Anaesth Crit Care Pain Med 41 (2022) 101060

Contents lists available at ScienceDirect

Anaesthesia Critical Care & Pain Medicine

journal homepage: www.elsevier.com

Guidelines

Guidelines for the management of patients with severe acute pancreatitis, 2021☆,☆☆

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☆ Validated by the SFAR Clinical Guidelines Committee on the 24th of June 2021 and by the SFAR Board of Directors on the 30th of June 2021.

☆☆ Guidelines issued by the French Society of Anaesthesia and Intensive Care Medicine (Société française d'anesthésie et de réanimation - SFAR), in collaboration with: the French National Society of Gastroenterology (Société nationale française de gastro-entérologie - SNFGE), the French Association of Surgery (Association française de chirurgie - AFC), the French Society of Radiology (Société française de radiologie - SFR), the French Speaking Society of Clinical Nutrition and Metabolism (Société francophone de nutrition clinique et métabolisme - SFNCM), and the French Society of Digestive Endoscopy (Société française d'endoscopie digestive - SFED).

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https://doi.org/10.1016/j.accpm.2022.101060

ARTICLE INFO

Historique de l'article :
Available online 25 May 2022

ARTICLE INFO

Historique de l'article :
Available online 25 May 2022

Keywords:
Guidelines
Severe acute pancreatitis
Acute respiratory distress syndrome
Sepsis
Intensive care unit
Critical care

ABSTRACT

Objective: To provide guidelines for the management of the intensive care patient with severe acute pancreatitis.
Design: A consensus committee of 22 experts was convened. A formal conflict-of-interest (COI) policy was developed at the beginning of the process and enforced throughout. The entire guideline construction process was conducted independently of any industrial funding (*i.e.* pharmaceutical, medical devices). The authors were required to follow the rules of the Grading of Recommendations Assessment, Development and Evaluation (GRADE®) system to guide assessment of quality of evidence. The potential drawbacks of making strong recommendations in the presence of low-quality evidence were emphasised.
Methods: The most recent SFAR and SNFGE guidelines on the management of the patient with severe pancreatitis were published in 2001. The literature now is sufficient for an update. The committee studied 14 questions within 3 fields. Each question was formulated in a PICO (Patients Intervention Comparison Outcome) format and the relevant evidence profiles were produced. The literature review and recommendations were made according to the GRADE® methodology.
Results: The experts' synthesis work and their application of the GRADE® method resulted in 24 recommendations. Among the formalised recommendations, 8 have high levels of evidence (GRADE 1+/−) and 12 have moderate levels of evidence (GRADE 2+/−). For 4 recommendations, the GRADE method could not be applied, resulting in expert opinions. Four questions did not find any response in the literature. After one round of scoring, strong agreement was reached for all the recommendations.
Conclusions: There was strong agreement among experts for 24 recommendations to improve practices for the management of intensive care patients with severe acute pancreatitis.

Introduction

Acute pancreatitis is a frequent pathology, with prevalence of around 30/100,000 male inhabitants and 20/100,000 female inhabitants in western countries, corresponding in France to about 15,000 cases each year.

Acute pancreatitis involves inflammation of the pancreas ranging from a simple oedema to necrosis by intraglandular activation of the pancreatic enzymes. Its evolution is marked by two phases:

- initial (first week), accompanied by organ dysfunction(s) and failure(s);
- delayed (after the first week), accompanied by local complications (infected necrosis, abscess, or pseudocyst formation...).

In most cases (80–90%), acute pancreatitis is a disease of moderate severity (interstitial oedematous acute pancreatitis). On the other hand, in 10–20% of cases acute pancreatitis is severe and may necessitate resuscitation.

Organ failure and/or local complications (necrosis, infectious hematopoietic necrosis, or pseudocyst) characterise severe acute pancreatitis.[1]

The main complications of severe acute pancreatitis are the following:[1]

1 Organ failure and systemic complications of acute pancreatitis:
   - Respiratory: PaO2/FiO2 $<$ 300 mmHg
   - Cardiovascular: systolic arterial pressure $<$ 90 mmHg without response to vascular loading, without catecholamine or pH $<$ 7.3
   - Renal: creatinine $>$ 170 μmol/L
2 Local complications of acute pancreatitis:
   - Fluid collection
   - Pancreatic pseudocyst
   - Pancreatic necrosis (isolated or not)

Notwithstanding the numerous controversies that have arisen in the literature, the broad outlines for treatment and management of severe acute pancreatitis have been established. That said, the most recent SFAR-SNFGE guidelines on treatment of severe acute pancreatitis patients date back to 2001, while new international guidelines were published in 2013.[2] Given the many studies published and advances in critical care over the last 20 years, particularly as regards severe acute pancreatitis, it appeared necessary to update the previous guidelines. The objectives of these new guidelines are not only to propose criteria for admission to critical care of adult patients with severe acute pancreatitis, but also to consider treatment modalities during the initial phase and according to progressive complications.

Our recommendations have been constructed in accordance with the GRADE® method and are for the most part based on evidence from the international literature. They have been designed by multidisciplinary expert teams, the objective being to create an updated and validated instrument to assist clinicians in treatment of critical care patients presenting with severe acute pancreatitis.

Methodology

During an initial, introductory phase, it was along with the expert coordinators that the organising committee decided on the questions to be formulated and designated the experts in charge of each. The questions were formulated in accordance with the PICO format (Patients, Intervention, Comparison, Outcome). Extensive bibliographic research was carried out on the PubMed and Cochrane data bases. To be selected for analysis, publications had to have taken place after 2000 and been in English or French language.

[1] Working Group IAPAPAAPG. IAP/APA evidence-based guidelines for the management of acute pancreatitis. Pancreatology 2013 Jul-Aug; 13(4 Suppl 2):e1–15.

[2] Conférence de consensus: pancréatite aiguë. Gastroenterol Clin Biol 2001;25(2):177–92.

General introduction to the GRADE® method

The different recommendations were elaborated in accordance with the GRADE® method, through which it is possible, following qualitative and quantitative analysis of the literature, to initially determine the quality of the evidence, and subsequently estimate the confidence one may have in the quantitative analysis, the objective being to propose a level of recommendation. There exist four categories of level of evidence:

- High: Future research will likely not modify confidence in treatment effect estimation.
- Moderate: Future research will probably modify confidence in the effect estimation and could modify the estimation itself.
- Low: Future research will likely have an impact on confidence in the effect estimation and will probably modify estimation of the effect itself.
- Very low: The effect estimation is of uncertain validity.

Analysis of the quality of evidence will be carried out for each criterion of evaluation, after which an overall or global level of evidence will be determined, based on the quality of evidence concerning the crucial criteria.

The final formulation of the recommendations is invariably binary: either positive or negative, and either strong or weak:

- Strong: it is recommended/it is not recommended (GRADE 1+ or 1−).
- Weak: it is probably recommended/it is probably not recommended (GRADE 2+ or 2).

General introduction to the GRADE Grid method

The strength of a recommendation is determined according to five key factors and validated by the experts following a vote, using the GRADE Grid method:

- Estimate of the effect.
- Overall level of evidence: The higher the level of evidence, the more probable a ''strong'' recommendation.
- The balance between desirable and undesirable effects: The more favorable the balance, the more probable a ''strong'' recommendation.
- Values and preferences: In the event of uncertainty or pronounced variability, the probability of a ''weak'' recommendation will be high; values and preferences shall be ascertained to the greatest possible extent through the good offices of the concerned persons (patient, physician, decision-maker).
- Costs: The higher the costs or the greater the use of resources, the more probable a ''weak'' recommendation.

To validate a recommendation, at least 50% of the participants had to express an opinion, while fewer than 20% preferred an opposed proposition. For a recommendation to be ''strong'', at least 70% of the participants had to agree. If the experts were not in possession of any study dealing precisely with the subject, or if no data on the main evaluation criterion existed, no recommendation was issued. In its formulation, an expert opinion was clearly distinguished from the recommendations. Only if more than 70% of the participants agreed was an expert opinion validated.

Results

The fields of the recommendations

We chose to address 14 questions divided into three fields. The questions were selected for three different reasons: (a) They seemed particularly important; (b) They touched on areas where significant progress has been made since the preceding recommendations; (c) They raised questions that were addressed in the literature. The following fields and questions were selected for data collection and analysis of the literature:

Field 1: Evaluation and admission to critical care of the adult patient

1. What are the criteria to evaluate when deciding on admission to a critical care unit of patients presenting with severe acute pancreatitis, the objective being to prevent the appearance of secondary complications?
2. In patients admitted to critical care for severe acute pancreatitis, what are the complementary examinations to be carried out within the first 72 h, the objective being to establish the etiological diagnosis?
3. In patients admitted to critical care for severe acute pancreatitis, what are the specific monitoring elements to be put into place within the first 72 h, the objective being to ensure early diagnosis of complications?

Field 2: Treatment during the initial phase

1. In patients admitted to critical care for severe acute pancreatitis, which modalities of haemodynamic treatment help to reduce morbi-mortality?
2. In patients admitted to critical care for severe acute pancreatitis, which strategies help to prevent respiratory complications?
3. In patients admitted to critical care for severe acute pancreatitis, which modalities of nutritional management help to reduce morbi-mortality?
4. In patients admitted to critical care for severe acute pancreatitis, which emergency medical and surgical interventions help to reduce morbi-mortality?
5. In patients admitted to critical care for severe acute pancreatitis, what is the role for unconventional drug (somatostatin, insulin) or non-drug (plasma exchange) therapies, the objective being to reduce morbi-mortality?
6. In patients admitted to critical care for severe acute pancreatitis, what is the analgesic treatment to administer, the objective being to reduce morbi-mortality?

Field 3: Treatment and management of progressive complications

1. In patients admitted to critical care for severe acute pancreatitis, should preventive anti-infective therapy be administered to reduce morbi-mortality?
2. In patients admitted to critical care for severe acute pancreatitis, which method(s) should be applied to establish the diagnosis of infected pancreatic necrosis?
3. In patients admitted to critical care for severe acute pancreatitis, which method(s) for drainage of infected pancreatic necrosis should be applied to reduce morbi-mortality?
4. In critical care patients in whom the evolution of severe acute pancreatitis has been complicated with infectious necrosis, which type(s) of antibiotic therapy should be applied to reduce morbi-mortality?

5. In patients admitted to critical care for severe acute pancreatitis, which method(s) should be applied to prevent and treat vascular complications?

Recommendations

Following synthesis of the expert opinions and application of the GRADE method, 24 recommendations were formalised, all of which were submitted to the expert group for rating according to the GRADE Grid method. After two rounds of grading, strong agreement was reached regarding 100% of the recommendations, among which 9 showed a strong level of evidence (GRADE 1+/−), while 11 had a moderate level of evidence (GRADE 2+/−). Regarding 4 questions, the GRADE method could not be applied, and the recommendation was based on expert opinions. It was not possible to adjudicate on 4 recommendations.

These expert guidelines supersede the preceding SFAR guidelines regarding a given field of application. The SFAR urges all intensive care physicians to comply with the guidelines to ensure high-quality patient care. When applying these recommendations, however, a practitioner is called upon to exercise his own judgement, taking into full account his field of exercise and the specificities of his establishment, the objective being to decide on the means of intervention best adapted to the state of the patient for whom he is in charge.

FIELD 1: Evaluation and admission to critical care

Question 1: What are the criteria to evaluate when deciding on admission to a critical care unit of patients presenting with severe acute pancreatitis, the objective being to prevent the appearance of secondary complications?

Experts: Eric Levesque (SFAR), Emmanuel Weiss (SFAR)

R1.1 – In patients admitted to a hospital for acute pancreatitis, it is probably recommended to apply the following criteria for admission to a critical care unit to prevent secondary complications: existence of severe acute pancreatitis (defined as a form associated with (cardiovascular, respiratory, renal) organ failure(s) with or without infectious pancreatic necrosis; or acute pancreatitis considered as at risk of becoming severe. The decision is made after multidisciplinary assessment of the patient's clinical and biological data (use of a specific score cannot presently be recommended).

GRADE 2+ (STRONG AGREEMENT)

Rationale

Among patients presenting with acute pancreatitis, around 20% develop a severe form, associated with mortality in 13 to 35% of cases [1,2]. Several classifications have been proposed to define severity of acute pancreatitis, of which the two most widely used are the RAC (Revised Atlanta Classification) and the DBC (Determinant-Based Classification) [3,4]. In the presence of at least one transitory or persistent organ failure, the two classifications categorise acute pancreatitis in 3 grades (mild, moderate, or severe for the RAC) or 4 stages (mild, moderate, severe, or critical for the DBC). The severe or critical forms are defined by persistent organ failure and/or infectious peri-pancreatic necrosis. Organ failures are categorised according to the Modified Marshall Score [5] (Table 1). Several studies have shown the severe forms to be associated with rates of complication and mortality necessitating hospitalisation in a critical care unit [6–10]. It is consequently essential, prior to organ failure(s), to identify the patients presenting a potentially severe form (Fig. 1).

Numerous biological markers have been retained as predictive factors for severity of acute pancreatitis. For many specialists, C-reactive protein (CRP) is considered as the reference in estimation of the severity of acute pancreatitis; CRP > 150 mg/L during the 72 h following admission may be utilised as a prognostic factor for severe forms [11].

There exists no prognostic score sufficiently reliable to predict the occurrence of severe acute pancreatitis [12]. The list of criteria and scores helping to determine the risk of aggravation of acute pancreatitis is presented in **Appendix 1**. The BISAP (Bedside index of severity of acute pancreatitis score) is in all probability the most apt to predict occurrence of severe acute pancreatitis. It brings together five criteria for daily evaluation [13]; the presence of at least two of them is predictive of occurrence of a severe form [13]. Among these criteria, persistent systemic inflammatory response syndrome is a particularly identifiable risk factor for mortality [14].

The revised Atlanta classification distinguishes oedematous acute pancreatitis (80–85% of cases), which is ordinarily not severe, from acute necrotising pancreatitis, which is characterised by necrosis of the pancreatic gland and/or the peri-pancreatic tissues (also known as infection of the pancreatic necrosis). Abdominopelvic scan with contrast injection can quantify the extent of pancreatic necrosis (parenchyma not enhanced after contrast injection) and the quantity and extent of infectious pancreatic necrosis. Balthazar et al. established a (secondarily revised) CT score to assess acute pancreatitis severity according to degree of inflammation, presence of liquid collection, existence and extent of necrosis [14,15]. Even though this score is correlated with morbi-mortality, it does not contribute to hospitalisation decision-making [16–20]. The timing of the CT scan is particularly crucial; when carried out during the first 48 h of hospitalisation, it is liable to underestimate not only the extent and severity of pancreatic necrosis, but also the existence of local complications [1,21].

Table 1
Modified Marshall Score defining organ failure.

Organ	Score				
	0	1	2	3	4
Lung (PaO_2/FiO_2)[a]	> 400	301–400	201–300	101–200	≤ 100
Kidney (creatinine in μmol/l)	≤ 134	134–169	170–310	311–439	> 439
Cardiovascular (Systolic Blood Pressure in mmHg)[b]	> 90	< 90, response to fluid loading	< 90, no response to fluid loading	< 90, pH < 7.3	< 90, pH < 7.2

A score of at least 2 for each organ defines the existence of organ failure
Marshall JC, Cook DJ, Christou NV, et al. Multiple organ dysfunction score: a reliable descriptor of a complex clinical outcome. Crit Care Med 1995;23:1638–52.
[a] For non-ventilated patients, FiO_2 is estimated at 21% (in ambient air), at 25% (under 2 l/min of oxygen), at 30% under 2 l/min of oxygen, at 40% under 6-8 l/min of oxygen, and at 50% under 9-10 l/min of oxygen.
[b] Without vasopressors.

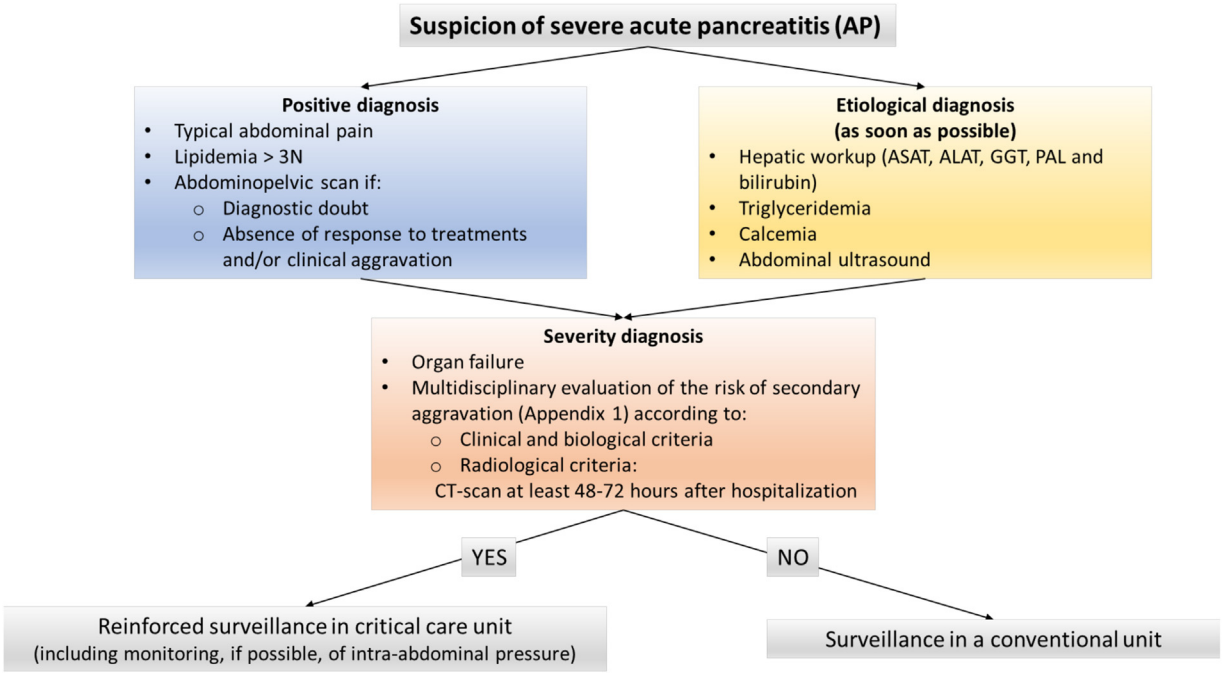

Fig. 1. Positive and aetiological diagnosis, hospitalisation modalities and early monitoring of severe acute pancreatitis

Question 2: In patients admitted to critical care for severe acute pancreatitis, what are the complementary examinations to be carried out within the first 72 h, the objective being to establish the diagnosis?

Experts: Emmanuel Weiss (SFAR), Claire Dahyot-Fizelier (SFAR)

R1.2.1 – In patients admitted to critical care for acute pancreatitis, in case of diagnostic doubt following anamnesis, clinical examination and lipasaemia assay, or in the absence of response to treatments or due to worsening of the clinical condition, it is recommended to carry out an abdominopelvic scan as soon as possible to confirm the positive diagnosis.
GRADE 1+ (STRONG AGREEMENT)

R1.2.2 – In patients admitted to critical care for severe acute pancreatitis, it is recommended to carry out as rapidly as possible the following additional tests: hepatic work-up (ASAT, ALAT, γGT, PAL and bilirubin), triglycerides blood test, calcium blood test and abdominal ultrasound, the objective being to establish the aetiological diagnosis.
GRADE 1+ (STRONG AGREEMENT)

Rationale

Positive diagnosis

In most cases, the diagnosis of acute pancreatitis can be established on the basis of typical abdominal pain and pancreatic hyperenzymaemia [22] (Fig. 1). Consequently, early abdominopelvic scan does not seem to modify patient treatment and diagnosis, even though few patients admitted to critical care have been included in multicentre observational studies [23,24]. It bears mentioning that early abdominal scan involving contrast agent injection may aggravate acute renal failure.

However, the limits of hyperlipasaemia (>3 N) in the diagnosis of acute pancreatitis were underlined in a Cochrane review [25] showing sensitivity of 0.79 CI 95% (0.54–0.92) and specificity of 0.89 95% CI (0.46–0.99). More than 32% of the patients with acute pancreatitis did not present with hyperlipasaemia > 3 N; conversely, 7% of the patients with hyperlipasaemia were not suffering from acute pancreatitis. Moreover, the longer the time elapsed between initial pain and lipase assay, the weaker the performance of the latter. Lastly, the absence of pancreatic enzymaemia and the absence of abdominal pain may quite possibly be associated with severe forms and heightened mortality [22].

In a context of diagnostic uncertainty, abdominopelvic scan can help to obtain a positive diagnosis in cases of uncategorised abdominal emergency. It can either confirm the diagnosis of acute pancreatitis or suggest an alternative diagnosis, for example digestive perforation, intestinal occlusion, or mesenteric ischaemia. In accordance with the international Atlanta guidelines, the diagnosis of acute pancreatitis requires fulfillment of at least two of the three following criteria: abdominal pain suggestion of pancreatitis, serum amylase or lipase level greater than three times the upper normal value and characteristic imaging finding (CT-scan being the technique of choice [3]. The scanography abnormalities suggestive of acute pancreatitis are the following [26]: focal or diffuse enlargement of the pancreatic parenchyma, oedema-associated or hyperdensity in haemorrhagic form, blurring of the pancreatic edges due to inflammation, infiltration of the surrounding retroperitoneal fat, necrosis of the pancreatic parenchyma translated by lack of parenchymal enhancement (ideally one week after appearance of symptoms so as to distinguish the latter from the lack of pancreatic enhancement secondary to the oedema). To conclude, when diagnostic uncertainty persists following clinical examination and biological assessment, or if the clinical data and lipasaemia are discordant, an abdominal scan is recommended. When there is no response to initial treatment or in the case of clinical deterioration, CT-scan can help to identify an early complication [15].

Aetiological diagnosis

In Western countries, calculus of the bile duct, also known as cholelithiasis, constitutes the most frequent cause of acute pancreatitis (40–50% of cases). As the second most frequent cause, alcohol is responsible for 20 to 30% of cases, with variations from one area of the world to another [27,28]. The other causes of acute pancreatitis are hypercalcaemia, hypertriglyceridaemia, medicinal

products (losartan, valproic acid, azathioprine, methyldopa, didanosine, pentamidine...), endoscopic retrograde cholangiopancreatography (ERCP) (2–20%), a virus or a trauma. Rapid determination of acute pancreatitis aetiology facilitates adaptation of initial management and early initiation of a specific treatment (if it exists). Clinical context, history taking, and physical examination are major orientative elements in the aetiological diagnosis of acute pancreatitis. On admission, an alanine aminotransferase (ALAT) level twice as high as the normal level has 88% positive predictive value, 84% specificity and 74% sensitivity in the diagnosis of gallstone migration [29]. That said, after the first 48 h following admission, a high transaminase level is no longer of diagnostic value, which means that timing of assays is of paramount importance. Liver test may also contribute to an associated angiocholitis diagnosis.

In the event of triglyceride concentration exceeding 2000 mg/dL, which is generally considered as a sign of pancreatic toxicity, triglyceride assay may be suggestive of hypertriglycaeridemic pancreatitis. When hyperglycaeridemia exists but is lower than 1000 mg/dL, it is probably associated with hyperlipidaemia secondary to pancreatic inflammation. While it indeed constitutes an indicator of severity [30], it should not be considered as the cause of pancreatitis. Search for cholelithiasis should be carried out by ultrasound scan, which is an easily available, non-invasive, and inexpensive test. Gallstones or dilated main bile duct are suggestive of cholelithiasis aetiology, even if the distal portions of the bile ducts and the pancreas are often poorly visualised. The ultrasound test must be carried early to limit the risk of lithiasis induced by fasting. In 10 to 25% of cases, pancreatitis aetiology remains undetermined [27]; in idiopathic pancreatitis, second-line testing is necessary, including echo-endoscopy designed to sensitise lithiasis detection [29].

Question 3: In patients admitted to critical care for severe acute pancreatitis, what are the specific monitoring elements to put into place within the first 72 h, the objective being to ensure the early diagnosis of complications?

Experts: Claire Dahyot-Fizelier (SFAR), Emmanuel Weiss (SFAR)

R1.3 – In patients admitted to critical care for severe acute pancreatitis and invasively ventilated, it is recommended to monitor intra-abdominal pressure in view of diagnosing and rapidly treating intra-abdominal hypertension.
GRADE 1+ (STRONG AGREEMENT)

Rationale

In cases of severe acute pancreatitis, major inflammatory responses and associated volaemic resuscitation are conducive to the development of peritoneal and visceral oedema, leading to intra-abdominal hypertension (IAH), which is found in more than half of the acute pancreatitis patients hospitalised in critical care [31]. IAH is defined by a sustained increase in intra-abdominal pressure (IAP) equal to or exceeding 12 mmHg, and abdominal compartment syndrome (ACS) is defined by prolonged IAP level exceeding 20 mmHg and associated with at least one instance of organ failure. The most widely used assessment of IAP consists in measuring bladder pressure, with the patient in a supine recumbent position, with the blood pressure cuff at the iliac crest at zero at end tidal, following instillation of a saline solution not exceeding 25 mL. To be valid, the measurement necessitates good patient-ventilator synchrony (neither inspiratory nor expiratory efforts during the procedure).

A meta-analysis of 14 studies showed acute pancreatitis to be an independent risk factor of IAH [OR = 4.73; 95% CI (1.96–11.41)] and that in patients with acute pancreatitis, high severity and administration of large volumes of crystalloids during the initial phase of resuscitation represented IAH risk factors [32]. In a recent multicentre prospective study covering all relevant pathologies, critical care patients with IAH presented significantly higher mortality at D28 and D90 than those without IAH (27.1% *vs.* 10.8%) and (36.7% *vs.* 16.3%) respectively. IAH severity [grade II (IAP: 16–20 mmHg) and grade III (IAP: 21–25 mmHg)] during the first two weeks of hospitalisation in critical care was likewise an independent risk factor for mortality at D90 [33].

Indeed, intra-abdominal hypertension (IAH) may be a causative factor for abdominal compartment syndrome (ACS), which is responsible for increased organ failure and significantly higher mortality in critical care patients. A systemic review on ACS (7 studies; n = 271 patients) reported 38% prevalence of patients with acute pancreatitis and significantly higher mortality among them (49% *versus* 11%) [34].

To conclude, continuous monitoring for IAP is justified as a means of achieving early detection of possible IAH and taking measures favouring its limitation (Fig. 1).

First-line management of abdominal compartment syndrome consists in medical conservative treatment, which can associate digestive tract suction, drainage of peritoneal effusion, limitation of voleamic load, deepened sedation and, in some cases, curarisation [35]. In the event of failure, surgical decompression may be considered, even though up until present, no study has shown it to be beneficial regarding mortality [36].

FIELD 2: Treatment during the initial phase

Question 1: In patients admitted to critical care for severe acute pancreatitis, which modalities of vascular loading help to reduce morbi-mortality?

Experts: Olivier Joannes-Boyau (SFAR), Matthieu Jabaudon (SFAR)

R2.1 – In patients admitted to critical care for severe acute pancreatitis, it is probably not recommended to systematically carry out infusion with large quantities of fluid (from 3 to 5 mL/kg/h over the first 24 h) during the acute phase to reduce mortality, acute renal failure or hospital stay duration.
GRADE 2- (STRONG AGREEMENT)

Rationale

While there exists considerable literature on the subject, its quality is mediocre, with a number of randomised controlled studies containing biases and involving only a small population. There exists only one meta-analysis including randomised controlled trials and prospective or retrospective cohort studies. In this meta-analysis concerning 1229 patients having received "aggressive fluid filling" (from 3 to 5 mL/kg/h during the first 24 h) and 1397 patients having received "standard fluid filling", there was no difference in mortality favouring one strategy rather than the other (RR 1.3 95% CI (0.79–2.12); I^2 51%) [37]. Moreover, given its moderate methodological quality and the absence of source data, the meta-analysis failed to justify any conclusion regarding mortality. On the other hand, an increased risk of acute renal failure was highlighted in the group of patients having been rapidly infused with large quantities of fluid (RR 2.17 95% CI (1.67–2.83); I^2 0%).

The few available randomised studies, which trended toward a higher death rate in the "aggressive fluid filling" group [38,39], involved a small population (fewer than 100 patients), and present a very low level of evidence. Notwithstanding the meta-analysis and given the insufficient level of evidence in the different studies, the experts have decided to downgrade the level of recommendation to GRADE 2.

Even if, in the literature, there does not exist any clearly formulated argument favouring their position, the experts deem it important to base fluid loading on the results of haemodynamic monitoring, especially when the volumes to be used are sizable.

Lastly, the present-day literature does not allow us to draw definitive conclusions on the impact on morbi-mortality of type of solution used, utilisation of albumin, haemodynamic monitoring, "goal-directed therapy" or use of vasopressors [40].

Question 2: In patients admitted to critical care for severe acute pancreatitis, which strategies are best suited to prevent respiratory complications?

Experts: Matthieu Jabaudon (SFAR), Olivier Joannes-Boyau (SFAR)

R2.2 – In patients admitted to critical care for severe acute pancreatitis, it is probably not recommended to administer probiotics by enteral route to reduce mortality or the occurrence of health care-associated pneumonia.
GRADE 2- (STRONG AGREEMENT)

Rationale

In the one available multicentre randomised controlled study on the subject, while enteral administration of a preparation of several probiotics had no impact on occurrence of care-associated pneumonia (24/152 patients in the interventional group *vs.* 16/144 in the control group, $P = 0.31$), it was associated with a higher rate of mortality (RR 2.53 95% CI (1.22–5.25), $P = 0.01$) and higher incidence of mesenteric ischaemia (9/152 patients in the interventional group *vs.* 0/144 in the control group, $P = 0.004$) [41].

ABSENCE OF RECOMMENDATION – As regards patients admitted to critical care for severe acute pancreatitis, it is not possible at this time to issue a recommendation on the utilisation of non-invasive ventilation or high-flow oxygen therapy or on the implementation of strategies of invasive mechanical ventilation or sedation aimed at preventing respiratory complications.

Rationale

In today's literature there exists no study assessing the impact of non-invasive ventilation, high-flow oxygen therapy, invasive mechanical ventilation or sedation on patients admitted to critical care for severe acute pancreatitis.

Question 3: In patients admitted to critical care for severe acute pancreatitis, which modalities of nutritional management help to reduce morbi-mortality?

Experts: Philippe Seguin (SFAR), Ronan Thibault (SFNCM)

R2.3 – In patients admitted to critical care for severe acute pancreatitis, it is recommended to use enteral rather than parenteral nutrition to reduce morbi-mortality.
GRADE 1+ (STRONG AGREEMENT)

Rationale

Several meta-analyses have highlighted a significant reduction of mortality when patients received enteral nutrition (EN) rather than parenteral nutrition alone. An initial meta-analysis of randomised trials published in 2010 included 348 patients and showed a significant reduction in mortality regarding acute pancreatitis in general [RR 0.50 95% CI (0.28–0.91)] and in a sub-group involving 136 cases of severe acute pancreatitis and encompassing four studies [RR 0.18 (0.06–0.58)] [42]. Two more recent meta-analyses, published in 2018 and including 500 and 348 patients respectively, confirmed a significant reduction of mortality in cases of severe acute pancreatitis [RR 0.36 (0.20–0.65) and 0.31 (0.18–0.54)], respectively [43,44]. The expected effect of EN concerning risk of infection by bacterial translocation from the digestive tract is supported by hypothesised improvement of locoregional infusion, intestinal motility and the protective action of the intestinal mucous membrane [45]. The 2010 meta-analysis of heterogeneous studies by Al-Oman distinguished systemic infections from local infections and highlighted a significant reduction of systemic infections without an effect in pancreatic infections [42]. After the inclusion in the latest meta-analyses of recently published randomised prospective studies, a significant reduction of pancreatic infections (among others) has been observed [44,46–50]. Three meta-analyses have likewise reported a significant reduction in organ failure, the one exception being the meta-analysis of Al-Oman regarding the sub-group consisting in the most severe cases of acute pancreatitis; that much said, the studies under consideration are highly heterogeneous [42–44]. Enteral nutrition has not had a significant impact on hospital stay duration or local non-infectious complications [42,44,47], and in two randomised studies, the effects of EN on reduction of systemic inflammatory response have been divergent [49,51].

R2.4 – In patients admitted to critical care for severe acute pancreatitis, it is not recommended to systematically initiate early enteral nutrition (during the first 24–48 h of treatment) in view of reducing mortality infections or organ failure.
GRADE 1- (STRONG AGREEMENT)

Rationale

While it is commonly admitted that compared to parenteral nutrition, enteral nutrition (EN) reduces morbi-mortality, the interest of early administration ($\leq$ 48 h) is more controversial. On this subject, two systematic reviews were recently published [52,53]. They included cases of acute pancreatitis without differentiating them according to severity or means of feeding the "control" group (by mouth, enteral or parenteral nutrition); in the studies, definition of early nutrition was based on imprecise clinical criteria, leading to considerable heterogeneity [52,53]. Given these shortcomings, no significant difference between early and late nutrition was found in terms of mortality, organ failure(s) or local infectious complications [52,53]. Another meta-analysis involved indirect comparison between randomised studies of which one of the arms involved EN; the patients were divided into two groups (early EN $\leq$ 24 h *vs.* $>$ 24 h) [54]. As regards the entire population (n = 165), in terms of risk of organ failure(s) and a composite endpoint including pancreatic infection, organ failure and mortality, a significant reduction was observed (respectively, OR = 0.42 [0.19–0.94] and OR = 0.44 [0.20–0.96]) [3]. On the other hand, when the endpoints were separated, EN reduced neither mortality [OR = 0.38 [0.09–1.56]] nor risk of pancreatic infection [OR = 0.65 [0.21–1.99]]. Moreover, a patient sub-group (n = 95) with severity predictive criteria was studied and as regards the aforementioned endpoints, early EN did not differ from later nutrition [54]. A recent meta-analysis assessed early EN ($\leq$ 48 h) in acute pancreatitis patients with severity predictive criteria or severe acute pancreatitis [46]. While a significant effect on (pancreatic and overall) infections appeared, there was no effect on mortality, about which the studies under consideration were significantly heterogeneous [46].

Two prospective randomised studies more specifically included patients with severity predictive criteria [55,56]. The prospective multicentre study by Bakker et al. included 205 patients [55], comparing early EN ($\leq$ 24 h) with later oral feeding ($>$72 h) and revealed no significant difference between the two groups regarding the main objective, which was a composite endpoint including major infection or mortality (RR = 1.07 (0.79–1.44)). The same results were observed in a predefined severe acute pancreatitis sub-group [APACHE II $\geq$ 13, n = 92; RR = 0.92 (0.57–1.49)]. Taken separately, mortality and infections did not significantly differ between the two

groups, nor did (single, multiple, transient or persistent) organ failure(s). Tolerance of early nutrition was satisfactory, without any intergroup difference concerning nausea, vomiting, diarrhea, ileus or inhalation pneumonia [55]. The single centre study by Stimac et al. compared early EN ($\leq$ 24 h) to oral feeding of 214 patients starting on the day 3 [56]. Reduction of systemic inflammatory response did not differ between the groups [56]. The main criticism of the two studies has to do with the inclusion of patients not all of who were severely ill (55% and 73% respectively in the studies by Bakker [55] and Stimac [56]).

In most cases, EN tolerance has been reported as satisfactory, even when administered at an early stage [51,57,58]. That said, digestive intolerance during the first days of initialisation has been observed, leading to temporary discontinuation or diminution of feeding procedures [51,57,58]. In a prospective randomised study, gastrointestinal symptoms did not differ between EN and parenteral nutrition [59]. Moreover, when compared with parenteral nutrition, while EN was not associated with an increased number of intra-abdominal hypertension cases during the first 8 days of hospitalisation, it was linked to less satisfactory digestive tolerance for pressure >15 mmHg [58]. On this subject, the role of early EN ($\leq$ 48 h) in a non-selected population of resuscitation patients was recently reviewed by an expert panel [46]. Notwithstanding a lack of conclusive evidence, it was recommended to delay EN initiation under some circumstances, of which several can be incorporated in management of severe acute pancreatitis: uncontrolled shock, uncontrolled hypoxaemia and acidosis, non-controlled upper digestive tract haemorrhage, gastric aspirate > 500 mL/6 h, bowel ischaemia, bowel obstruction, abdominal compartment syndrome and high-output fistula without distal feeding access [46].

R2.5 – In patients admitted to critical care for severe acute pancreatitis, it is not recommended to use a nasojejunal tube as first-line treatment to improve tolerance of enteral nutrition.

GRADE 1- (STRONG AGREEMENT)

Rationale

A recent meta-analysis showed that EN by nasogastric tube did not differ from EN by nasojejunal tube regarding mortality, infections and organ failure. What is more, complications associated with EN and pain exacerbation did not differ according to digestive nutrition site [60]. There is consequently no reason to systematically treat severe acute pancreatitis patients undergoing post-pyloric feeding with a nasojejunal as opposed to a nasogastric tube.

On the other hand, when it is impossible to carry out EN by means of a nasogastric tube, EN by means of a nasojejunal tube is preferable to parenteral nutrition. In fact, most of the studies included in the meta-analyses evaluating EN as compared to parenteral nutrition were conducted using a nasojejunal tube [42–44]. A recent single-blind randomised controlled study suggested that addition of polydextrose to EN by nasojejunal tube improved digestive tolerance (lessened incidence of abdominal distension, diarrhea, constipation) and shortened the time needed to reach the energy goal [61].

R2.6 – In patients admitted to critical care for severe acute pancreatitis, it is probably not recommended for enteral nutrition to prefer semi-elemental or elemental mixtures to polymeric mixtures, or to utilise enteral immuno-nutrition rather than ''standard'' enteral nutrition, to reduce morbi-mortality and improve tolerance of enteral nutrition.

GRADE 2- (STRONG AGREEMENT)

Rationale

Semi-elemental mixtures

A randomised study compared EN using a semi-elemental mixture (composed of small peptides and a high proportion of medium-chain triglycerides) to a polymeric mixture [62]; it was a single centre study involving a small number of patients with non-severe acute pancreatitis, and did not yield any clinically relevant conclusion other than satisfactory tolerance of EN in the two groups [62]. In the absence of randomised prospective studies, Petrov et al. conducted a meta-analysis through indirect comparison of ten randomised studies, with one arm employing EN in a semi-elemental mixture or a polymeric mixture [63]. There was no difference between the two types of EN regarding mortality, infectious complications and digestive tolerance [63]. More recently, a retrospective study drawn from nationwide Japanese data included 948 patients with acute pancreatitis and compared elemental mixtures *vs.* semi-elemental/polymeric mixtures [64]. Whatever the endpoint (mortality, infection, hospital stay duration, tolerance) and the degree of severity, no difference between the different types of EN mixture was evidenced [64].

Immuno-nutrition

Pharmaconutrients and immuno-nutrients are nutrients that possess pharmacological or immune-strengthening properties independent of their nutritional value [65]. The potential benefits of ω-3 polyunsaturated fatty acids and antioxidant micronutrients have been evaluated in cases of acute pancreatitis as regards their anti-inflammatory and antioxidant properties [66–71]. Numerous meta-analyses have been published, essentially dedicated to non-severe acute pancreatitis. The immuno-nutrients involved in immuno-nutrition have varied considerably from one study to another, in some instances associating antioxidants that were not nutrients and/or inadequate "control" groups (patients on an empty stomach or receiving nothing other than water) [66–68,70,71]; the results should then be interpreted cautiously. A meta-analysis included six highly heterogeneous randomised prospective studies and pinpointed no significant difference in terms of mortality, infectious complications or organ failures [67]. Nor was there any major difference between groups on these criteria when the control group received (polymeric ± fibers) EN [67], or in the two studies including severe acute pancreatitis [67]. Moreover, in sub-group analysis other meta-analyses have shown that the addition to NE of immuno-nutrients (particularly glutamine) did not reduce mortality or infectious complications [66,68,70].

R2.7 – In patients admitted to critical care for severe acute pancreatitis, in the event of proven intolerance or contraindication to enteral nutrition, it is probably recommended to infuse glutamine by intravenous route (0.20 g/kg/day of L-glutamine) as a complement to parenteral nutrition in view of reducing morbi-mortality.

GRADE 2+ (STRONG AGREEMENT)

Rationale

In accordance with guidelines on nutrition for critical care patients (in the broad sense of the word), exclusive or complementary parenteral nutrition can become necessary in the event of proven intolerance, contraindication to EN and/or impossibility to reach nutritional goals [72]. That much said, in the context of acute pancreatitis, the meta-analysis by Asrani et al. highlighted the benefits of intravenous glutamine supplementation in terms of mortality, infectious complications and hospital stay duration, in patients having received parenteral nutrition, but not in those having received EN [66]. What is more, the meta-analyses by Jafari et al. [68] and Jeurnink et al. [73] laid emphasis on the benefits of intravenous glutamine as opposed to parenteral nutrition alone, in terms of mortality, infectious complications and hospital stay duration. A meta-analysis focused on severe acute pancreatitis

likewise reported that compared to parenteral nutrition alone, intravenous glutamine supplementation in association with parenteral nutrition effectively reduced mortality, infectious complications and hospital stay [69]. Lastly, the meta-analysis by Zhou et al. studied the benefits of enteral and/or parenteral immuno-nutrition in patients with acute pancreatitis [70]. The immuno-nutriments tested were glutamine, ω-3 polyunsaturated fatty acids, and a combination of glutamine and arginine. When administered by parenteral route, immuno-nutrition was associated with a reduction of mortality, infectious complications and hospital stay duration, whereas when administered by enteral route, they had no effect [70]. In fact, by either enteral or parenteral route, only the risk of organ failure was reduced by immuno-nutrition [70]. A randomised study suggested that as compared to administration after day 5, administration of glutamine by intravenous route on the day of admission in the form of dipeptide alanyl-glutamine could reduce the durations of organ failures, digestive ileus and hospital stay [74].

R2.8 – In patients admitted to critical care for severe acute pancreatitis, it is probably not recommended to use antioxidants complementarily to enteral or parenteral nutrition in view of reducing morbi-mortality.

GRADE 2- (STRONG AGREEMENT)

Rationale

Two meta-analyses have evaluated, in patients suffering from acute pancreatitis with varying degrees of severity, the administration of antioxidants, nutrients and non-nutrients alike (vitamins A, C, E, glutamine, selenium, S-adenosylmethionine, *N*-acetylcysteine, antoxyl®, pentoxifylline, activated protein C) [71,73]. The overall results of the meta-analysis by Jeurnink et al. suggested that while antioxidant supplementation reduced the risks of mortality and systemic complications, it had no conclusively proven effect on hospital stay duration [73]. However, given the wide variety of antioxidants and routes of administration (oral, intravenous, or intramuscular), the results of the meta-analysis are difficult to interpret. It also bears mentioning that five out of the 11 studies compared parenteral nutrition + glutamine to parenteral nutrition alone [73]. The meta-analysis by Moggia et al. included four studies and showed no significant effect of the antioxidants (vitamins A, C, E, selenium, *N*-acetylcysteine, antoxyl®, pentoxifylline) with regard to mortality, severe complications after at least three months and risk of organ failure(s) at three months [71].

Question 4: In patients admitted to critical care for severe acute pancreatitis, which emergency medical and surgical intervention helps to reduce morbi-mortality?

Experts: Fanny Bounes (SFAR), Jean-Baptiste Chevaux (SFED), Jean-Pierre Tasu (SFR), Karim Asehnoune (SFAR)

R2.9 – In patients admitted to critical care for severe acute biliary pancreatitis, it is not recommended to use emergency endoscopic retrograde cholangiopancreatography to reduce morbi-mortality in patients other than those with associated angiocholitis.

GRADE 1+ (STRONG AGREEMENT)

Rationale

A systematic review of seven randomised controlled trials involving a total of 757 patients found that endoscopic retrograde cholangiopancreatography (ERCP) had no systematically beneficial effect for patients presenting with acute pancreatitis of biliary origin [75]. In this meta-analysis, analysis of trials including patients with associated angiocholitis highlighted not only reduced mortality [RR 0.20 95% CI (0.06–0.68)], but also a lower number of systemic and local complications according to the Atlanta classification [RR 0.41 (0.21–0.82) and RR 0,37 (0.18–0.78) respectively], and in patients with biliary obstruction, early ERCP was associated with a reduction in local complications [RR 0.54 (0.32–0.91)].

In a single centre trial [76] that included patients suffering from acute biliary pancreatitis without angiocholitis, ERCP performed during the first 72 h of acute pancreatitis brought about no reduction of mortality as compared to the conservative treatment group [OR 2.04 (0.17-23.2)]. In a randomised controlled trial [77], ERCP performance within 72 h in critical care patients presenting with acute biliary pancreatitis likewise brought about no reduction in mortality. Lastly, the APEC trial [78], a multicentre randomised controlled trial including cases of acute pancreatitis without associated angiocholitis, compared ERCP with endoscopic sphincterotomy during the first 24 h to conservative treatment and observed no difference between groups with regard to death or any major complication during the first six months [RR 0.87 (0.64–1.18)].

Question 5: In patients admitted to critical care for severe acute pancreatitis, what is the role of unconventional drug (somatostatin, insulin, etc.) or non-drug (plasma exchanges, etc.) therapies, the objective being to reduce morbi-mortality?

Experts: Thomas Rimmelé (SFAR), Louis Buscail (SNFGE), Philippe Levy (SNFGE)

R2.10 – In patients admitted to critical care for severe acute pancreatitis, it is probably not recommended to apply unconventional drug therapies in view of reducing morbi-mortality.

GRADE 2- (STRONG AGREEMENT)

Rationale

A very large number of molecules, acting at different pathophysiological levels, have been appraised as possible adjuvant medical treatment in cases of acute pancreatitis. Some prophylactic antibiotics, some antioxidants, aprotinin, calcitonin, cimetidine, ethylenediaminetetraacetic acid (EDTA), gabexate, glucagon, iniprol, lexipafant, non-steroidal anti-inflammatory drugs, octreotide, oxyphenonium, probiotics, activated protein C, somatostatin, thymosin and ulinastatin have been the subject of at least one randomised controlled study [71]. While none of these molecules has been found to reduce mortality in cases of severe acute pancreatitis, the overall level of scientific evidence is low. It would stand to reason that in future studies, criteria such as quality of life and cost of treatment should be assessed, and that at least one year of follow-up be proposed. It would also appear necessary to take into full account the chronobiology and the kinetic models of pathophysiological events. For example, if an anti-enzyme is tested, it would be necessary to appraise its clinical interest during the very first hours of treatment. As for anti-inflammatory drugs, they would have to be evaluated during the first 48 h. Regarding anti-infective therapies, on the contrary, only be as of day 2 might they be of potential interest.

R2.11 – In patients admitted to critical care for severe acute pancreatitis of hypertriglyceridaemic origin (HTGP), in the event of medical treatment failure the experts suggest initiation of therapeutic plasma exchange (TPE) to rapidly reduce severe hypertriglyceridaemia.

EXPERT OPINION (STRONG AGREEMENT)

Rationale

Acute pancreatitis of hypertriglyceridaemic origin presents a higher mortality rate than that found in other types of acute pancreatitis [79]. Hypertriglyceridaemia can be quite transitory,

and blood testing is called for, on admission (Cf. R1.2.2). While its pathophysiology is imprecise, a commonly recognised mechanism is put into play with triglyceride hydrolysis by a pancreatic lipase enzyme, in a process favouring the accumulation of free fatty acids in the capillaries of the vascularised pancreatic islet and leading to their obstruction and downstream ischaemia (perilobular distribution of lesions associated with capillary ischaemia) [80].

As regards first-line medical treatment, in addition to lipid-lowering agents such as fibrates, heparin and insulin activate lipoprotein lipase, a key enzyme facilitates triglyceride breakdown. Insulin induces the synthesis and activation of lipoprotein lipase, which accelerates chylomicron degradation. As for heparin, it prevents lipoprotein lipase from binding with its receptor, thereby increasing the proportion of free lipoprotein lipase and accelerating lipoprotein metabolism, leading to decreased triglyceride levels [81]. As regards the type of heparin therapy to be proposed, there seems to be little if any difference between unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH). Lastly, it seems preferable to associate heparin with insulin rather than using only one of these molecules in monotherapy [82]. That said, the level of evidence for this therapeutic strategy has remained relatively limited [83].

When first-line medical treatment is insufficient, therapeutic plasma exchange (TPE) may be initiated; more precisely, this extracorporeal approach may be contemplated in the event of severe ($>$ 11.3 mmol/L) or very severe ($>$ 22.4 mmol/L) and persistent hypertriglyceridaemia associated with organ failure [84]. There exists no randomised study comparing insulin and/or heparin treatment *versus* therapeutic plasma exchange, which can reduce triglyceride concentration by eliminating plasma and replacing it with albumin or fresh frozen plasma. In most cases, a single plasma exchange session suffices to bring triglyceridaemia down to a level lower than 11.3 mmol/L [85], the final objective being to reach a triglyceride level $<$ 5.7 mmol/L; according to some studies, this threshold seems associated with improved clinical course [86]. Citrate anticoagulation of the extracorporeal circuit may be a path to explore, with an observational study on 103 patients having reported an association between mortality reduction and citrate anticoagulation as compared to heparin treatment (1% *versus* 11%) [87]. According to the only available observational studies, while plasma exchange reduces triglyceride concentration, it has not been demonstrated that it also reduces mortality and recurrence [88]. That said, it remains problematic to compare patient cohorts having received plasma exchange with those having received standard medical treatment; after all, the former are generally more seriously ill than the latter. To conclude, it seems advisable to propose plasma exchange either after failed medical treatment or immediately, in the event of severe and very severe and persistent hypertriglyceridaemia associated with hyperlactatemic acidosis and/or at least one instance of organ failure [89].

Question 6: In patients admitted to critical care for severe acute pancreatitis, what is the antalgic treatment to prioritise, the objective being to reduce morbi-mortality?

Experts: Matthieu Jabaudon (SFAR), Olivier Joannes-Boyau (SFAR)

ABSENCE OF RECOMMENDATION – In the absence of data evaluating the analgesia experienced by patients admitted to critical care for severe acute pancreatitis, it is not possible to issue a recommendation on the type of analgesia to prioritise in view of reducing morbi-mortality.

Rationale

Even though pain control remains an essential objective in treatment of acute pancreatitis, present-day data in the literature do not allow us to draw conclusions as to the relative impact of morphinics, non-steroidal anti-inflammatory drugs, paracetamol or epidural anaesthesia on the morbi-mortality associated with severe acute pancreatitis [90–97].

FIELD 3: Treatment and management of progressive complications

Question 1: In patients admitted to critical care for severe acute pancreatitis, should preventive anti-infective therapy be administered to reduce morbi-mortality?

Experts: Philippe Montravers (SFAR)

R3.1 – In patients admitted to critical care for severe acute pancreatitis, it is probably not recommended to administer preventive (*i.e.*, in the absence of documented infection) intravenous anti-infective therapy to reduce mortality or the occurrence of infected pancreatic necrosis or extra-pancreatic infections, particularly healthcare-associated pneumonia.
GRADE 2- (STRONG AGREEMENT)

Rationale

The objective of preventive anti-infective therapy is to avoid secondary or superinfection of pancreatic necrosis by germs generally originating from the digestive tract. Even though the pathways of contamination remain only partially identified, bacterial translocation is recognised as being a major factor.

Given the poor methodological quality of trials conducted prior to 2000, the 2001 consensus conference did not recommend prophylactic treatment in patients with severe forms of pancreatitis. The numerous analyses published up until a recent period all included trials conducted prior to 2000, and the results were consequently difficult to interpret [71,98–109]. The literature analysed (subsequent to 2000) is devoid of prophylactic agents other than carbapenems (imipenem [110–120] and meropenem [115,120–122]) and fluoroquinolones (ciprofloxacin) [123–125], which are reputed for their diffusion in cases of pancreatic necrosis as well as their spectrum of activity against the main digestive germs. However, these broad-spectrum molecules are also responsible for the emergence of multidrug-resistant bacteria.

The analysed literature presents numerous shortcomings: lack of power due to the small population involved, inadequate description of patient severity, unspecified proportion of patients in critical care, absence of satisfactory explanation of the (generally low) dosage used, absence of plasma assay for the agents used (unsuited to the patient), absence of prophylaxis monitoring criteria (toxicity, tolerance, efficacy), absence of justification for prophylaxis duration, piecemeal microbiological analyses (missing analysis of the emergence of multi-resistant bacteria), sparse intent-to-treat analyses, follow-up of limited duration. Notwithstanding the large number of studies considered, only a GRADE 2 recommendation could be issued.

Reduced incidence of infected pancreatic necrosis by prophylaxis is the most frequent primary endpoint [110–118,121–127]. We have carried out a meta-analysis excluding studies prior to 2000 and taking into account the results of English-language works published up until 2020 [111–113,116,118,121,123–125,127]. On the contrary, studies comparing one prophylactic agent to another [110,115,119,120,126] and works published, as abstracts alone have not been taken into account. No difference has been observed between patients receiving or not receiving prophylaxis in terms of incidence of necrotising infection. The same result was found in randomised, double blind placebo-controlled trials [111,121,123,125]. That said, the two most competently constructed studies were suspended before the end of the inclusion phase due to intermediary analysis [125] or

insufficient inclusion [121], without having reached their expected power. While two other studies analysed reduction by prophylaxis of candidiasis infections, methodological obstacles precluded a conclusion [126,127].

The secondary endpoints in the literature are essentially mortality [111,112,114–116,118–127] and extra-pancreatic infections [110,111,113,115,116,121–125]. The meta-analysis carried out in the framework of the present recommendations revealed no difference in incidence according to these criteria between the groups with or without preventive antibiotic treatment. This result is similar to those reported in randomised double blind studies with regard to mortality and extra-pancreatic infections [111,121,123,125]. More specifically, preventive parenteral antibiotherapy is not associated with a reduction in the respiratory complications of acute pancreatitis (tracheal intubation, acute respiratory distress syndrome, health care associated pneumonia) [111,116,128].

To summarise, no robust data from methodologically well-conducted studies adequately prove the benefits of antibiotic therapy as a means of preventing superinfection of necrotic tissue, mortality or occurrence of extra-pancreatic infections.

Question 2: In patients admitted to critical care for severe acute pancreatitis, which method(s) should be applied to establish the diagnosis of infected pancreatic necrosis?

Experts: Claire Roger (SFAR) and Céline Savoye-Collet (SFR)

R3.2 – In patients admitted to critical care for severe acute pancreatitis, it is probably recommended not to limit management to the clinical examination and the C-reactive protein (CRP) test, and to use the procalcitonin assay and abdominal CT scan to establish the diagnosis of infected pancreatic necrosis.

GRADE 2+ (STRONG AGREEMENT)

Rationale

Infectious pancreatic necrosis occurs in 20%–40% of cases of severe acute pancreatitis, with peak incidence between week 3 and week 4, and is associated with a high rate of mortality (30%–40%) [129]. Occurrence or persistence of fever, resurgence of abdominal pain, occurrence or persistence of organ failure and persistent positive blood cultures (particularly after 14 days) should be suggestive of infected pancreatic necrosis. It nonetheless bears mentioning that these clinical signs are minimally specific, and that they may be observed over the course of severe acute pancreatitis yet be exterior to infected pancreatic necrosis [130,131].

CRP has been widely studied as a means of assessing the actual severity of severe acute pancreatitis. However, only a few small-population observational studies have dealt with CRP performance in the diagnosis of infected pancreatic necrosis [132–134]. CRP sensitivity ranges from 0.44 to 0.86 and specificity from 0.89 to 0.75, according to the threshold chosen (257.5–300 mg/L respectively); while it represents a good indicator of the severity of acute pancreatitis, it remains insufficiently specific to justify the diagnosis of infected necrosis.

The performance of procalcitonin in diagnosis of infected pancreatic necrosis was evaluated in a systematic review including seven prospective non-randomised studies [135]. Procalcitonin sensitivity ranges from 0.72 to 0.95 and specificity from 0.75 to 0.88 according to the threshold chosen (0.5–2 ng/L); its negative predictive value is high (91%) with regard to a threshold of 2 ng/L [135]. Repeated procalcitonin measurement (on two consecutive days) seems to be associated with improved predictive value of infected pancreatic necrosis associated with organ failure (sensitivity 93%, specificity 88%) [136]. That said, the existing data have not determined the optimal time for measurement of procalcitonin in view of establishing the diagnosis of infected pancreatic necrosis. The presence in abdominal CT scan of excess digestive gas in intra/extra-pancreatic diagnosis should raise suspicion of infection; this sign is present in 40–50% of cases of infection [137]. However, its diagnostic performance remains low, with sensitivity ranging from 45 to 60% and specificity from 81 to 100%. To conclude, while diffusion MRI appears to be of interest in diagnosis of infection, evidence of its diagnostic performance remains preliminary.

R3.3 – In patients admitted to critical care for severe acute pancreatitis, the experts suggest that fine-needle aspiration should not be used to diagnose infected pancreatic necrosis in the absence of clinical signs of sepsis and/or computed tomography scan suggestive of superinfection.

EXPERT OPINION (STRONG AGREEMENT)

Rationale

While fine-needle aspiration has shown good diagnostic performance with regard to other associated clinical-biological and radiological signs, its interest is limited; false negatives range from 20% to 25% and false positives from 4% to 15% [138,139]. The procedure is associated with iatrogenic infectious complications (peritoneal contamination, digestive perforation) and haemorrhagic complications, as well. It should be reserved for cases characterised by a high degree of suspicion of infected pancreatic necrosis with clinical, biological signs and/or suggestive but not totally conclusive imagery.

Question 3: In patients admitted to critical care for severe acute pancreatitis, which method(s) of drainage of infected pancreatic necrosis should be used, the objective being to reduce morbi-mortality?

Experts: Lucie Darrivere (SFAR), Geoffroy Vanbiervliet (SFED, SNFGE), Jean-Pierre Tasu (SFR)

R3.4 – In patients admitted to critical care for severe acute pancreatitis, it is probably recommended to drain the infected pancreatic necrosis, and not limit the treatment to systemic anti-infectious drugs, to reduce morbi-mortality.

GRADE 2+ (STRONG AGREEMENT)

Rationale

The literature on this subject is quite limited. Numerous studies have compared surgical treatment *versus* mini-invasive treatment for pancreatic necrosectomy during acute pancreatitis, whether the pancreatic necrosis be infected or not. As of now, the literature leads us to conclude that therapeutic abstention (*i.e.*, not proceeding to draining "as a matter of principle") is to be preferred in cases of acute pancreatitis without infected necrosis. That said, given the past practice, even in the absence of infection, of ample necrosis drainage, and by analogy with the practices having been validated with regard to other intra-abdominal infections, therapeutic strategies for infected necrosis have compared surgical to mini-invasive drainage techniques (cf. R3.5) rather than to conservative drainage techniques limited to antibiotic therapy.

A meta-analysis on this subject [140] included 12 studies, only one of which was randomised; most were small-scale (low population), and the proportion of severely ill patients was unclear. The meta-analysis came to the conclusion that conservative treatment was effective in 64% of patients, with relatively low mortality of 12% (6%–18%), as compared to 26% (15%–37%) in the necrosectomy surgery group. However, from 20% to 100% of the patients included in the "conservative" group had received mini-invasive percutaneous

drainage. While comparison between patients not having received any drainage and those having received percutaneous drainage reported no difference in terms of mortality, it bears mentioning that the predominantly retrospective study design would suggest that drainage was carried out in the most severely ill patients and/or in those whose evolution with antibiotic therapy alone was unfavourable, which means that the absence of difference in terms of mortality is not an argument convincingly suggesting a good prognosis with antibiotic therapy alone.

In conclusion, by analogy with other types of intra-abdominal infections and in the absence of persuasive proof in the literature of at least an equivalence between antibiotic therapy alone and (generally mini-invasive) drainage, the experts have formulated a GRADE 2 recommendation in favour of an association of systemic antibiotic therapy and drainage of infected pancreatic necrosis in patients suffering from severe acute pancreatitis.

R3.5.1 – In patients admitted to critical care for severe acute pancreatitis, it is recommended as first-line treatment to apply a graduated, mini-invasive endoscopic and/or radiology-guided percutaneous approach for drainage of infected pancreatic necrosis, taking into account the local expertise of the centre and the location of the infected necrosis, to reduce the morbidity associated with the procedure.

GRADE 1+ (STRONG AGREEMENT)

R3.5.2 – The experts suggest that in the absence of a local interventional endoscopy and/or interventional radiology team trained in mini-invasive drainage, the patient presenting with severe acute pancreatitis with infected necrosis should be transferred to an adequately equipped expert centre.

EXPERT OPINION (STRONG AGREEMENT)

Rationale

The advantages of "mini-invasive" techniques over surgery have been highlighted in several randomised studies published since 2010. A Cochrane meta-analysis (8 randomised therapeutic trials, 306 patients) showed that as compared to laparoscopic necrosectomy, a graduated ("step-up") multidisciplinary approach involving first-line "mini-invasive" techniques was beneficial in terms of severe adverse events [141]. In one of the randomised therapeutic trials included in the meta-analysis and involving 88 patients, the risk of major complications and organ failure(s) was statistically higher in the "surgery" than in the "mini-invasive approach" group undergoing first-line radiology-guided percutaneous drainage followed, if necessary, by laparoscopic retroperitoneal necrosectomy (12% *versus* 42%). Long-term complications such as new-onset diabetes or exocrine pancreatic insufficiency also increased, whereas there was no difference in terms of mortality (19% *versus* 16%) [142].

Endoscopic necrosectomy was more specifically studied in a randomised therapeutic trial involving 20 patients [143], and was found to be superior to surgery in terms of postoperative progression of plasma inflammatory profile and occurrence of major complications. While mortality was four times lower in the "endoscopy" group, it did not reach statistical significance. Moreover, a recent randomised therapeutic trial showed that as regards major complications and mortality, an endoscopic approach was comparable to the "step-up" approach of radiology-guided percutaneous drainage followed, if necessary, by laparoscopic retroperitoneal necrosectomy. That said, the rate of pancreatic fistulas (5% *versus* 32%) and hospital stay duration were lower in the "endoscopy" group [144].

Lastly, two meta-analyses including three randomised trials and comparing endoscopic drainage and a graduated ("step-up") strategy to so-called invasive (laparotomy) or mini-invasive (laparoscopy or video-assisted retroperitoneal debridement) are concordant; while no benefit was found in terms of mortality, reduced hospital stay duration, digestive complications (fistulas), and organ failures were observed in the "endoscopy" group, as was, in some cases, improved quality of life [145–147]. More recently, a network meta-analysis including seven randomised studies (400 patients) reported that the most effective therapeutic strategy for infective necrosis in terms of reduced intra-hospital morbi-mortality was the "step-up" approach leading to endoscopic necrosectomy, followed by the other mini-invasive techniques [148]. On the contrary, strategies of early or late surgical necrosectomy and techniques of percutaneous peritoneal lavage were associated with more unfavourable progression.

To conclude, a "proactive" strategy associating multiple percutaneous drainage procedures and frequent and early drain upsising (when the evolution of infected necrosis is not satisfactory) could be associated with less need for surgery and shorter hospital stays than a "wait-and-see" strategy [149].

As for cases where surgery remains necessary, a meta-analysis (four studies including a randomised therapeutical trial, 336 patients) reported that retroperitoneal surgical necrosectomy was preferable to surgery by laparotomy in terms of organ failure and diverse digestive complications. However, the highly heterogeneous data render it impossible to draw definitive conclusions from this single study [150].

Question 4: In patients in critical care whose severe acute pancreatitis is complicated with infectious necrosis, which types of antibiotic treatment should be applied in view of reducing morbi-mortality?

Experts: Laurent Muller (SFAR), Philippe Levy (SNFGE), Louis Buscail (SNFGE)

R3.6.1 – In patients admitted to critical care whose severe acute pancreatitis is complicated by infected necrosis, it is probably recommended to administer probabilistic anti-infective therapy targeting resistant enterobacteria, *Enterococcus faecium*, *Pseudomonas aeruginosa* and yeast, to reduce morbi-mortality.

GRADE 2+ (STRONG AGREEMENT)

ABSENCE OF RECOMMENDATION – In the present-day state of the literature, it is not possible to issue a recommendation on the type of antibiotic to administer to reduce morbi-mortality.

R3.6.2 – In critical care patients whose severe acute pancreatitis is complicated by infected necrosis, the experts suggest that antibiotic therapy be secondarily adapted to the microorganisms isolated during culturing of the fluid extracted after percutaneous puncture and/or endoscopic drainage and/or surgical drainage, and/or isolated from hemocultures, according to interdisciplinary (intensive care, gastro-enterology, infectiology) decision, to reduce the spectrum of antibiotic therapy and preserve bacterial ecology.

EXPERT OPINION (STRONG AGREEMENT)

Rationale

Antibiotic therapy in authenticated cases of pancreatic necrosis superinfection is logical and justified due to the severity of the

phenomenon. Necrosis superinfection during severe acute pancreatitis is frequent (15%–30% of cases) and delayed [55,142,151]. The identified mechanism is translocation from the digestive tract [152]. Superinfection increases mortality and the number of new hospital admissions after an initial episode [129,151]. Drainage of collections suspected of infection being an important part of treatment [152–154], antibiotic therapy adapted to the microorganisms found in cultures is logical, even though its contribution has yet to be demonstrated in relevant studies, which as of now are highly unlikely to be conducted.

Bacterial superinfections are the most frequent, representing 75%–80% of cases [155,156]. Enterobacteria (particularly *E. coli*, *Klebsiella*) and enterococci are most often responsible [156,157]. Recent findings have shown heightened incidence of resistant non-digestive bacteria of the *Pseudomonas* and *Acinetobacter genera*. While Gram positive infections are relatively rare, *Enterococcus faecium* has become increasingly frequent [156].

Fungal superinfections occur in around 30% of severe acute pancreatitis cases [158]. A recent meta-analysis showed that these fungal infections are associated with a significant increase in mortality [OR 3.95 95% CI (2.60–5.80)], number of admissions to intensive care and hospital stay duration [158].

Not all antibiotics show equivalent diffusion in infectious necrosis. There exists no data providing a reliable link between prognosis and penetration of antibiotics into the pancreas in acute pancreatitis or, *a fortiori*, in severe acute pancreatitis. While carbapenems have been recommended on account of their supposedly good pancreatic dissemination in the pancreas at high doses, when systematically utilised they expose the patient to a risk of selection of drug-resistant mutants and altered ecology [159]. At high doses, piperacillin/tazobactam is apparently acceptably disseminated in the pancreas and constitutes an alternative to the carbapenems [159], and while the dissemination of ceftriaxone seems acceptable [159] and that of metronidazole appears excellent, the results with the aminoglycosides have been mediocre [159]. That much said, these data remain largely preliminary, having been drawn up from animal models or small cohorts of not necessarily severely ill patients, and new evidence of better quality would be necessitated to come to definitive conclusions on the type of antibiotic therapy to prioritise both in empirical and documented situations.

Question 5: In patients admitted to critical care for severe acute pancreatitis, what method(s) should be applied to prevent and treat vascular complications?

Experts: Yoann Launey (SFAR) and Céline Savoye-Collet (SFR)

R3.7 – In patients admitted to critical care for severe acute pancreatitis, it is probably recommended to privilege a technique of endovascular interventional radiology to control gastrointestinal haemorrhage complications.

GRADE 2+ (STRONG AGREEMENT)

Rationale

While haemorrhagic complications during acute pancreatitis are rare, they are often associated with mortality (34% to 52%). Their incidence is estimated at 1%–6% [160–162]. In 60% of cases, they are due to pseudo-aneurysm rupture, but bleeding of other origins may also occur: vascular erosion, trauma to vessels caused by drain, bleeding in pancreatic pseudo-cyst, and spontaneous intra-abdominal bleeding [163]. There has been no randomised study comparing the efficacy of surgery *versus* interventional radiology in bleeding control. That said, necrosectomy surgery is responsible for more haemorrhagic postoperative complications (34%) [164], and in the retrospective study by Balachandra et al., initial haemorrhage control surgery as compared to interventional radiology was responsible for a higher rate of mortality (29% *vs.* 13%, respectively, $p < 0.01$) [165]. As for interventional radiology techniques, they have been found to rapidly and relatively non-invasive control bleeding, with a success rate ranging from 69% to 100% in the recent meta-analysis by Sagar et al. [166]. However, procedure failure may occur (6% on average) and necessitate a second embolisation procedure or an operation. While the data from the literature are retrospective and heterogeneous, for the most part they strongly point to the efficacy and long-term safety of this type of treatment. The rare reported complications include splenic infarctus and hepatic or mesenteric ischaemia. The retrospective study by Vander Mijnsbrugge et al. reported a 94% survival rate at two years in patients treated by interventional radiology [167]. Given the intrinsic severity of haemorrhagic complications, discovery by CT-scan of a pseudo-aneurysm is an unmistakable warning sign that should prompt a collegial discussion involving the surgeon, the interventional radiologist, and the intensivist on measures to be taken (image-based monitoring, perhaps preventive embolisation...).

ABSENCE OF RECOMMENDATION – As of now, the literature does not suffice to adjudicate on the risk/benefit balance of the initiation of a high-dose anticoagulant therapy as prophylactic treatment in patients at high risk of splanchnic venous thrombosis or as curative treatment in patients with proven splanchnic venous thrombosis.

Rationale

The incidence of splanchnic venous thrombosis (SVT) in acute pancreatitis ranges from 14% to 22% [168]. The main venous axes involved are the portal vein (24%–36%), the splenic vein (80%–86%) and the superior mesenteric vein (27%–29%) [169,170]. While SVT is often asymptomatic, it can be clinically expressed in hepatic ischaemia, in mesenteric ischaemia by occlusion of the superior mesenteric vein or in gastrointestinal bleeding by rupture of varicose veins due to portal hypertension at the site of the hepato-splenic venous obstruction. In the literature, an association between SVT and necrosis/infected necrosis often appears [171]. While awaiting more robust data, the following SVT risk factors have been proposed: a mCTSI score (modified CT severity index or Mortele score) ≥ 6 [172], intra-abdominal hypertension (> 12 mmHg), major pancreatic necrosis, infected pancreatic necrosis [173,174] and two items reported in the same study [175]: hypo-albuminaemia and bowel wall thickening (> 4 mm). However, given the heterogeneity of the relevant data, most of which are retrospective, it is difficult to determine with certainty a causal link between SVT and the above-mentioned SVT-associated factors.

Preliminary retrospective data suggest that SVT incidence could be reduced by early preventive systemic anticoagulation (21.3% [36/169] *versus* 46.2% [48/104], $P < 0.001$) and that the incidence of isolated splenic venous thrombosis could likewise be reduced (13.0% [22/169] *versus* 27.9% [29/104]), $P = 0.002$) [176]. By contrast, no data are available on the possible interest of high-dose prophylactic anticoagulation in terms of more robust prognostic criteria for morbi-mortality. Similarly, the relevant data in the literature are heterogeneous and of limited quality, with levels of evidence not sufficing to issue a recommendation on the risk/benefit ratio of curative anticoagulation for proven SVT occurring during acute pancreatitis [177]. Even though most of the studies have not mentioned a significant difference in terms of recanalisation with or without anticoagulation, in the retrospective single-centre study by Pagliarial. 2020 [178], the rate of repermeabilisation of the occluded vessel was significantly higher

in anticoagulated SVT patients. On the contrary, the rate of distance cavernoma with or without anticoagulation did not differ. It bears mentioning that effective anticoagulation could be associated with additional haemorrhagic complications [179,180].

Conflicts of interest

SJ reports receiving consulting fees from Drager, Medtronic, Baxter, Fresenius-Xenios, Mindray, and Fisher & Paykel.

KA reports receiving personal fees from Baxter, LFB, Edwards, and Payckel.

LB reports consulting for CVasThera.

JBC reports links of interest with Boston Scientific, and Norgine.

OJB reports links of interest, which are not related to the guidelines, with Jafron, Baxter and BBraun (consulting activities), and personal fees for lectures and teaching activities from Baxter, BBraun, and Fresenius.

YL reports links of interest, which are not related to the guidelines, with LFB BIOMEDICAMENTS, PFIZER PFE France, and IDORSIA Pharmaceuticals Ltd.

PM reports links of interest with MSD and Pfizer.

LM reports paid conferences and congress invitations from General Electrics, Baxter, Fresnius Medical Care, and Pfizer.

TR reports receiving consulting and symposium presentation fees from from bioMerieux, Fresenius Medical Care, Baxter, Nikkiso, Medtronics, Bbraun, and Estor.

CR reports receiving speaker fees from Pfizer, MSD, Shionogi, Biomérieux and Fresenius Medical Care.

RT reports receiving consulting fees from Aguettant, Baxter, Fresenius-Kabi, Nestlé Health Science, Nutricia, Roche, and Servie.

GV reports consulting activities for Boston Scientific, Cook Medical, and FujiFilm Inc., and reports conferences and training activities for Gilead, MSD France, Boston Scientific Corporation, M.I.Tech, Cook Medical, Ferring, Olympus Europe, Norgine, Mayloy Spindler, Pentax Inc., and FujiFilm Inc.

EW reports receiving congress travel fees from GRIFOLS, lecture fees from MSD, Akcea Therapeutics, and LFB.

ADJ reports receiving consulting fees from Drager, Medtronic and Fisher & Paykel.

MG, FB, CDF, LD, MJ, EL, PL, CSC, PS and JPT have no conflict of interest to declare.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.accpm.2022.101060.

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