ESPEN practical guideline on clinical nutrition in acute and chronic pancreatitis

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Based on: ESPEN guideline on clinical nutrition in acute and chronic pancreatitis

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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.

Keywords

Acute pancreatitis, Chronic pancreatitis, pancreatic diseases, nutrition, nutritional support, medical nutrition

Abbreviations

ACS, acute compartment Syndrome; ANP, acute necrotizing pancreatitis; AP, acute pancreatitis; BMI, body mass index; CP, chronic pancreatitis; DXA, dual-energy X-ray absorptiometry; EN, enteral nutrition; IAH, intra-abdominal hypertension; IAP, intra-abdominal pressure; MCT, medium chain triglycerides; ONS, oral nutritional supplements; 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

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 nutrition (EN) over parenteral nutrition (PN) 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 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. The recently published guideline from European Society for Clinical Nutrition and Metabolism (ESPEN) provided specific recommendations focused on clinical nutrition for patients with acute or chronic pancreatitis to fulfill the gap [6].

2 Methodology

The present practical guideline consists of 42 recommendations and six statements and is based on the aforementioned ESPEN guideline on clinical nutrition in acute and chronic pancreatitis [6]. The original guideline was shortened by focusing the commentaries on the evidence and literature on which the recommendations are based on. The recommendations were not changed, but the presentation of the content was transformed into a graphical presentation. The original guideline was developed according to the standard operating procedure for ESPEN guidelines and consensus papers [7]

A comprehensive, systematic literature search was performed on 1st December 2018, based on 31 clinical questions in PICO (population of interest, interventions, comparisons, outcomes) format. Existing evidence was graded according to the SIGN (Scottish Intercollegiate Guidelines Network) grading system. Recommendations were developed and graded into four classes (A/B/0/GPP) [7].

All recommendations were agreed in a multistage consensus process, which resulted in a percentage of agreement (%). The guideline process was funded exclusively by the ESPEN society. For further details on methodology, see the full version of the ESPEN guideline [6] and the ESPEN standard operating procedure [7].

3 Acute pancreatitis (Fig. 1)

1) Patients with acute pancreatitis 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.

(S1, strong consensus, 97%)

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 [8]. 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 [9]. Along with the increased catabolic state related to the disease, patients with predicted severe AP are considered at nutritional risk [10]. 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 [11].

3.1 Acute pancreatitis – mild to moderate disease (Fig. 2)

3.1.1 Nutritional screening

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

(R1, grade B, strong consensus, 100%)

Commentary

Scoring systems such as the NRS 2002 [12], can be helpful in identifying these patients [13-16]. 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 [17].

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 [18].

3.1.2 Oral feeding with low fat soft diet

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

(R2, grade A, strong consensus, 100%)

Commentary

Four randomized controlled trials (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) [8, 19-22]. Furthermore, one of these trials revealed that oral food intake is safe and well-tolerated independently of the course and normalization of serum lipase [19].

4) Low-fat, soft oral diet shall be used when reinitiating oral feeding in patients with mild acute pancreatitis.

(R3, grade A, strong consensus, 100%)

Commentary

Immediate oral feeding with a soft diet seems to be more beneficial regarding caloric intake and equally tolerated compared with clear liquid diets [22-24]. A meta-analysis confirmed that early oral feeding was feasible in patients with predicted mild AP and reduced length of stay [25]. A recent meta-analysis including 17 studies identified that 16.3% of patients with AP will subsequently have intolerance to oral feeding [26]. Hyperlipidemia is the third most common cause of AP and accounts for 4-10% of cases, while it has been reported to be associated with a worse prognosis compared to other etiological factors [27-29]. Specific management includes initially putting patients on a nil by mouth regimen for 24-48 hours, followed by subsequent dietary modifications, medical management with the different classes of anti-hyperlipidemic agents, in-hospital pharmacological treatment with insulin and/or heparin and plasmapheresis [27, 28].

3.1.3 Enteral nutrition in case of intolerance to oral feeding

5) In patients with acute pancreatitis and inability to feed orally, enteral nutrition shall be preferred to parenteral nutrition.

(R4, grade A, strong consensus, 97%)

Commentary

EN is supposed to preserve the integrity of the gut mucosa, stimulate intestinal motility, prevent bacterial overgrowth, and increase the splanchnic blood flow [9]. 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 [30-40]. 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]) [34]. 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]) [34]. These results were confirmed by more recent meta-analyses, including a latest publication including only critically ill patients with AP [38]. 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).

6) Enteral nutrition should be started early, within 24 - 72 hours of admission, in case of intolerance to oral feeding

(R5, grade B, strong consensus, 92%)

Commentary

Several meta-analyses have investigated the clinical effects and tolerance of early EN in patients with AP either within 24 hours [41-43] or 48 hours [44-46] 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 [41-45]. One meta-analysis, compared early

(within 24 hours) with late EN (after 72 hours), but no comparison was made between 24 and 48 hours [43].

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 [43]. A second RCT (214 patients with AP) confirmed these results [47].

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 [48].

7) In patients with acute pancreatitis a standard polymeric diet shall be used.

(R6, grade A, strong consensus, 97%)

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 [49]. 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

[50]. Finally, a second, more recent meta-analysis, including 15 trials (1376 participants), showed no evidence to support a specific enteral formula [51]. Nevertheless, a subgroup of patients with severe AP may have malabsorption and therefore, semi-elemental diets could be of interest.

8) If enteral nutrition is required in patients with acute pancreatitis, it should be administered via a nasogastric tube. Administration via a nasojejunal tube should be preferred in case of digestive intolerance, such as pain and vomiting.

(R7, grade B, strong consensus, 95%)

Commentary

Three RCTs compared nasojejunal with nasogastric support route in patients with severe AP [52-54] showed no differences regarding tolerance, complications rates and mortality. Four meta-analyses [55-58] 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 [55, 56] 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.

3.2 Acute pancreatitis – severe disease (Fig. 3)

3.2.1 Parenteral nutrition in case of intolerance of enteral nutrition

9) PN should be administered in patients with acute pancreatitis who do not tolerate enteral nutrition or who are unable to tolerate targeted nutritional requirements, or if contraindications for EN exist.

(R8, grade GPP, strong consensus, 97%)

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 [59]. 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 [16].

10) When enteral nutrition is not feasible or contraindicated and parenteral nutrition 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 acute pancreatitis.

(R16, grade B, strong consensus, 94%)

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 [60]. Among patients with AP, antioxidant therapy resulted in a borderline significant

reduction in hospital stay, a significant decrease in complication rate and a non-significant decrease in mortality rate. 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 [61]. 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 [62]. Another meta-analysis of twelve RCTs (including 505 patients) demonstrated a significantly reduced infection rate and mortality after glutamine supplementation in patients with AP [63]. 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 [60, 64]. Nevertheless, the risk of bias of the included studies is important due to many reasons: (i) small sample size (ii) possible heterogeneity and (iii) confounding factors.

3.2.2 Substances not recommended in severe disease

11) Probiotics cannot be recommended in patients with severe acute pancreatitis.

(R17, grade 0, consensus, 89%)

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 [65]. 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 [66].

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

(R18, grade B, strong consensus, 97%)

Commentary

There are only two RCTs with a total of 78 patients randomized to pancreatic enzyme supplementation or placebo [67, 68]. In the study by Kahl *et al.* 20 of the 56 patients showed low fecal elastase values indicating pancreatic exocrine insufficiency (PEI). Although the pancreatic enzyme supplement group showed a tendency for better outcome this did not reach statistical significance [67]. In the second small study by Patankar *et al.* there was also no significant difference in laboratory or clinical outcomes [68]. Therefore, no conclusion can be drawn, but enzyme supplementation should be considered in patients with proven or obvious PEI and malabsorption with steatorrhea.

3.3 Acute pancreatitis – severe disease with necrosectomy (Fig. 4)

3.3.1 Oral feeding with low fat soft diet

13) 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.

(R9, grade GPP, strong consensus, 95%)

Commentary

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 [69]. After proven benefits of the "step-up" (minimally invasive approach) over the open approach for the treatment of ANP, minimally invasive techniques have been used extensively [70, 71]. To date there are limited published data on nutritional support in patients with ANP treated by the minimally invasive approach (endoscopic, radiological, or minimal invasive surgery). In a comparative trial including patients undergoing endoscopic or surgical step-up approach for infected necrotizing pancreatitis [72], all patients received oral nutrition, if tolerated. If not, a nasojejunal feeding tube was introduced and EN was started. If gastrointestinal feeding was contraindicated, the patient received PN.

3.3.2 Enteral nutrition in case of intolerance to oral feeding or insufficiency of oral feeding

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

(R10, grade B, strong consensus, 91%)

Commentary

See commentary to recommendation 10. In the RCT by Bakker et al. [43], showing no superiority of early (first 24 hours) nasojejunal tube feeding when compared with an oral diet after 72 hours, interventional procedures included percutaneous catheter drainage, endoscopic transgastric drainage or necrosectomy and surgical necrosectomy (invasive or open approach). The authors did not find any difference in the number of patients who underwent interventions between the groups. 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 [64]. In one prospective study on video-assisted retroperitoneal debridement, 40 patients were fed by nasojejunal tube as the preferred route when tolerated; otherwise, PN was given [65]. Therefore, based on small series, nasojejunal feeding seems safe in patients having undergone minimally invasive necrosectomy.

3.3.3 Complementary or exclusive parenteral nutrition in case of intolerance to enteral nutrition

15) Parenteral nutrition 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 enteral nutrition.

(R11, grade GPP, strong consensus, 94%)

Commentary

See commentary to recommendations 10 and 11.

3.3.4 Measurement of intra-abdominal pressure

16) In patients with severe acute pancreatitis and intra-abdominal pressure < 15 mmHg early enteral nutrition shall be initiated via nasojejunal, as the preferred route, or nasogastric tube. Intra-abdominal pressure and the clinical condition of patients during enteral nutrition shall be monitored continuously.

(R12, grade A, strong consensus, 91%)

Commentary

Although, it has been clearly demonstrated that EN in patients with severe AP reduces mortality and infectious complications, it has been reported to potentially increase intraluminal pressure with subsequent elevation of intra-abdominal pressure (IAP) and development of severe complications [73, 74]. In an observational study, 274 patients with AP had intra-abdominal hypertension (IAH) and 103 developed an acute compartment syndrome (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 [76].

17) In patients with severe acute pancreatitis and intra-abdominal pressure > 15 mmHg enteral nutrition should be initiated via nasojejunal route starting at 20 mL/hour, increasing the rate according to the tolerance. Temporary reduction or discontinuation of enteral nutrition should be considered when intra-abdominal pressure values further increase under enteral nutrition.

(R13, grade B, strong consensus, 94%)

Commentary

Because the majority of patients with IAH present digestive intolerance, EN should be initiated with caution via nasojejunal tube, starting at 20ml/min and increasing the rate progressively, according to the IAP measurement [77].

18) In patients with severe acute pancreatitis and intra-abdominal pressure > 20 mmHg or in the presence of acute compartment syndrome, enteral nutrition should be (temporarily) stopped and parenteral nutrition should be initiated.

(R14, grade GPP, strong consensus, 94%)

Commentary

In patients with IAP above 20 mmHg or in the presence of ACS, EN should be stopped and total PN should be initiated [74].

3.3.5 Open abdomen

19) In patients with severe acute pancreatitis and open abdomen enteral nutrition should be administered, at least in a small amount. If required for achievement of nutritional requirements, supplementary or total parenteral nutrition should be added.

(R15, grade B, strong consensus, 97%)

Commentary

A decompressive laparotomy (laparostomy) may be necessary in up to 74% of patients who develop ACS during course of AP [78]. Several cohort studies reported that initiation and feeding by EN was feasible and safe despite a relatively high rate of digestive

intolerance, ranging from 48-67% [79-84]. Two studies concluded that that early EN in patients with an open abdomen resulted in higher fascial closure rates, lower fistula rates, reduced nosocomial infections and lower hospital costs [83, 84].

4 Chronic pancreatitis (Fig. 5)

20) Risk of malnutrition in chronic pancreatitis is high and malnutrition is common in patients with chronic pancreatitis.

(S2, strong consensus, 100%)

Commentary

Malnutrition is often a late, but important manifestation in the course of CP and depends on the intensity and duration of the underlying disease. 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[4, 85].

Despite the inconsistency of the data there is an evident risk of malnutrition in patients with CP [86-88]. 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 [89]. Similarly, 26% underweight patients with a nutritional risk were identified in a study of outpatients with CP [90].

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[91-93]. In addition, PEI leads to the increased risk of developing significant bone loss and severe osteoporosis [94, 95]. A recent prospective study [93] 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).

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

(S3, strong consensus, 97%)

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 [96]. 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 [97]. 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 [96].

4.1 Diagnostics

4.1.1 Evaluation of nutritional status and screening for micro- and macronutrient deficiencies (Fig. 6)

22) Nutritional status should be assessed according to symptoms, organic functions, anthropometry, and biochemical values. Solely body mass index should not be used, because it does not register sarcopenia in the obese patient with chronic pancreatitis.

(R19, grade GPP, strong consensus, 97%)

Commentary

Studies assessing malnutrition have identified many biochemical factors that are associated with malnutrition [98, 99] 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 [90], 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 [91]. 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 [100]. 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.

23) 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.

(R20, grade GPP, strong consensus, 100%)

Commentary

Patients with CP are at high risk of malnutrition, both in terms of body weight and altered body composition [91]. This has an impact on quality of life [90] and survival after surgery [101, 102]. Nutritional intervention can improve nutritional markers and is associated

with reduced pain [103] 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 PEI, these are diverse in presentation with some studies reporting biochemical deficiencies [91, 94, 104] and case reports document clinical manifestations including night blindness [105, 106]. 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.

4.1.2 Check for exocrine insufficency and pancreatic enzyme replacement therapy (Fig. 7)

24) When pancreatic exocrine insufficiency is diagnosed through clinical signs and symptoms and/or laboratory tests of malabsorption, pancreatic enzyme replacement therapy shall be initiated. An accurate nutritional assessment is mandatory to detect signs of malabsorption.

(R34, grade A, strong consensus, 100%)

Commentary

The most frequent clinical sign of PEI is steatorrhea [107], 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 [108].

PEI is consistently associated with biochemical and clinical signs of malnutrition Management of PEI involves replacing the inadequate pancreatic enzymes, which should be used to maintain weight and improve the symptoms of maldigestion [109, 110].

Awareness of PEI among many physicians is poor outside of referral centers and especially among physicians in primary care [111, 112]. Nevertheless, untreated PEI has also a deleterious impact on the quality of life of patients [113]. It is recommended that enzyme replacement is started when clinical signs of malabsorption, or anthropometric and/or biochemical signs of malnutrition are present [87, 114-117]. Symptoms include weight loss, alteration of body compartments at bioimpedance analysis, and low nutritional markers (albumin, cholinesterase, prealbumin, retinol-binding protein, and magnesium) [114, 118-121].

25) pH-sensitive, enteric-coated microspheres pancreatic enzyme replacement preparations shall be used for treating pancreatic exocrine insufficiency.

(R35, grade A, strong consensus, 100%)

Commentary

Several factors affect the efficacy of pancreatic enzyme supplementation: (i) mixture with meal; (ii) gastric emptying with meal; (iii) mixing with chyme and bile acids and rapid release of enzymes in duodenum [122].

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 [122-124].

The efficacy of these more recent formulations has been demonstrated in several recent studies [125-128] and in a recent meta-analysis [108]. 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 [129]. 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 [130]. 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 [131].

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

(R36, grade B, strong consensus, 100%)

Commentary

The efficacy of pancreatic enzyme supplements presupposes the mixing of enzymes and chyme [123]. While one study evaluating the impact of the scheduling of pancreatic enzyme replacement therapy (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 [132]. 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 [124, 132]. 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).

27) 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.

(R37, grade A, strong consensus, 100%)

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 [133]. 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 PERT 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 [127, 128, 132, 134-136]. 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 [137, 138].

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 [139].

28) Pancreatic enzymes should be supplemented in patients requiring enteral nutrition, if signs of exocrine failure manifest.

(R31, grade GPP, strong consensus, 100%)

Commentary

In patients with exocrine failure, who do not improve with semi-elemental formulae, pancreatic enzymes can be administered with the formula [140]. 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.

29) The efficacy of pancreatic enzyme replacement therapy 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).

(R38, grade B, strong consensus, 97%)

Commentary

The aforementioned recent meta-analysis including 14 RCTs [108] 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 [126, 141]. A review of reported data [98] 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 [142].

In patients who do not respond, pancreatic function tests [108] 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 [143].

30) In case of unsatisfactory clinical response, pancreatic enzyme replacement therapy dosage should be increased or a protein pump inhibitor should be added. If these methods fail, other causes of malabsorption such as small intestinal bacterial overgrowth should be excluded.

(R39, grade B, strong consensus, 97%)

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 [108]. 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 [139].

The inhibition of gastric acid secretion by proton pump inhibitors (PPI) 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) [144]. Nevertheless, a review including 34 clinical trials failed to show improvement in the efficacy of PERT with PPI or histamine-2 receptor antagonists [145]. It is noteworthy that the populations included and the therapeutic schemes were very heterogeneous, therefore, suggesting significant bias.

Small intestinal bacterial overgrowth (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 [146].

31) Long-term pancreatic enzyme replacement therapy and nutritional status are similarly affected by all surgical procedures. Tissue-preserving procedures shall be preferred.

(R40, grade A, strong consensus, 100%)

Commentary

Common indications for surgical intervention in CP include poorly controlled pain, duodenal, biliary and pancreatic duct obstruction, and suspicion of cancer [147].

Surgery for CP can be broadly classified into three categories: drainage procedures, partial pancreatic resection including or not the duodenum, and total pancreatectomy.

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 [148, 149].

Meta-analyses showed better postoperative pain relief and improved quality of life with the Beger procedure compared with conventional pancreaticoduodenectomy [150, 151]. 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 [152].

A 2015 meta-analysis of 23 studies compared outcomes of the Frey procedure with pancreaticoduodenectomy and the Berger procedure [153]. 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 [154].

4.1.3 Diagnosis and management of bone diseases (Fig. 8)

32) Patients with chronic pancreatitis 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).

(S6, strong consensus, 97%)

Commentary

A systematic review and meta-analysis including ten studies revealed, 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%) [155]. Two of the included studies revealed osteoporosis rate for controls respectively 8.6 and 10.2%. 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 [156].

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) [157]. 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) [158]. 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).

33) Basic preventive measures should be advised to all patients with chronic pancreatitis 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.

(R42, grade GPP, strong consensus, 97%)

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 [110]. In patients with osteopenia it is recommended to repeat the dual-energy X-ray absorptiometry (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].

34) Dual-energy X-ray absorptiometry shall be used to identify patients with chronic pancreatitis with osteopathy.

(R41, grade A, strong consensus, 100%)

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 [159]. 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 [160]. 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 [161], a baseline bone density assessment for all patients with CP may be worth considering.

4.2 Nutritional management

4.2.1 Oral nutrition (Fig. 9)

4.2.1.1 Well-nourished patients without deficiencies

35) Patients with chronic pancreatitis do not need to follow a restrictive diet.

(S4, strong consensus, 94%)

36) Chronic pancreatitis patients with a normal nutritional status should adhere to a well-balanced diet.

(R21, grade GPP, strong consensus, 94%)

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 [95, 111]. International guidelines are consistent in their recommendation that patients should have a balanced diet and avoid fat restriction [4, 162-165]. 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) [166] 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 [167] 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 [103]. Improvements in nutritional status

and pain control were observed in patients receiving nutritional intervention and the authors did not report any adverse events [103].

37) In patients with chronic pancreatitis, diets very high in fiber should be avoided.

(R23, grade B, strong consensus, 91%)

Commentary

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 [168].

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

(S5, strong consensus, 100%)

4.2.1.2 Malnourished patients

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

(R22, grade GPP, strong consensus, 94%)

Commentary

See commentary to recommendation 36.

40) 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.

(R26, grade GPP, strong consensus, 95%)

Commentary

The reported prevalence of deficiency of fat-soluble vitamins is 3–14.5% for vitamin A deficiency [91, 94, 169], 58–77.9% for vitamin D deficiency [91, 94, 169, 170], 9-24% for vitamin E deficiency [91, 94, 98, 169, 170] and 13–63% for vitamin K deficiency [91, 94, 169, 170]. 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 [91]. 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 [94]. 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%) [114].

Thiamine deficiency secondary to concomitant alcoholism must be considered [98].

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 [98] and magnesium [114] have been observed. Furthermore, low magnesium concentrations seemed to correlate with exocrine failure [114].

4.2.2 Oral nutritional supplements (Fig. 9)

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

(R24, grade GPP, strong consensus, 100%)

Commentary

Very few studies have investigated the benefit of oral nutritional supplements (ONS) in patients with CP. Eighty percent of patients can be treated with diet and enzyme supplementation, the rest need oral supplementation [87]. 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.

42) If adequate enzyme supplementation and exclusion of bacterial overgrowth has not led to relief of malabsorption and its accompanying symptoms, oral nutritional supplements with medium chain triglycerides can be administered.

(R25, grade 0, strong consensus, 97%)

Commentary

There are no RCTs investigating the relative efficacy of different formulae (e.g. standard or peptide-based with medium chain triglycerides (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 [171]. 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 [171, 172]. One RCT investigated the efficacy of ONS in patients with CP and severe malnutrition [103]. 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.

4.2.3 Enteral nutrition (Fig. 10)

43) Enteral nutrition should be administered in patients with malnutrition who are not responding to oral nutritional support.

(R27, grade GPP, strong consensus, 100%)

Commentary

Oral nutritional support with dietary counselling is usually sufficient to improve nutritional status in patients with CP [105]. EN is indicated in approximately 5% of patients with CP [90]. Regarding indications and outcomes of EN in these patients, evidence is based on few cohort studies and RCTs are generally lacking [4].

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

(R28, grade GPP, strong consensus, 100%)

Commentary

Four retrospective series have shown the benefits of EN in patients with CP regarding weight gain and pain control [173-176]. Two of them included 58 [174] and 50 patients [176] respectively, in whom a naso-jejunal tube was placed.

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

(R30, grade GPP, strong consensus, 94%)

Commentary

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 [177]. In two of the aforementioned studies [174, 176], 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.

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

(R29, grade GPP, strong consensus, 97%)

Commentary

Long-term access with a percutaneous endoscopic gastrostomy with jejunal extension or a direct percutaneous endoscopic jejunostomy was used in 57 [173] and 58 patients [175].

All studies showed that this type of nutritional support was safe and effective in patients with CP, even in case of gastric outlet syndrome [175, 176].

4.2.4 Parenteral nutrition (Fig. 10)

47) Parenteral nutrition may be indicated in patients with gastric outlet obstruction and in those with complex fistulating disease, or in case of intolerance of enteral nutrition.

(R32, grade GPP, strong consensus, 100%)

Commentary

PN is infrequently uses in patients with CP [4, 88]. 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 [87, 165]. 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.

48) For parenteral nutrition the preferable route is central venous access.

(R33, grade GPP, strong consensus, 100%)

Commentary

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.

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 with legitimate interest upon request to the ESPEN executive.

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Figure legends

Figure 1

Nutritional management of acute pancreatitis. AP, acute pancreatitis.

Figure 2

Management of mild to moderate acute pancreatitis. AP, acute pancreatitis; EN, enteral nutrition; NRS-2002, Nutritional Risk Screening – 2002; PN, parenteral nutrition.

Figure 3

Management of severe pancreatitis. AP, acute pancreatitis; EN, enteral nutrition; PEI, pancreatic exocrine insufficiency; PN, parenteral nutrition.

Figure 4

Management of severe pancreatitis with necrosectomy. ACS, abdominal compartement syndrome; AP, acute pancreatitis; EN, enteral nutrition; IAP, intra-abdominal pressure; PN, parenteral nutrition.

Figure 5

Nutritional management of chronic pancreatitis. CP, chronic pancreatitis; EN, enteral nutrition; ONS, oral nutritional supplements; PEI, pancreatic exocrine insufficiency; PERT, pancreatic enzyme replacement therapy; PN, parenteral nutrition.

Figure 6

Evaluation of nutritional status and screening for micro- and macronutrient deficiencies in chronic pancreatitis. CP, chronic pancreatitis; DXA, dual energy X-ray absorptiometry.

Figure 7

Check for pancreatic exocrine insufficiency and pancreatic enzyme replacement therapy in chronic pancreatitis. EN, enteral nutrition; PEI, pancreatic exocrine insufficiency; PERT,

pancreatic enzyme replacement therapy; PPI, proton pump inhibitor; SIBO, small intestinal bacterial overgrowth.

Figure 8

Diagnosis and management of bone diseases. CP, chronic pancreatitis; DXA, dual energy X-ray absorptiometry.

Figure 9

Oral nutritional management of chronic pancreatitis. CP, chronic pancreatitis; MCT, medium chain triglycerides; ONS, oral nutritional supplements.

Figure 10

Management of malnourished patients with chronic pancreatitis in whom oral nutrition is insufficient. CP, chronic pancreatitis; EN, enteral nutrition; MCT, medium chain triglycerides; PN, parenteral nutrition.

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Fig. 1

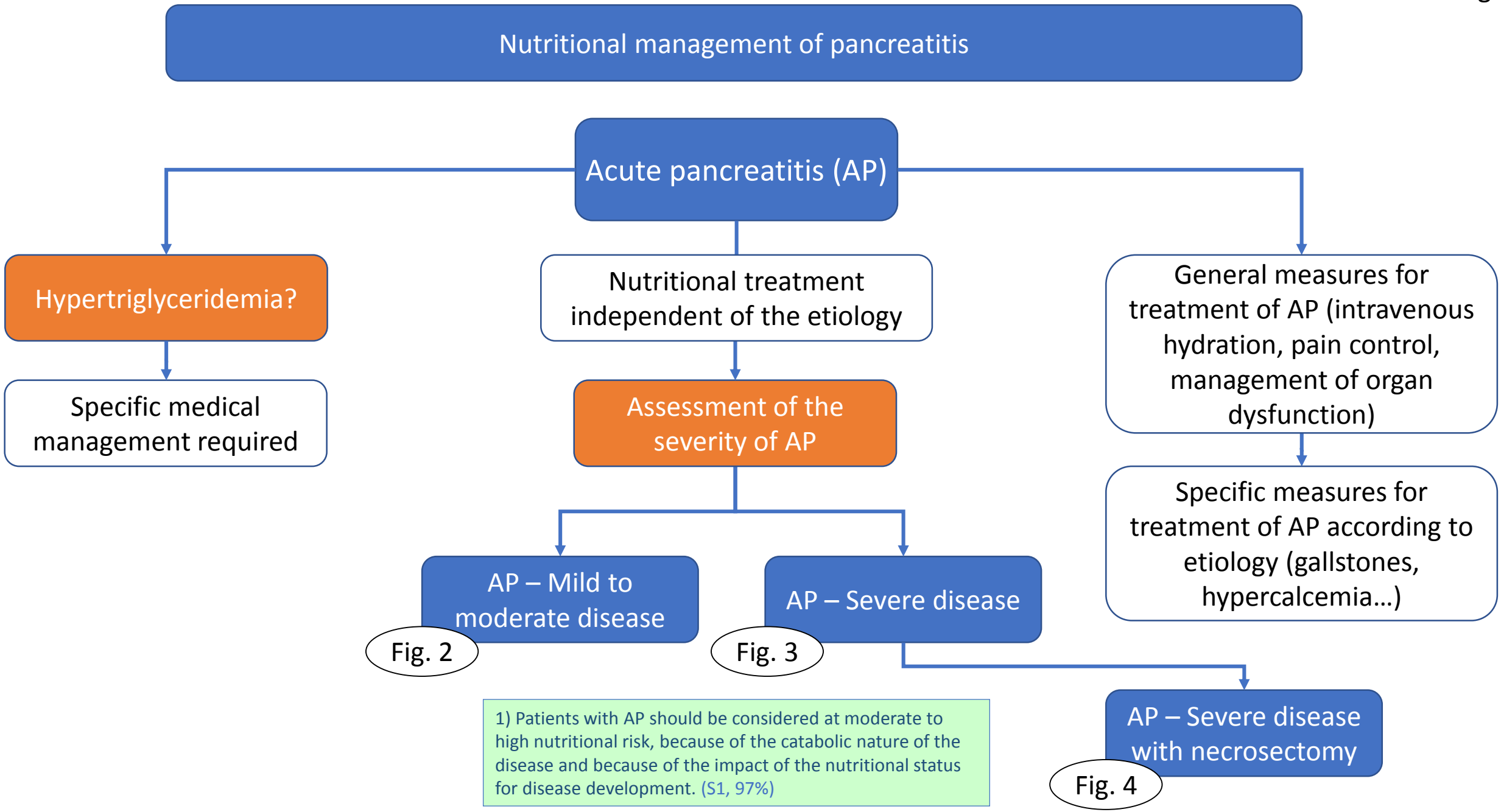

Nutritional management of pancreatitis
Acute pancreatitis (AP)
Hypertriglyceridemia?
Specific medical management required
Nutritional treatment independent of the etiology
Assessment of the severity of AP
AP – Mild to moderate disease
Fig. 2
AP – Severe disease
Fig. 3
AP – Severe disease with necrosectomy
Fig. 4
General measures for treatment of AP (intravenous hydration, pain control, management of organ dysfunction)
Specific measures for treatment of AP according to etiology (gallstones, hypercalcemia…)
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. (S1, 97%)

Fig. 2

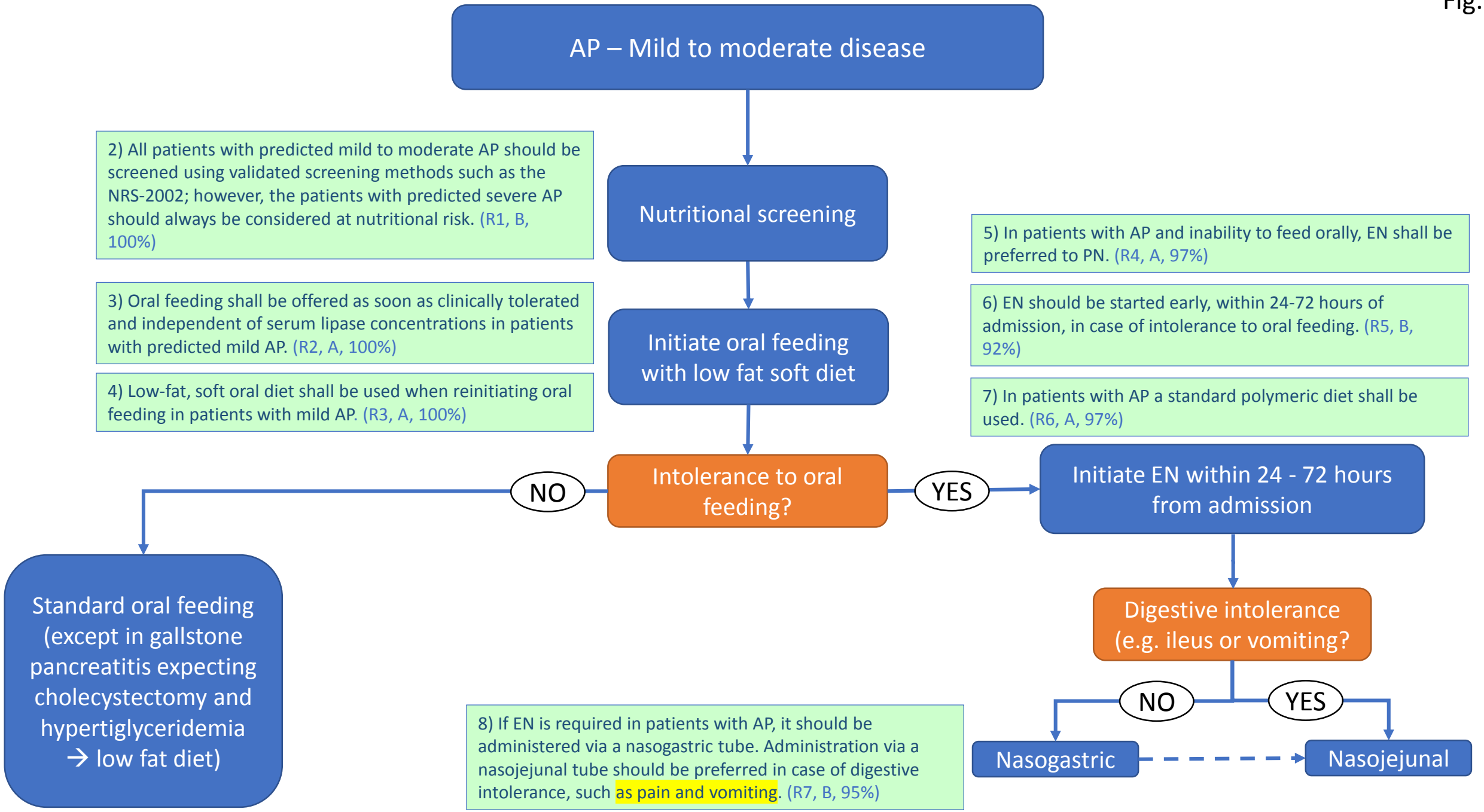
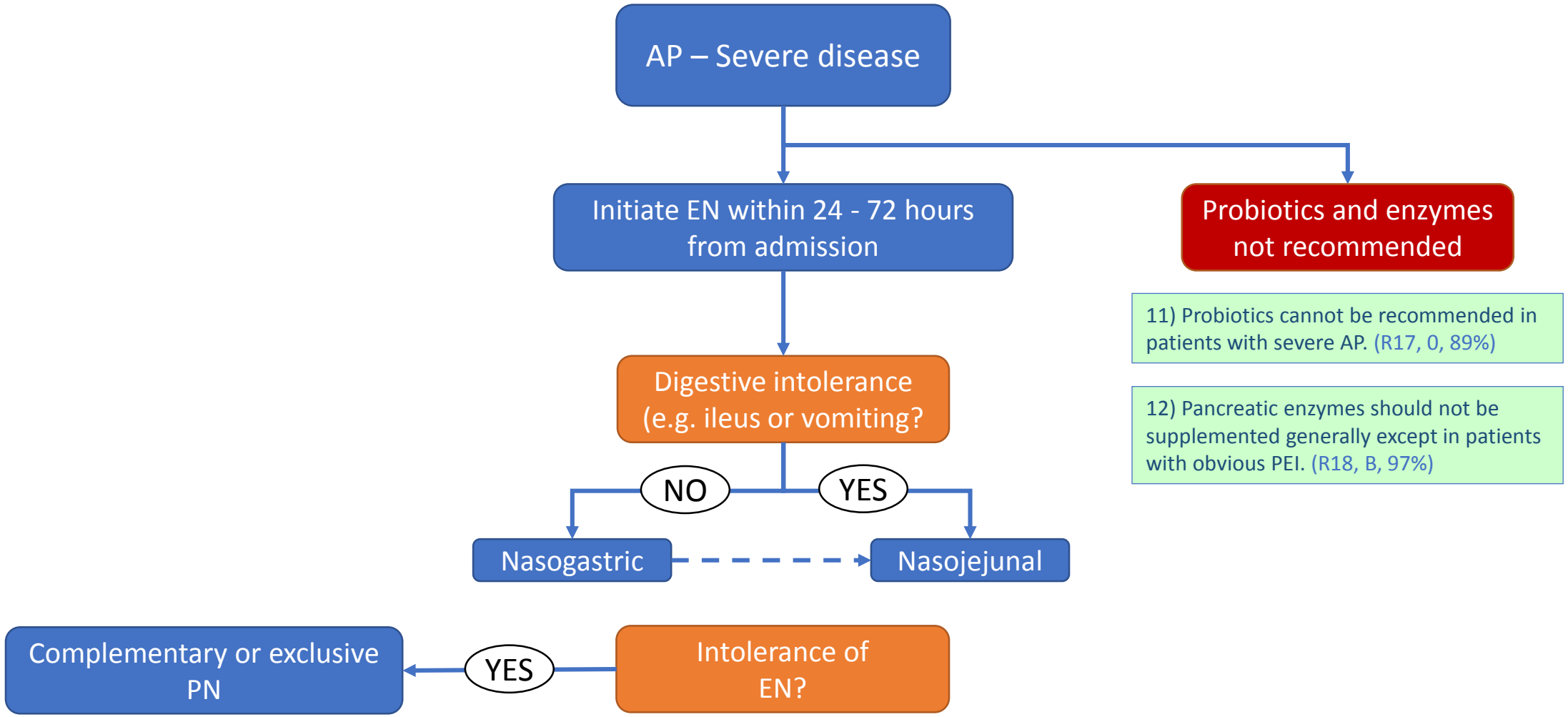

AP – Mild to moderate disease
Nutritional screening
2) All patients with predicted mild to moderate AP should be screened using validated screening methods such as the NRS-2002; however, the patients with predicted severe AP should always be considered at nutritional risk. (R1, B, 100%)
Initiate oral feeding with low fat soft diet
3) Oral feeding shall be offered as soon as clinically tolerated and independent of serum lipase concentrations in patients with predicted mild AP. (R2, A, 100%)
4) Low-fat, soft oral diet shall be used when reinitiating oral feeding in patients with mild AP. (R3, A, 100%)
Intolerance to oral feeding?
NO
YES
Standard oral feeding (except in gallstone pancreatitis expecting cholecystectomy and hypertiglyceridemia → low fat diet)
5) In patients with AP and inability to feed orally, EN shall be preferred to PN. (R4, A, 97%)
6) EN should be started early, within 24-72 hours of admission, in case of intolerance to oral feeding. (R5, B, 92%)
7) In patients with AP a standard polymeric diet shall be used. (R6, A, 97%)
Initiate EN within 24 - 72 hours from admission
Digestive intolerance (e.g. ileus or vomiting?
NO
YES
Nasogastric
Nasojejunal
8) 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, such as pain and vomiting. (R7, B, 95%)

Fig. 3



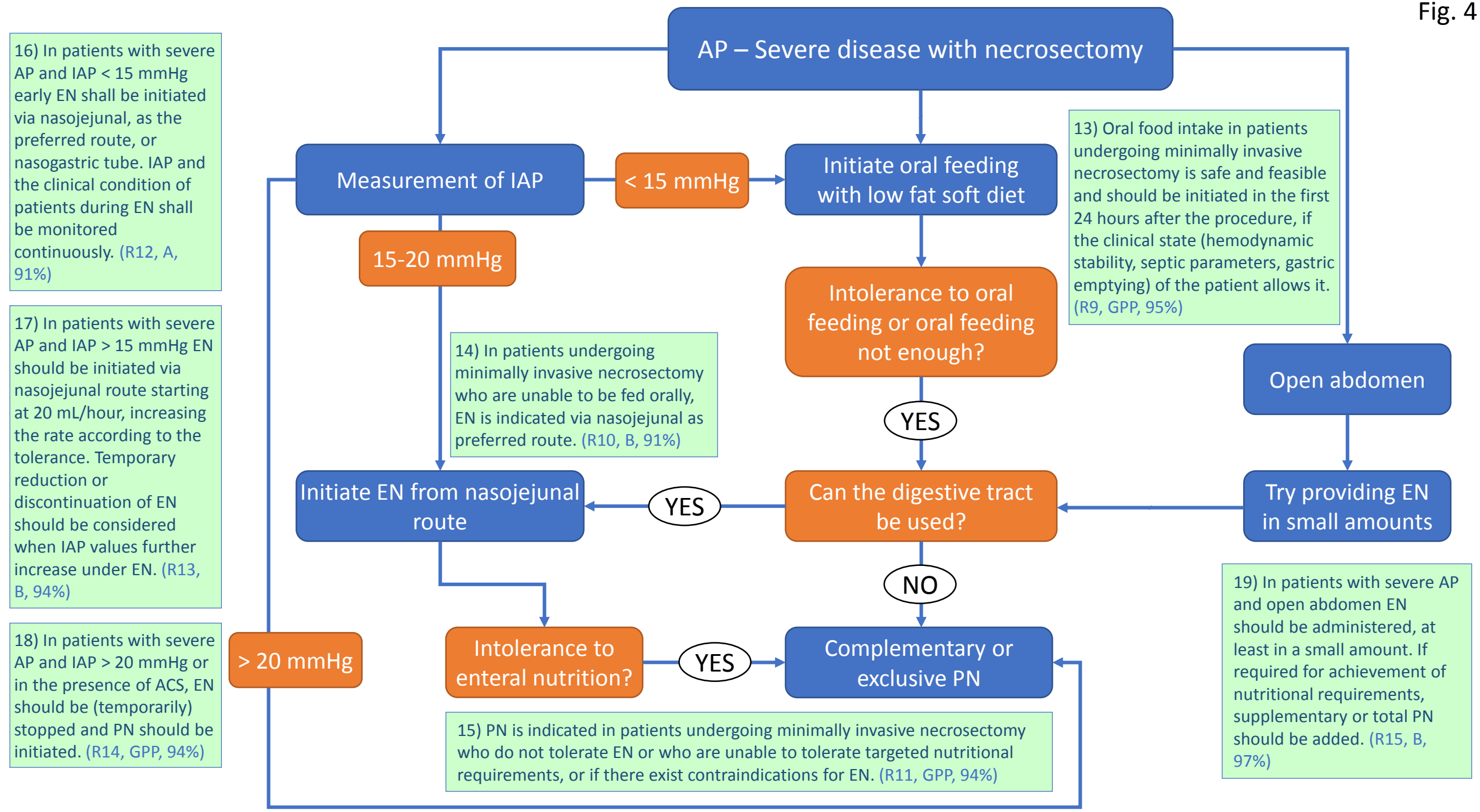
11) Probiotics cannot be recommended in patients with severe AP. (R17, 0, 89%)

12) Pancreatic enzymes should not be supplemented generally except in patients with obvious PEI. (R18, B, 97%)

9) 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. (R8, GPP, 97%)

10) 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. (R16, B, 94%)

Fig. 4


AP – Severe disease with necrosectomy
Measurement of IAP
< 15 mmHg
Initiate oral feeding with low fat soft diet
15-20 mmHg
Intolerance to oral feeding or oral feeding not enough?
YES
Initiate EN from nasojejunal route
YES
Can the digestive tract be used?
Open abdomen
Try providing EN in small amounts
NO
> 20 mmHg
Intolerance to enteral nutrition?
YES
Complementary or exclusive PN
16) In patients with severe AP and 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. (R12, A, 91%)
17) 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. (R13, B, 94%)
18) 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. (R14, GPP, 94%)
13) 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. (R9, GPP, 95%)
14) In patients undergoing minimally invasive necrosectomy who are unable to be fed orally, EN is indicated via nasojejunal as preferred route. (R10, B, 91%)
19) 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. (R15, B, 97%)
15) 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. (R11, GPP, 94%)

Nutritional management of pancreatitis

Chronic pancreatitis (CP)

20) Risk of malnutrition in CP is high and malnutrition is common in patients with CP. (S2, 100%)

21) Pancreatic insufficiency, abdominal pain, alcohol abuse, lower food intake, diabetes mellitus and smoking are the main causes of malnutrition in CP. (S3, 97%)

Diagnostics

- Evaluation of nutritional status and screening for micro- and macronutrient deficiencies — Fig. 6
- Check for PEI and PERT — Fig. 7
- Diagnosis and management of bone diseases — Fig. 8

Nutritional management

- Oral nutrition and ONS — Fig. 9
- EN and PN — Fig. 10

Evaluation of nutritional status and screening for micro- and macronutrient deficiencies

22) 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. (R19, GPP, 97%)

23) 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. (R20, GPP, 100%)

Anthropometric assessment

- Change in body weight
- Functional assessment (hand grip/sit to stand test/6 min walk
- Skin fold thickness, waist and mid-arm circumference
- Presence of ascites/edema

Biochemical assesment

- General (Na, K, Cl, liver tests, kidney function)
- Fat soluble vitamins (A, D, E, K)
- Bone health (parathyroid hormone, Ca)
- Trace elements (Mg, Se, Zn, Copper)
- Anemia screening (Hemoglobin, iron studies, ferritin, vitamin B12, folate)
- Inflammation (C-reactive protein)
- Albumin/prealbumin

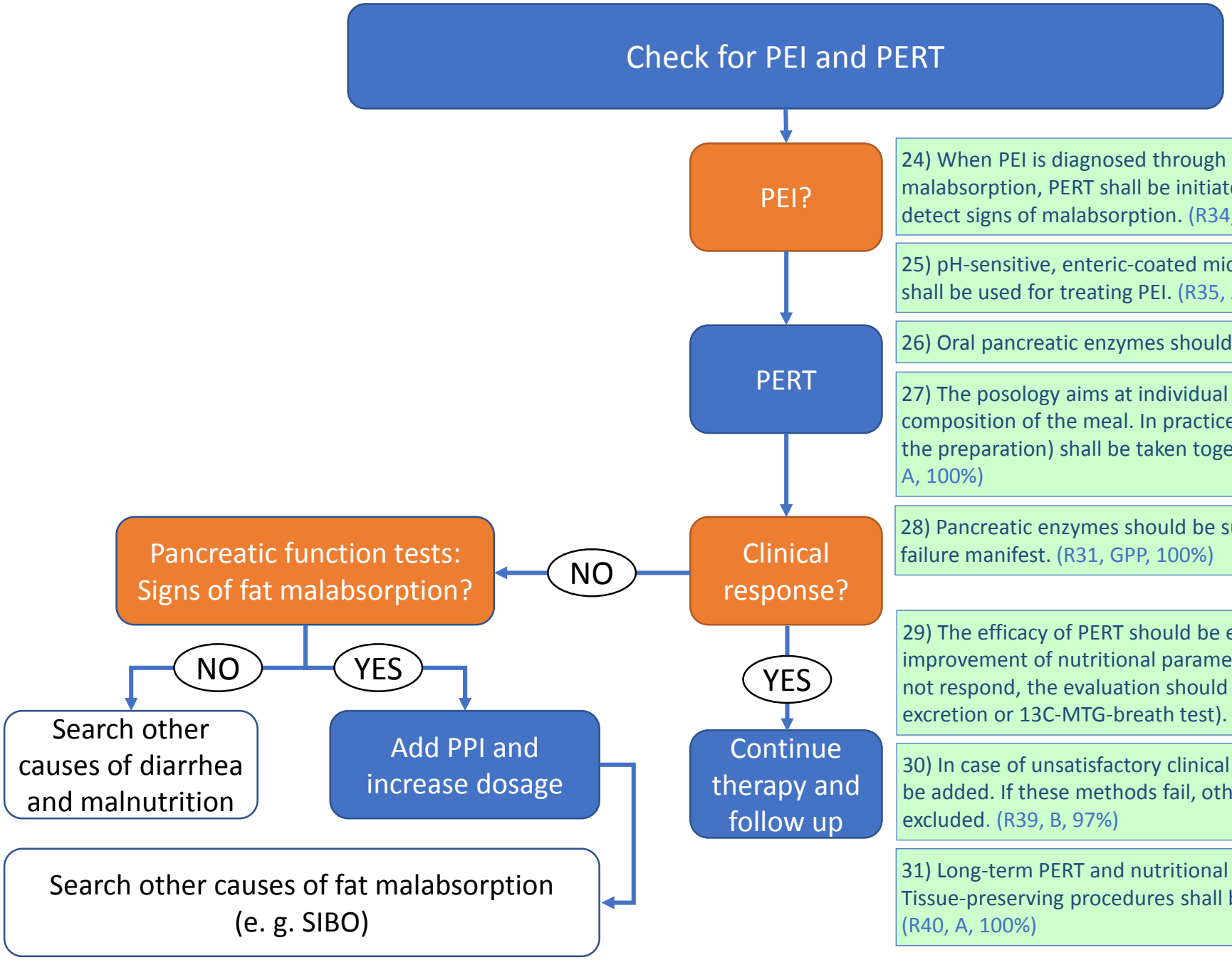
Symptom assessment

- Change in appetite and dietary intake
- Presence of symptoms that impact on oral intake (nausea/ pain / indigestion /early satiety)
- Presence of exocrine /endocrine dysfunction

Body composition

- Computed tomography / ultrasound imaging of muscle stores (muscle mass)
- DXA scanning (bone mineral density)

Fig. 7



24) 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. (R34, A, 100%)

25) pH-sensitive, enteric-coated microspheres pancreatic enzyme replacement preparations shall be used for treating PEI. (R35, A, 100%)

26) Oral pancreatic enzymes should be distributed along with meals and snacks. (R36, B, 100%)

27) 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. (R37, A, 100%)

28) Pancreatic enzymes should be supplemented in patients requiring EN, if signs of exocrine failure manifest. (R31, GPP, 100%)

29) 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 13C-MTG-breath test). (R38, B, 97%)

30) In case of unsatisfactory clinical response, PERT dosage should be increased or a PPI should be added. If these methods fail, other causes of malabsorption such as SIBO should be excluded. (R39, B, 97%)

31) Long-term PERT and nutritional status are similarly affected by all surgical procedures. Tissue-preserving procedures shall be preferred.
(R40, A, 100%)

Fig. 8

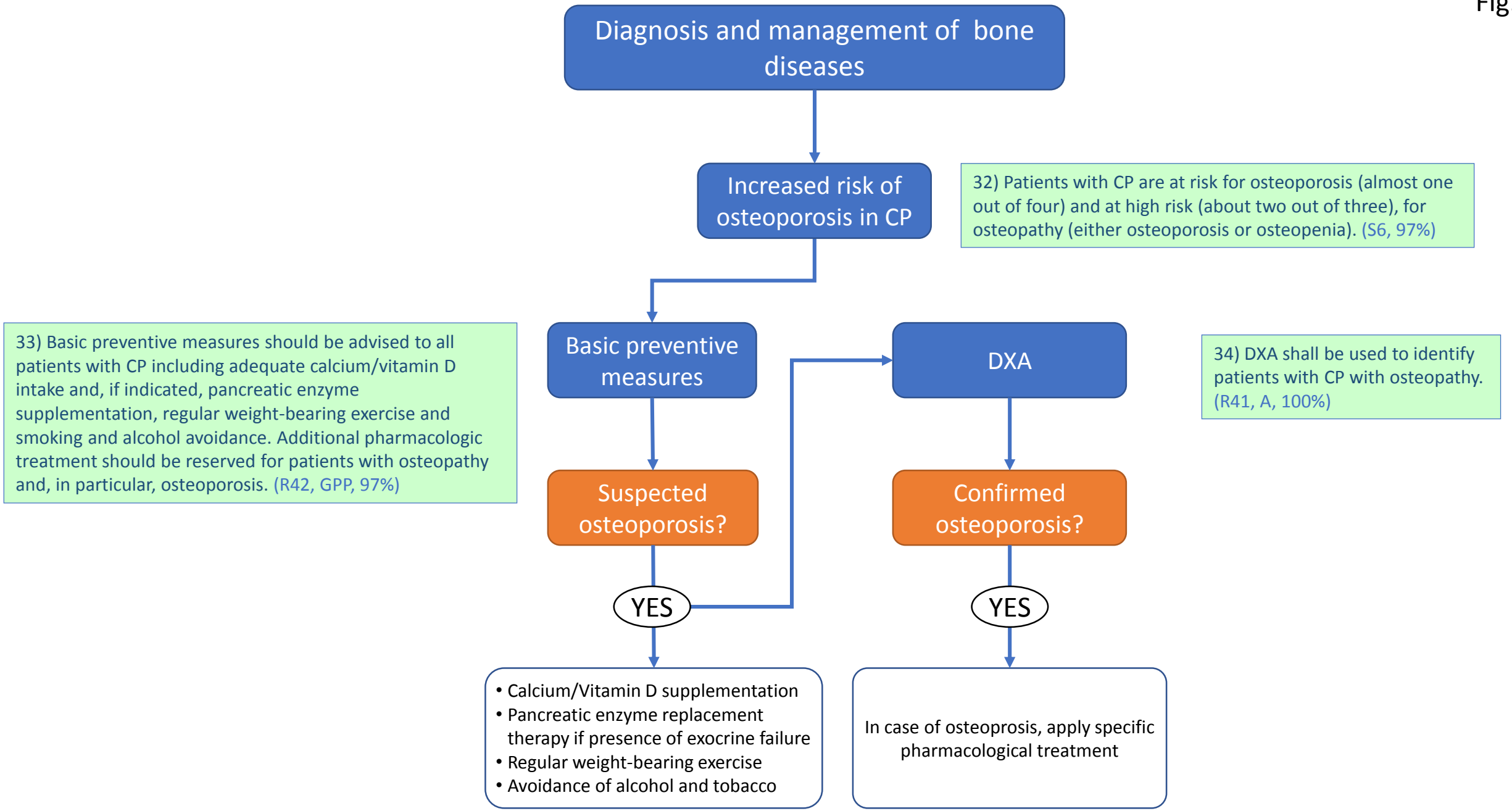

Diagnosis and management of bone diseases
Increased risk of osteoporosis in CP
32) Patients with CP are at risk for osteoporosis (almost one out of four) and at high risk (about two out of three), for osteopathy (either osteoporosis or osteopenia). (S6, 97%)
33) Basic preventive measures should be advised 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. (R42, GPP, 97%)
Basic preventive measures
DXA
34) DXA shall be used to identify patients with CP with osteopathy. (R41, A, 100%)
Suspected osteoporosis?
Confirmed osteoporosis?
YES
YES
• Calcium/Vitamin D supplementation
• Pancreatic enzyme replacement therapy if presence of exocrine failure
• Regular weight-bearing exercise
• Avoidance of alcohol and tobacco
In case of osteoprosis, apply specific pharmacological treatment

Fig. 9

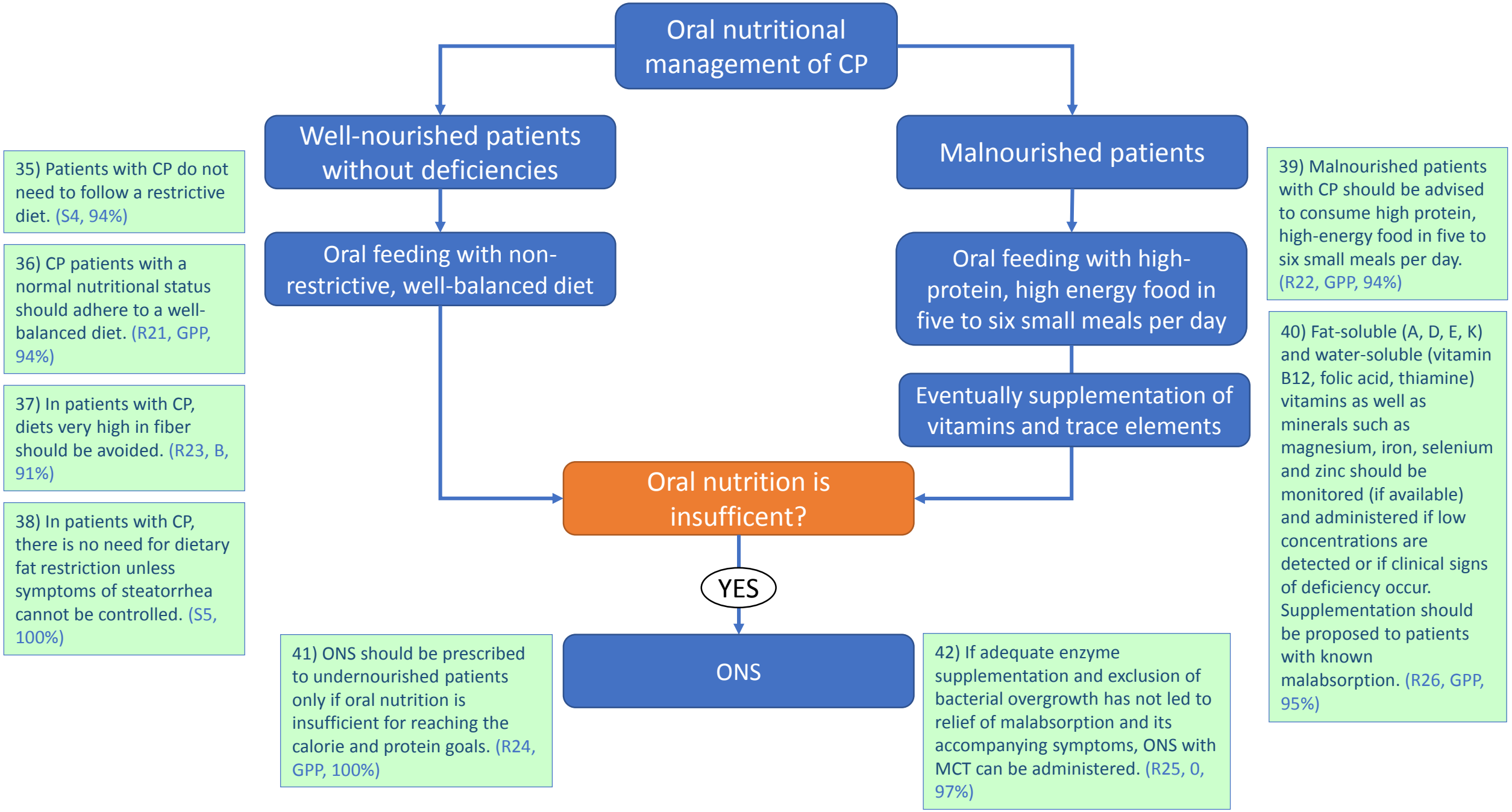
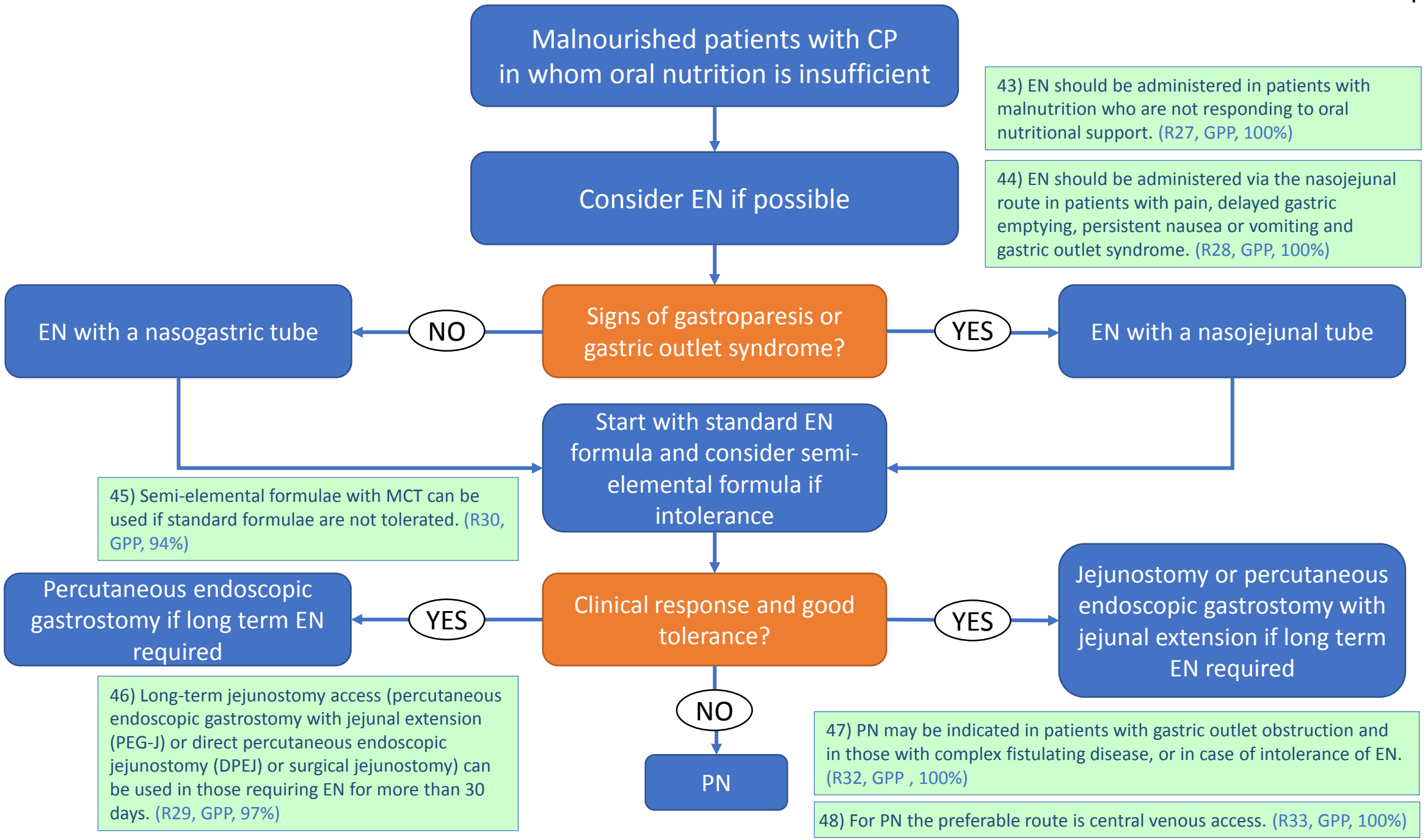

Oral nutritional management of CP
Well-nourished patients without deficiencies
Malnourished patients
35) Patients with CP do not need to follow a restrictive diet. (S4, 94%)
36) CP patients with a normal nutritional status should adhere to a well-balanced diet. (R21, GPP, 94%)
37) In patients with CP, diets very high in fiber should be avoided. (R23, B, 91%)
38) In patients with CP, there is no need for dietary fat restriction unless symptoms of steatorrhea cannot be controlled. (S5, 100%)
Oral feeding with non-restrictive, well-balanced diet
Oral feeding with high-protein, high energy food in five to six small meals per day
39) Malnourished patients with CP should be advised to consume high protein, high-energy food in five to six small meals per day. (R22, GPP, 94%)
Eventually supplementation of vitamins and trace elements
40) 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. (R26, GPP, 95%)
Oral nutrition is insufficent?
YES
ONS
41) ONS should be prescribed to undernourished patients only if oral nutrition is insufficient for reaching the calorie and protein goals. (R24, GPP, 100%)
42) 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. (R25, 0, 97%)

Fig. 10


Malnourished patients with CP in whom oral nutrition is insufficient
Consider EN if possible
Signs of gastroparesis or gastric outlet syndrome?
NO
EN with a nasogastric tube
YES
EN with a nasojejunal tube
Start with standard EN formula and consider semi-elemental formula if intolerance
Clinical response and good tolerance?
YES
Percutaneous endoscopic gastrostomy if long term EN required
YES
Jejunostomy or percutaneous endoscopic gastrostomy with jejunal extension if long term EN required
NO
PN
43) EN should be administered in patients with malnutrition who are not responding to oral nutritional support. (R27, GPP, 100%)
44) EN should be administered via the nasojejunal route in patients with pain, delayed gastric emptying, persistent nausea or vomiting and gastric outlet syndrome. (R28, GPP, 100%)
45) Semi-elemental formulae with MCT can be used if standard formulae are not tolerated. (R30, GPP, 94%)
46) 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. (R29, GPP, 97%)
47) PN may be indicated in patients with gastric outlet obstruction and in those with complex fistulating disease, or in case of intolerance of EN. (R32, GPP , 100%)
48) For PN the preferable route is central venous access. (R33, GPP, 100%)