: 0–0–4) or distributed along with meals (schedule C:

	University Hospital of Santiago de Compostela, Spain ***Funding Sources:*** partially supported by the Health Institute Carlos III, Grant ref. GO3/156, Ministry of Health, Spain, together with a research grant of Solvay Pharmaceuticals, Germany ***Dropout rates:*** 0 ***Study limitations:*** n/a	**Exclusion criteria:** patients who suffered from an acute relapse of pancreatitis within the 6 months preceding the study; any known gastrointestinal illness, hepatic disease or major gastrointestinal or pancreatic surgery; any severe restrictive pulmonary disease; any medication influencing gastrointestinal physiology	1–2–1) for three consecutive 1-week crossover periods in a randomized order - fat digestion before and during the three treatment periods was evaluated by an optimized mixed 13 C-triglyceride breath test
Notes	**Author's Conclusion:** The efficacy of pancreatic enzyme supplements for the treatment of exocrine pancreatic insufficiency may be optimized by administration during or after meals		
Outcome measures/results	primary endpoint: therapeutic efficacy of oral pancreatic enzyme supplements for improving fat digestion according to the administration schedule which was defined by the 6-h cumulative recovery rate of 13 CO2 as measured by the 13 C-MTG-breath test		- before therapy, the 13 CO2 recovery in the breath test was 23.8 ± 15.8 % - during therapy, the 13 CO2 recovery tended to be higher when capsules were taken along with meals or just after meals than when taken just before meals - the percentage of patients who normalized fat digestion under therapy was 50, 54 and 63% with schedules A, B and C respectively

57. Safdi M, Bekal PK, Martin S, Saeed ZA, Burton F, Toskes PP. The effects of oral pancreatic enzymes (Creon 10 capsule) on steatorrhea: a multicenter, placebo-controlled, parallel group trial in subjects with chronic pancreatitis. Pancreas. 2006;33:156-62.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1++	***Countries:*** US ***Centers:*** multicenter ***Setting:*** n/a ***Funding Sources:*** n/a ***Dropout rates:*** 3 %	**Total no. Patients:** 27 **Inclusion criteria:** 12-month history of PEI requiring enzyme supplements; prior supplementation of at least 6	- Placebo: n= 14; Creon 10: n= 13 - after a placebo run-in („washout") phase, the effect on coefficient of fat absorption (%), daily fat excretion before and after treatment, and stool frequency and consistency were assessed

	Study limitations: small sample size	months with satisfactory symptom control **Exclusion criteria:** Subjects with cystic fibrosis, ileus, acute abdomen, or acute pancreatitis (within 60 days of enrollment)	- study consisted of 2 consecutive, outpatient phases: a 2-week, single-blind, placebo run-in phase (B - „washout“) and a 2-week, double blind treatment phase - Creon 10 was administered as 4 capsules with each meal and 2 capsules with snacks
Notes	**Author's Conclusion:** Creon 10 treatment controlled steatorrhea, as reflected in reduced fat excretion, decreased stool frequency and improved stool consistency		
Outcome measures/results	primary outcome: effect of Creon 10 in the control of steatorrhea in chronic pancreatitis patients secondary outcomes: evaluation of stool parameters and global improvement of symptoms scales		- in Creon 10 - treated subjects, the change in mean coefficient of fat absorption (%) from run-in to double-blind phase was significantly higher compared with placebo-treated subject - stool consistency improved significantly more with Creon 10 than with placebo - daily mean fat excretion in stool decreased significantly more in Creon 10- treated subjects compared with placebo-treated subjects - global disease symptom scores showed greater improvement for both physicians and subjects in the Creon 10 group relative to those receiving placebo

58. O'Keefe SJ, Cariem AK, Levy M. The exacerbation of pancreatic endocrine dysfunction by potent pancreatic exocrine supplements in patients with chronic pancreatitis. J Clin Gastroenterol. 2001;32:319-23.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+	***Countries:*** n/a ***Centers:*** n/a ***Setting:*** the Pancreatic Clinic ***Funding Sources:*** Kali-Chemie Pharma, Germany ***Dropout rates:*** 27 % ***Study limitations:*** n/a	**Total no. Patients:** 40 **Inclusion criteria:** suppressed cholecystokinin-stimulated enzyme secretion or steatorrhea; chronic pancreatitis **Exclusion criteria:** gastroparesis; pancreatic pseudocysts; antibiotic therapy	- two sections: run-in period: placebo, non supplemented, 7-day study followed by a 7-day observation period on standard pancreatic enzyme supplementation and a randomized, parallelgroup, 14-day comparison of enzyme supplements versus placebo - enzyme supplement group (n= 15): four capsules with meals, two with snacks; content/capsule: lipase 10,000 USP units, protease 37,500 units, amylase 33,200 units - placebo group (n=14): placebo capsules
Notes	**Author's Conclusion:** high-dose pancreatin minimicrospheres improved, but did not normalize, fat absorption		

Outcome measures/results	primary outcome: coefficients of absorption of fat and protein secondary outcome: effects on 72-hour stool weight, fat, and nitrogen measurements	- after enzyme supplementation, stool fat and nitrogen excretion decreased, whereas fat absorption increased from 54.0 ± 9.7% to 80.8 ± 3.8% per day and protein from 80.5 ± 3.4% to 86.8 ± 2.2% per day - changing treatment from active enzyme supplementation to placebo (and vice versa) resulted in major problems with glucose control - average stool frequency was lower and the stools were firmer in the treatment group - reduction of stool nitrogen excretion in the treatment group

59. Halm U, Loser C, Lohr M, Katschinski M, Mossner J. A double-blind, randomized, multicentre, crossover study to prove equivalence of pancreatin minimicrospheres versus microspheres in exocrine pancreatic insufficiency. Aliment Pharmacol Ther. 1999;13:951-7.			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1++	***Countries:*** Germany ***Centers:*** n/a ***Setting:*** n/a ***Funding Sources:*** n/a ***Dropout rates:*** 51 % ***Study limitations:*** n/a	**Total no. Patients:** 37 **Inclusion criteria:** chronic pancreatitis with less than six acute attacks per year; exocrine pancreatic insufficiency had to be demonstrated by fecal elastase 1, chymotrypsin or fat in the stool **Exclusion criteria:** severe somatic or psychiatric disease; major surgery, cholecystectomy; bile or pancreatic duct stents; diabetes mellitus; malignancy of the GIT; pancreatic pseudocysts; alcohol/drug abuse; pancreatin and other enzymes; allergy to pancreatin	- run-in period: 2 weeks: first week with placebo, second week with Creon 10.000 microspheres - two crossover periods of 2 weeks duration followed the run-in period in cases of fat excretion > 7.5 g/day - n= 23 for the crossover period - randomized either to treatment sequence with pancreatin minimicrospheres followed by pancreatin microspheres (n=11) or vice versa (n=12) - during entire study: four capsules each containing 10.000 Ph. Eur. Units lipase, during every meal and two capsules with every snack
Notes	**Author's Conclusion:** Pancreatin minimicrospheres have been shown to be equally effective as microspheres		

Outcome measures/results	primary outcome: coefficient of fat absorption secondary outcomes: stool weight, clinical symptoms and the safety of the preparations	- per protocol analysis (n=18): the 90% confidence intervals for the coefficient of fat absorption of both crossover periods lay entirely within the equivalence range (P= 0.02) - the intention-to-treat analysis revealed similar results, the inclusion of the 90 % confidence interval for the ratio minimicrospheres/microspheres between 0.905 and 1.105 was slightly missed in favor of superiority of minimicrospheres over microspheres (P= 0.07) - similar results for the secondary outcomes