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INTENSIVE CARE MANAGEMENT OF ACUTE PANCREATITIS: THE 2012 SEMICYUC GUIDELINES

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- The abridged version of these Guidelines are attached PDF in Intensive Care Online: http://www.semicyuc.org/

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Table of Contents

EXECUTIVE SUMMARY.

Background & Objective: Significant changes in the management of acute pancreatitis have taken place since the 2004 Pamplona Consensus Conference. The objective of these guidelines has been to revise and update the previous 2004 guidelines in order to provide updated recommendations and standardize the management of patients with acute pancreatitis that are treated in an Intensive Care Unit (ICU).

Participants: Spanish and international intensive medicine physicians, radiologists, surgeons, gastroenterologists, emergency care physicians and other physicians involved in the treatment of acute pancreatitis.

Levels of evidence and grades of recommendation: The GRADE system has been used to determine the level of evidence and grade of recommendation.

Development of recommendations: The relevant literature published between 2004 and 2012 was reviewed independently by several experts and 16 blocks of questions pertinent to management of acute pancreatitis in an ICU were formulated. All the questions were discussed within the groups first and then a draft of the guidelines was prepared. The draft was debated and then ratified first at the SEMICYUC congress and then at the dedicated Consensus Conference.

Conclusions: A total of 82 recommendations for acute pancreatitis management in an ICU have been presented. Of these, the 2012 determinant-based international multidisciplinary classification of acute pancreatitis, new minimally-invasive approaches to management of necrotizing pancreatitis, and evolving role of nutritional management are considered to be the most important recent developments.

JUSTIFICATION OF THE CONSENSUS CONFERENCE.

Acute pancreatitis (AP) management has changed in recent years, thanks to a better understanding of physiopathology, the improvement of therapeutic armamentarium in Intensive Care Units ([1]), advances in nutritional support in acute pancreatitis ([2]), dynamic approaches of continuous extra renal replacement techniques (TCRR – TCDE) ([3], [4]), acknowledgement of the central role of pancreatic infection, and improvements in surgical techniques ([5], [6]).

While the pathways for AP in an Intensive Care Unit (ICU) ([7]) were published, the Committee realized that many aspects of ICU management were suboptimal and out-of-date. In particular, the lack of uniformity in applying the AP severity criteria is evident and that could be one the reasons for different mortality rates between the studies. We also agree with Dr. Petrov and colleagues that the classification of AP should be based on actual severity factors rather than predicted factors. The new international classification of AP stresses the importance of defining the severity only on the basis of factors that determining the natural course: (peri)pancreatic necrosis and organ failure (OF) ([8]).

Further, some of the recommendations of the Severe Acute Pancreatitis (SAP) Consensus Conference of the Spanish Society of Intensive Medicine and Coronary Units - SEMICYUC 2004 ([9]) had changed, and other emerging recommendations provided basis for the current revision and update of the guidelines. Taking these arguments into account, the AP Pathways Study Group of the SEMICYUC initiated the update of recommendations for AP patients hospitalized in an ICU.

The objective of this new project is to revise recommendations for management of AP in Intensive Medicine.

METHODOLOGY AND DESIGN.

Panel Composition

Firstly, the "scientific support" of the Scientific Committee of the SEMICYUC was requested and subsequently granted on 11 November 2011. Secondly, a call for panel members was issued by means of an "invitation" addressed to all the members of the aforementioned HR group, both in Spain and in other countries, to all the SEMICYUC members and doctors in the corresponding medical specialties, through the Infectious Diseases Group (GTEI) and the Scientific Committee of the SEMICYUC. The "CC Group – 2012 PSAP Recommendations. GTEI-SEMICYUC "was formed during the Assembly of the XXII GTEI Meeting on November 18, 2011 in Barcelona. Thirdly, the panel members were chosen from all the members of the Spanish and foreign groups (Appendix 1).

General Description of the Process

The organizing committee for the new edition of the AP recommendations designed the project, organization, the subcommittee (in multidisciplinary working groups composed of specialists in Emergencies, Digestive Medicine, Radiology, General Surgery and Intensive Medicine), the reference terms and the development of an adaptation plan and the writing up of the recommendations. In addition, the Consensus Conference was presented with the collaboration of SEMICYUC at the XLVI National SEMICYUC Congress held in Santander (Spain) in 2012. Lastly, an international meeting was held, in line with the regulations of the Society, in order to officially present these recommendations in Madrid on 30th October, 2012.

Function and Methodology of the Panel.

The group has decided to use the existing recommendations on the treatment of severe AP and adapt them to the needs of the target population, using the **GRADE** method in adapting the ACCP (American College of Chest Physicians)([10]) articles, due to their applicability and simplicity, although similar versions exist ([11], [12], [13], [14]).

The **GRADE** classification system in adapting ACCP standards, enables us to issue recommendations in a simple manner, on the basis of clinical trials, revisions and published meta-analyzes. For this purpose, this system assesses the articles according to their impact, workload or the strength of the conclusions and the quality of the underlying evidence. The GRADE system describes simple and transparent **criteria** for classifying studies or randomized trials. These criteria are based on the clarity of the methodology and the coherence with current methodological approaches to the classification process.

The GRADE method (Table 1) **classifies** the ***recommendations*** according to:

Grades of recommendation. According to the balance between benefits, risks, costs and potential workloads:

1. **Grade 1**: Strong recommendation, or
2. **Grade 2**: Weak recommendation.
3. **No grade**: There is no recommendation in this regard.

Quality of evidence. The system classifies the quality of the evidence in accordance with the factors that include study design, the consistency of the results, and the availability of evidence, as follows:

A. **Evidence A**: Higher,
B. **Evidence B**: moderate, or
C. **Evidence C**: low.

Revision and Analysis of the Literature

Electronic search in MEDLINE, SCOPUS and EMBASE from 2004 to September 2012 of the literature regarding "severe acute pancreatitis" and everything related to the questions that had been posed.

Development of the Consensus Based on the Evidence

The working group decides to use the 2004 Pamplona Recommendations on the treatment of severe acute pancreatitis and update them to 2012 by using the GRADE method.

Revision Dates

A. First phase.
    a. Beginning: Monday 6 February 2012. Documents were sent for revision to each member of the group by email, and the final wording was the responsibility of the panel supported by the Coordinator.
    b. This revision was subsequently sent to the Group members for their approval.
    c. End of the first phase: Friday, 30th March, 2012. This document was sent to the Coordinator.
B. Second phase.
    a. Beginning: Monday, 2nd April 2012. The final draft of the recommendations was then sent to all the panels of all the groups for their suggestions or corrections.
C. Third phase.

a. Beginning and end: From the 2nd to 31 de may 2012. The General Coordinator prepared the final document. It was subsequently distributed to all the Group members for their final approval.
b. Preliminary presentation to the XLVI SEMICYUC National Congress in Santander – Spain, 11th June 2012.

D. Fourth and final phase. Development of an International "Consensus Conference" Meeting for the official presentation to the entire Group and general public, in Madrid, 30th October2012. Redacción final y publicación.

Guideline and conflicts of interest

All the group members complied with the policy on conflicts of interest, which requires disclosure of any financial or other interest that could be interpreted as a real, potential or apparent conflict of interest. Group members filled out a SEMICYUC declaration of conflict of interest and were asked to identify any ties to companies developing products that might be affected by the publication of the guideline. We requested information on employment, consultancies, stock ownership, fees, research funding, role as a hired consultant and / or membership in committees acting as company consultants. *The Panel made decisions on any case based on whether an individual's role should be limited as the result of a conflict of interest.*

No limitations on conflicts of interest were identified.

Definitions and abbreviations used.

- Acute kidney injury (AKI)
- Patient controlled analgesia (PCA)
- Antinflammatory no esteroideo (AINE)
- Endoscopic retrograde cholangiography pancreatography and Endoscopic sphincterotomy ; ERCP-EE)
- Sistemic decontamination digestive (SDD)
- Multiorganic disfunction (MOD)
- Randomized controlled trial (RCT).
- Multiorganic failure (MOF)
- Organic failure (OF)
- Acute renal failure (ARF).
- Hemofiltration (HF)
- Continuous veno-venous hemofiltration (HFVVC)
- High volume hemofiltration (HVHF)
- Intermittent hemodialysis (IHD)
- Intra abdominal hypertension (IAH)
- Continuous regional arterial infusión (CRAI)
- Enteral nutrition (EN)
- Total parenteral nutrition (TPN)
- Acute Pancreatitis (AP)
- Mild Acute Pancreatitis (MiAP)
- Moderate Acute Pancreatitis (MAP)
- Severe Acute Pancreatitis (SAP)
- Critical Acute Pancreatitis (CAP)
- Potentially severe acute pancreatitis (PSAP)
- Post-ERCP pancreatitis (PPC)
- Procalcitonin (PCT)
- Systolic blood pressure (SBP)
- Intra abdominal pressure (IAP)
- C-reactive protein
- Abdominal fine needle puncture (FNA)
- Magnetic resonance imaging (MRI)

- Risk, Injury, Failure, Loss, End stage kidney disease (RIFLE)
- Abdominal compartment syndrome (ACS).
- Systemic inflammatory response syndrome (SIRS)
- Nasojejunal tube (SNY)
- Continuous renal replacement therapy techniques (CRRT)
- Continuous techniques debug bypass (TCDE)
- Renal replacement techniques (TDE)
- Computed tomography (CT)

Definitions. The definitions and complications of the illness are summarized in each chapter and in the subsequent tables that are shown in this document and in the 2011 AP Pathways (7).

EXECUTION MEASURES

At annual intervals the Main Coordinator and Chair of the SEMICYUC Scientific Committee will determine the need for revisions of the recommendations guidelines on the basis of an assessment of the current literature.

The Group and the SEMICYUC would like to have a dedicated meeting on AP *every five years* to discuss possible changes and propose a revision to the Scientific Committee for its approval.

INTENSIVE CARE MANAGEMENT OF ACUTE PANCREATITIS: THE 2012 SEMICYUC GUIDELINES

Questions. Questions have been distributed into 16 blocks, which are answered by one or more numbered recommendations. The authors are mentioned in the Annex / Appendix:

1st Question: Diagnosis of Acute Pancreatitis in Emergency Services.

AP generally has a mild and self-limited evolution but approximately 20-30% of patients suffer from a severe stage, associated with the onset and maintenance of a SIRS, MOF and death.

The main complications of PA are the development of necrosis, infection, sepsis and BMD.

The necrosis infection appears in 30-40% of patients with necrosis> 30% ([15], [16], [17]) and is three times the mortality rate (15).

The overall AP mortality is 5%, and it is less than 3% in the absence of necrosis, whereas it can reach 17% in the case of pancreatic necrosis (30% with infected necrosis, 12% with sterile necrosis 12%). The mortality in the absence of any organ failure is 0%; with single organ failure it is 3% and with mutiorganic failure the figure is 47% ([18]). Mortality in the development of PA has two peaks: one is early (within 2 weeks) and the second one is later in its development. In the first phase mortality is due mainly to the development of SIRS caused by sterile necrosis, and in the later phase it is associate with sepsis infection which is secondary to pancreatic necrosis ([19], [20]).

Patients with sterile necrosis were treated conservatively, while those with proven infection and systemic signs of sepsis are candidates for surgical treatment (16).

For these reasons, a definition and classification of this pathology has been sought for over a century. The Atlanta classification defined the PA as an acute inflammatory process of the pancreas with variable involvement of other local tissues and distant organ systems. It is associated with pancreatic enzyme

elevation in blood and / or urine ([21], [22]). The clinical definition of AP in the presence or absence of underlying chronic pancreatitis requires two of the three following findings:

a. Abdominal pain strongly suggestive of AP (epigastric pain radiating to the back)
b. Serum amylase and / or lipase activity at least 3 times the normal value.
c. Findings characteristic of AP with abdominal ultrasound, CT or MRI ([23], [24]).

The onset of the AP is defined as the exact time when abdominal pain begins (not the time of hospital admission), and it should be carefully noted (21, 22, 23, [25]). At other times AP may appear without abdominal pain. Diabetic coma, severe hypothermia or failures of other organs such as shock, severe gastrointestinal bleeding and respiratory distress may sometimes be the symptoms of acute pancreatitis and they may conceal abdominal pain (19).

Amylase and lipase are important for AP diagnosis; lipase which is more specific than amylase, but they are not markers of clinical severity (4, 9).

Imaging techniques are essential for establishing the cause and severity.

Recommendation 1. Diagnosis of acute pancreatitis: At least two of the following criteria should be present. **Strong grade of recommendation (1), high quality of evidence (A).**

- Abdominal pain suggesting pancreatitis, which is a symptom considered at the onset of acute pancreatitis.
- Levels of lipase and/or amylase in serum which are three or more times greater than the normal value.
- Characteristic findings in CT or ultrasound studies.

2nd Question: Classification of Acute Pancreatitis.

Early identification of severity signs in a patient with AP during the first three days following hospital admission has been shown to improve the prognosis and reduce mortality (7). For this reason, prompt classification of severity is necessary. For this purpose, a new AP classification was drawn up in 2012 (8), which is based on two fundamental principles:

First, it is based on real severity factors instead of predictive factors. The use of systems with multifactorial scoring (APACHE II, Ranson criteria, Imrie-Glasgow criteria, etc.) which had been utilized in the original Atlanta classification complicates the situation and has little clinical applicability because of misclassification error in 30-40% of patients. Consequently, the identification of early persistent OF markers ([26]) and pancreatic alarm signs defined later on (7) is important.

Second, the new classification defines the severity only on the basis of the determining factors of the patient's progress: pancreatic (peri) necrosis and organ failure (OF). The three most frequent and determining OFs in the patient's progress are cardiovascular, renal y respiratory ([27]). The appearance of any one of them is sufficient for determining the severity.

The definitions used for the severity categories in the new classification are based on the characteristics of the "local determinants" (lack of, or sterile or infected peri/pancreatic necrosis) and "systemic determinant" (insufficiency of a lacking, transitory or persistent organ), as well as the possibility of

interaction among the determining factors during the same AP episode. Clinical or analytical parameters other than these determinants should not be used to classify severity of AP.

Definitions.

1. **Mild Acute Pancreatitis (MiAP)** is characterized by the absence of both pancreatic (peri) necrosis and organ failure.
2. **Moderate Acute Pancreatitis (MAP)** is characterized as the presence of any type of sterile pancreatic (peri) necrosis and/or transient organ failure.
3. **Severe Acute Pancreatitis (SAP)** is characterized as the presence of any degree of infected pancreatic (peri) necrosis or persistent organ failure.
4. **Critical Acute Pancreatitis (CAP)** is characterized as the presence of infected pancreatic (peri) necrosis and persistent organ failure.

Transitory organ failure: Data on an OF that are resolved in a short period of time after having applied adequate support measures.
Transitory organ failure: Data on an OF that are not resolved in a short period of time after having applied adequate support measures.

The authors of the new international multidisciplinary classification define transitory or persistent as an OF that is not resolved in less or more than 48 hours, although we believe that this deadline is too long for certain OFs and we adopted the definition of Sepsis Surviving Campaign ([28]).

Definition of Organ Failure (OF):

1. Hypotension: Systolic arterial pressure (SAPS) less than 90 mmHg or a reduction of 40 mmHg in basal SAP, with tisular hypoperfusion signs (lactate > 3 mMol/L); Saturation of central venous oxygen $SvcO_2$ < 70%.
2. Respiratory failure: PaO2 < basal 60 mmHg (with supplementary O_2); or PaO_2/FiO_2 < 300 mmHg.
3. Acute renal failure: an increase of basal creatinine by 2 (AKI-2, o RIFLE-I) and/or reduction of urinary flow (oliguria) < 0,5 ml/kg/h x 12 hours.

Another classification has also been proposed that suggests dividing AP into three categories ([29], [30], [31], [32], [33]).
- Mild AP: AP without complications or organ failure.
- Moderate AP: AP with local complications and without organ failure;
- Severe AP: AP with organ failure, with or without local complications.

Although both classifications have similarities ([34]), the Committee advocates the classification with four categories of severity as it emphasizes the worst-case prognosis of the relationship of organ failure and pancreatic infection, as compared to organ failure without pancreatic infection ([35], [36]).

Recommendation 2. We recommend to discontinue the use of the Atlanta classification. **Strong grade of recommendation (1), high quality of evidence (A).**

Recommendation 3. We recommend the use of the 2012 "determinant-based" international multidisciplinary classification of AP that classifies AP on the basis of four different levels and is based on the appearance or non-appearance of organ failure and local

complications: **MiAP** = lack of pancreatic (peri) necrosis and without OF; **MAP** = presence of any type of sterile pancreatic (peri) necrosis or transitory OF; **SAP** = presence of any grade of infected pancreatic (peri) necrosis or persistent OF; y **CAP** = presence of infected pancreatic (peri) necrosis or persistent OF and persistent OF. **Strong grade of recommendation (1), moderate quality of evidence (B).**

3rd Question: Organization for integral AP management. Protocolized management

Different AP treatment guides have been published in the last several years. A variety of medical specialists have contributed to these guides which have been drawn up in a multidisciplinary way. Many of these guides recommend that patients in severe stages of this illness be treated in hospitals with prior experience in treating this illness and that they should have a multidisciplinary team of physicians to handle AP ([37], [38], [39], [40]). The so-called "solitary AP" syndrome, which is defined as an AP patient who is left unattended in a waiting room without subsequent monitoring. Hospitals in Spain have AP Pathways with a multidisciplinary approach ensuring that an AP patient who is admitted to a hospital receives adequate treatment (7).

Nonetheless, we do not know of any study that compares protocolized and multidisciplinary treatment of AP to treatment according to clinical criteria followed by the acting physician.

A recently published study indicates that of the 49 hospitals surveyed in Sweden ([41]), only 25 (51,02%) had a standardized protocol treatment, although most of them are interested in participating in an AP register. According to another study performed in Great Britain, Ireland and Canada ([42]), only 23.2% of the hospitals covered by the study had a multidisciplinary team for AP treatment. Another two studies showed a very low level of compliance with the principal measures of the treatment guides ([43], [44]), although another study indicated a notable improvement ([45]).

To summarize, medical societies prepare treatment guides for multidisciplinary treatment, recommend the creation of specialized teams and the drawing up of AP management protocols, although their clinical impact has yet to be measured. In addition, the level of compliance on an International scale has been poor.

Since AP is an illness where a range of medical specialists are involved in its treatment, with a complex, prolonged and unpredictable patient recovery, we recommend that the patients in complicated stages of AP be referred to hospitals with multidisciplinary teams for AP management, and these hospitals should draw up their own protocol based on the recommendations made by the local medical societies.

Recommendation 4. We recommend that patients with MAP, SAP, and CAP be treated in hospitals with known expertise in AP treatment and that they have multidisciplinary teams for treating AP patients: Emergency Treatment, Digestive Medicine (with experienced endoscopy technicians), Radiology (with computerized tomography and invasive radiology), Biliary-pancreatic Surgery, Internal Medicine and Intensive Medicine. Otherwise, patients with MAP, SAP and CAP should be referred to a specialized hospital. **Strong grade of recommendation (1), low quality of evidence (C).**

Recommendation 5. We recommend that hospitals treating patients with MAP, SAP and CAP prepare pathways in a multidisciplinary way for AP treatment based on the recommendations made by the local medical societies and suitable to their resources. **Strong grade of recommendation (1), low quality of evidence (C).**

4th Question: Criteria for early admission to an ICU. New concepts.

1. Pancreatic alarm signs", versus previous early severe criteria. In Emergency Services, Digestive Medicine, ICU and others.
2. Potentially severe acute pancreatitis - PSAP
3. Assessment criteria and admission of PSAP patients in an ICU.

A new dynamic and evolutionary classification and assigning a category of severity (especially SAP and CAP) is therefore "a posteriori". This is a potential disadvantage of the new classification, since it is impossible to diagnose MAP, SAP, and CAP upon patient admission to the hospital (7). Consequently, from a practical standpoint, we introduced the concept of *"Potentially severe acute pancreatitis" (PSAP)*. To summarize, we define PSAP as a form of acute pancreatitis that presents one or more organ failures (arterial hypotension, respiratory problems, renal) or alarm signs (7) and it is useful for initial patient management.

At the same time, some of the previously published severity criteria (9) indicate that patients may fail to recover satisfactorily and we call these criteria "alarm signs". The alarm signs are those forms of data or symptoms/signs in an AP patient that indicate a possible failure to recover satisfactorily and these signs can be of a clinical, radiological or analytical nature or prognostic scales that were enumerated in the Atlanta classification.

The pancreatic alarm signs are the following (7):

1. Clinical: obesity, age, abdominal defenses, pleural effusion, alteration of consciousness.
2. Analytical: C-reactive protein (CRP) > 150mg/L, or a progressive increase in 48 h; Hematocrit > 44%, Procalcitonina (Procalcitonin) greater than 0.5 ng/ml during the first 24 hours.
3. Radiological: pleural effusion, free peritoneal fluid.
4. Prognosis scales: APACHE II > 8; APACHE-0 > 6; Ranson-Glasgow >3 points.

There is increasing evidence that any delay in reviving the patient, especially in the supply of volume, has a negative impact on AP patient recovery ([46], [47], [48], [49], [50], [51], [52], [53]). For this reason, we recommend the early detection of AP patients that are developing OF in order to revive the patient with the best material and human resources, according to the structure of each hospital. Reviving the AP and OF patients should be performed early, managed according to objectives and continuously monitored. Since postponing the treatment has a negative impact on the patient's recovery, and current clinical, radiological, and analytical markers show low sensibility and specificity (32), we suggest that AP patients receive a clinical, protocolized analytical, and regular follow-up during the first 72 hours for early detection of OF and commencing energetic treatment a quickly as possible (7). In other words, "solitary AP" syndrome should be avoided. This term is defined as an AP patient who is left unattended in a waiting room for the first several hours, without being subjected to a well-defined protocol or pathways or subsequent monitoring.

The major factor in AP patient recovery is the existence or non-existence of OF, especially if it persists for a long period of time ([54], [55], [56], [57], [58]). For this reason, all the patients with OF who do not respond to the initial support measures should be admitted to Intensive Care Service.

The development of pancreatic infectious complications is the second major factor in AP patient recovery, especially infected necrosis (29, 30, 54, 56). The appearance of a pancreatic infection without OF indicates a morbi-mortality which is much less than if it had been associated with an OF. We recommend close monitoring of patient recovery and quick admission of patients with pancreatic infection associate with OF to the Intensive Medicine Service.

Recommendation 6. We suggest using the category of PSAP for patients with either OF or an alarm sign at the onset of patient recovery, presuming that transitory or persistent organ failure or pancreatic infection will appear. **Strong grade of recommendation (1), low quality of evidence (C).**

Recommendation 7. We recommend the detection and early treatment of AP patients who are developing OF in order to initiate invasive measures to revive the patient as soon as possible. **Strong grade of recommendation (1), high quality of evidence (A).**

Recommendation 8. We recommend admitting patients who are developing OF and who do not respond to initial measures to revive them to an ICU. **Strong grade of recommendation (1), high quality of evidence (A).**

Recommendation 9. We recommend admitting patients with pancreatic infectious complications associated with OF to an ICU. **Strong grade of recommendation (1), high quality of evidence (A).**

5nd Question: Biomarkers. Inflammatory and Infection Markers

The high rate of PSAP morbidity and mortality, whether severe or critical (SAP or CAP), has forced us in recent decades to try to find a useful tool for the early prediction the severity and development of pancreatic infection during the course of AP and thus establish a prognosis and adequate treatment measures.

AP leads to initial damage to the peri-pancreatic and pancreatic tissue and induces inflammatory cascade activation with the release of proinflammatory mediators (including IL 6, 8, 18 and TNF). These mediators play a key role in the pathogenesis of PSAP, insofar as a SIRS may lead to the onset of MOD and death depending on its severity ([59],[60]).

Various methods have been used to predict the severity: scores grouping a combination of clinical, biochemical and radiological markers (Ranson, Imrie, APACHE, Atlanta, Balthazar), isolated analytical determinations centered on inflammatory response markers (CRP, cytokines, procalcitonin, etc.) and others such as elastase, phospholipase, trypsin, B2 microglobulin, pancreatic proteases ... (17, 19, 20, [61], [62], [63]).

Concerning the prediction scores named above, its main drawback is that it does not allow for early prognosis during hospital admission because the assessment is made 48 hours later and sometimes it is collected "a posteriori".

Despite numerous studies of different biomarkers, the results are different, so that we will review in this section the most relevant biomarkers that have proven to be useful in the early prediction of the severity and development of pancreatic infection during AP development.

CRP is an acute phase reactant synthesized by the liver. It has been supported by many studies as a predictive marker of severity. Its advantages are its rapid determination, ease of measurement, reproducibility and inexpensive cost. Its major drawback is that the peak appears after 48 hours from the onset of symptoms, so it is of no value in the first assessment. It has been established that a CRP figure of 150 mg / L after 48 hours acts as a good predictor of severity in AP, which is the reference value with a sensitivity and specificity> 80% and a negative predictive value (15, 19, 20, [64], [65], [66], [67]).

As mentioned previously, in the initial phase of the PA, as a result of tissue damage cascade activation occurs with the release of inflammatory mediators, such as proinflammatory cytokines IL-6, 8, TNF, etc. Cytokine levels reflect the magnitude of the inflammatory response. These cytokines precede CPR and could therefore be useful as predictors of severity in the acute phase.

IL-6 is considered the earliest marker of severity. It is segregated by macrophages in response to tissue injury and it is the main mediator in the synthesis of acute phase proteins such as fibrinogen or PCR ([68]).

IL 8 is also a potent cytokine similar to IL 6. Several studies have demonstrated the efficacy of both in predicting the severity of the acute phase in AP (19, 62, 64, 65, [69], [70]). A meta-analysis published in 2009 confirmed these results, with a sensitivity and specificity for IL 6, 83 and 75% in the first 24 hours. In regard to IL 8, the sensitivity and specificity data are lower than in IL-6 in the first 24 hours and greater in subsequent days (62, 68). Subsequent studies even reflect sensitivity figures close to 100% during the first hours following admission, and are thus greater than CRP in this early stage ([71]).The cutoff varies according to the different series, the most recent study reports a figures of 38 pg / ml for IL-6 and 37 pg / ml for IL 8 (61).

Procalcitonin (PCT) is the inactive propeptide of the hormone calcitonin. There have been many studies that have attempted to endorse its use in two ways: as a predictor of severity in the acute phase and as a predictor of infection in the developmental stage.

Regarding the first point, studies have established that the PCT is a useful marker of severity in the the acute phase, within 24 hours (better than CRP), with sensitivity and specificity data close to 80% and a negative predictive value. The established cutoff varies according to the articles reviewed. Up to three meta-analyzes in 2006, 2009 and 2010 provide good diagnostic accuracy with a threshold value of 0.5 ng / ml (59, 62, 63, 67). A later prospective study, in 2011, with a limited number of patients, concluded with a cutoff value of 1.7 ng / ml and that it has the best predictive capability (17).

In a developed case of pancreatitis pancreatic necrosis infection is a major cause of morbidity and mortality. The "gold standard" for diagnosis is the CT-guided FNA. This technique has certain limitations, requires an experienced staff for completion, requires a waiting period for microbiological confirmation and the result can be distorted in patients who are receiving prophylactic antibiotics. Therefore, attempts have been made to find a marker that identifies pancreatic infection in an early stage. The most supported marker in different studies to date is PCT.

Elevated PCT figures correlate with the presence of infection having a sensitivity and specificity of 90 and 100% and a high negative predictive value. The established cutoff is 1.8 ng / ml (15, 64, 68, 70, [72]).

Determining PCT does not make it unnecessary to perform FNA but it can act as an alarm sign and set the time for performing the puncture. It also helps us to select those patients who may benefit from prophylactic antibiotics.

In conclusion, early prediction of the severity of AP is essential for applying appropriate therapeutic measures aimed at reducing morbidity and mortality. For this reason, the biomarkers that have shown to be efficient are IL-6 and PCT in the first 24 hours following admission and CFP in 48 hours.

Many other variables, such as phospholipase A2, B2 microglobulin, IL 1, IL 18, TNF, elastase, trypsin, and trypsinogen have been studied, but so far they have not been shown to be superior to other biomarkers and their measurement is more complex and less accessible.

Recommendation 10. The decision to use CRP within 48 hours from the onset of symptoms with a cutoff value of 150 mg/L could help to identify promptly those patients that develop AP in its complicated stages. **Strong grade of recommendation (1), moderate quality of evidence (B).**

Recommendation 11. IL6 is a reliable and early predictor of severity in the first 24 hours following patient admission. **Strong grade of recommendation (1), moderate quality of evidence (B).**

Recommendation 12. PCT is an early severity marker in the first 24 hours following patient admission with a cutoff value of 0.5 ng/ml. **Strong grade of recommendation (1), low quality of evidence (C).**

Recommendation 13. The increase of PCT with values greater than 1.8 ng/ml in the developing phase of pancreatitis may prove useful for distinguishing between sterile pancreatic necrosis and infected pancreatic necrosis. **Strong grade of recommendation (1), moderate quality of evidence (B).**

6th Question: Role of Radiology in AP. Diagnosis of infected necrosis. Percutaneous Drainage.

The Role of Radiology in Acute Pancreatitis.

Less invasive techniques, alternatives to surgical necrosectomy such as percutaneous drainage, endoscopic transgastric drainage or minimally invasive retroperitoneal necrosectomy are increasingly being used, as described in the chapter on Surgery. It is not clear which is the best strategy in these patients and in many cases it is necessary to use more than one procedure (5). The success of the treatment depends on cooperation and joint efforts among intensivists, gastroenterologists, surgeons and radiologists.

In patients with PSAP and early MOF (in the first week) management is basically clinical and the role of radiology is lesser. In the second phase of the disease (after the first week), in the group of patients with PSAP who do not recover, a series of pancreatic and peripancreatic morphological changes take place, as well as local infections that can appear systemically, such as the infection of the necrotic tissue which leads to sepsis and late multiorgan failure.

In this second phase the role of radiology is crucial for identifying and defining these morphological changes, depending on which will be used to schedule the most appropriate treatment for each patient ([73], [74], [75], [76]).

Abdominal CT with intravenous contrast (iv) is considered the **choice imaging technique** for assessing AP patients (14). Not all AP patients require a CT study, as most present have mild cases that are quickly resolved. The **indications for abdominal CT** in the context of AP apply to those cases with diagnostic doubts about confirming the suspicion of AP in patients with PSAP, in patients with mild AP who do not improve after 72 hours, or in any patient with AP who has a bad clinical recovery.

- Firstly, CT enables us to **assess the presence and extent of pancreatic necrosis**. This requires performing CT scans with IV contrast, since the definition of pancreatic necrosis is based on the absence of pancreatic parenchymal enhancement after contrast administration. For proper assessment of the necrosis **the ideal option is to perform CT 48-72 hours following the onset of the outbreak,** because a study may underestimate early pancreatic necrosis (75).
- Secondly, CT enables us **to identify the existence of pancreatic and peripancreatic fluid collections and describe their morphology**. In these patients the description of abdominal collections is important for morphological classification, which will enable us to assess the best treatment for each case ([77]).Two types of collections, some without necrotic tissue, including acute fluid collection and the pseudocyst, and others with necrotic tissue, including postnecrosis collection and encapsulated necrosis are currently recognized.

Acute fluid collections appear early during the first 4 weeks, they have no solid components and are located adjacent to the pancreas, without a defined wall and confined by the peripancreatic fascia. Most of these collections **remain sterile and are resolved spontaneously**, although some may become infected or become pseudocysts ([78]). **Pseudocysts** correspond to the evolution of acute collections that are not resolved spontaneously and where a **minimum of 4 weeks** have elapsed from the onset of the illness, **have a characteristic wall which is a pseudocapsule** and there are no solid components in its interior, and they can be sterile or infected (74).

On the other hand there are **collections pancreatic / peripancreatic with necrotic tissue**, which are the natural evolution of necrosis. As is the case of acute collections, these collections can be infected or not. **After 4 weeks they may become encapsulated** and result in what is known as encapsulated necrosis (73, 78).

The main difference between these collections is the existence of necrotic tissue in its interior and it is important to objectively assess in order to treat them. From the radiological point of view, **this distinction is a diagnostic challenge**; radiographic findings often overlap and the characteristics of the collections evolve over time. Acute fluid collections are seen as low density homogeneous collections. Pseudocysts are also seen as homogeneous fluid collections but with a capsule that captures contrast. Inside postnecrosis collections **we identified areas of higher density** corresponding to necrotic tissue and in the encapsulated necrosis we also identified a capsule that captures contrast. (73, 78).

- Thirdly, a CT enables us to **identify extrapancreatic findings** that influence the evolution of AP (**gallstones, bile duct dilatation, venous thrombosis, pseudoaneurysms, ascites, pleural effusion,** inflammatory involvement of neighboring organs and others).
- Finally, CT, along with ultrasound, serves as a guide for **percutaneous surgical procedures**.

There are currently two radiological "scores" for **assessing the severity of an AP outbreak**, based on the CT findings:

The Balthazar Severity Index is the most widely used and it is based on the assessment of inflammatory morphological changes and the detection of pancreatic necrosis areas (75).

The Balthazar Severity Index	
Pancreatic Inflammation	**Points**
A. Normal pancreas	0
B. Enlargement of the focal size or diffused pancreas	1
C. Inflammation of the pancreas and/or peripancreatic fat	2
D. Only one pnacreatic Collection	3
E. Two or more peripancreatic collections and/or retroperitoneal gas	4
Pancreatic necrosis	**Points**
0	0
< 30 %	2
30-50 %	4
> 50 %	6
The score is associated with the morbidity and mortality o fan AP outbreak: - 0-3 points: 8% complications, 3% mortality - 4-6 points: 35% complications, 6% mortality - 7-10 points: 92% complications, 17% mortality	

Modified Mortele Severity Index; that adds extrapancreatic findings to the Balthazar Index (76).

Modified Mortele Severity Index	
Pancreatic Inflammation	**Points**
Normal pancreas	0
Pancreatic alterations without extrapancreatic involvement	2
Peri/pancreatic liquid collections or necrosis of peripancreatic fat	4
Pnacreatic Necrosis	**Points**
0	0
< 30 %	2
> 30 %	4
Extrapancreatic Complications	**Points**
Pleural effusion, ascites, vascular complications, complications in abdominal organs or gastrointestinal tract involvement	2

Ultrasonography in AP patients is the major indication to confirm the etiological diagnosis, basically **the presence of gallstones.** In some cases it serves for monitoring and controlling collections and can be used as **a guide for surgical procedures** (74).

MRI is not routinely used in AP patients, but it may be a **good alternative** to CT in cases of contraindication for iodinated contrast allergy or renal insufficiency. Some authors have even demonstrated the usefulness of MRI without intravenous contrast for assessing pancreatic necrosis ([79], [80]).

Diagnosis of infected necrosis.

In patients with necrotizing PA and clinical suspicion of infection **it is important to establish the diagnosis of infected necrosis** as soon as possible**.** As mentioned before, IV contrast-enhanced CT is the procedure of choice to assess the presence of necrosis, but it does not differentiate between sterile and infected necrosis in most patients. The detection of air in the necrotic areas raises high suspicions of infection, but this is a rare finding. **Puncture-needle aspiration (PNA) and CT radiological control** in the area of necrosis **is the technique of choice** for establishing a diagnosis of infection ([81], [82], [83]).

It is important to have access to necrosis by avoiding the bowels in order not to contaminate the sample. If the sample is sterile, the necrosis should be considered uninfected. However, it should be borne in mind that **10%** of FNA are **false negatives**, the puncture should be repeated a few days later if there is a strong suspicion of infection.

FNA is also the technique of choice for the diagnosis of collections and pseudocysts with suspected infection.

Percutaneous drainage. Indications, procedure, complications.

Indications:

- **Infected fluid collections or pseudocysts.** They are **the main indication of percutaneous drainage** in AP patients. **Sterile fluid collections should not be drained and** conservative treatment is recommended (82). The puncture or unnecessary drainage of sterile collections increases the risk of secondary infection (77).
- **Non-infected pseudocysts** are larger **than 5 cm** and have developed for more than 6 weeks **or generate symptoms** (abdominal pain, or compression of the biliary or gastrointestinal tract)**. It is a controversial indication,** but it is generally agreed that symptomatic pseudocysts should be treated although they are sterile (82).
- Peri / infected pancreatic necrosis (postnecrosis collections). The success of percutaneous treatment of infected acute collections or of pseudocysts is well established. In recent years more and more groups have been using percutaneous drainage to treat necrotizing AP ([84]).The **goal** of percutaneous drainage is not the resection of pancreatic tissue, but the **control of sepsis** by means of draining infected collections, which is achieved in approximately 75% of the patients (81). In a systematic review of the literature ([85]) there is evidence that **half the patients** with pancreatic necrosis treated with percutaneous drainage **survive without the need for subsequent surgery**. If surgical necrosectomy is required, using percutaneous drainage can **help to postpone surgery** for a few weeks, which is associated with a better clinical outcome. Another review of the literature shows that the drainage of peri / pancreatic necrosis **is possible in 84% of the patients** ([86]).

Procedure:

Percutaneous drains are placed under ultrasound or CT control. **The safest route should always be chosen** by avoiding the bowel and if possible solid organs to prevent bacterial contamination and risk of bleeding.

Wherever possible, **lateral retroperitoneal access** facing the previous peritoneal access **is recommended**, to promote gravity drainage of the collections (5, 77, [87]).

Thick and multiperforated catheters (> 14 Fr) are recommended, because the material to be drained is often viscous or partitioned off. The use of thick catheters is associated with a lower risk of blockage and an equal theoretical risk of complications than those of a smaller magnitude. The use of **various catheters** is sometimes necessary for draining the same collection. **The meticulous care** of these catheters once they are placed in position is essential for proper operation. The catheters should be attached to the skin by a minute piece of silk or hydrocolloid dressings, and it is necessary to monitor them to ensure that they do not lean or are withdrawn involuntarily. **Physiological serum instillation** is advised, ideally 5-10 ml every 8 hour to keep them permeable.

They should be removed when the sepsis has been clinically resolved, drainage is not purulent, the amount is less than 10 ml over 48 hours and the collection has disappeared by imaging (87). We should warn that these collections sometimes take weeks to resolve. The permeability of the catheter should be monitored in the event it's clogged. Attempts should be made to permeabilize the catheter with sterile saline or with a flexible guide prior to replacement of the catheter.

In the case of persistent debit and by disappearance of the collection by Imaging the risk of a pancreatic fistula due to disruption of the pancreatic duct should be considered (77).

Complications of percutaneous drainage:

Most of the described complications are **pancreatic-cutaneous or pancreatic-enteric fistulas** (15%). Complications **directly related to the catheter** are rare and include bleeding, intestinal perforation, pneumothorax or self-limited pain. Bleeding is usually venous self-limited, and, although there have been reports of massive bleeding and death due to vessel injury, such as the splenic artery or pseudoaneurysm ([88]).

RECOMMENDATIONS

Role of Radiology in Acute Pancreatitis.

Recommendation 14. Abdominal CT with IV contrast is not indicated for all AP patients, but only for PSAP patients. **Strong grade of recommendation (1), moderate quality of evidence (B).**

Recommendation 15. The following are considered severe alarm criteria of AP: the existence of pancreatic necrosis (defined as the lack of glandular enhancement with iodinated IV contrast) and/or the presence of peripancreatic collections (Grades D and E by CT of the Balthazar Index). **Strong grade of recommendation (1), moderate quality of evidence (B).**

Recommendation 16. Abdominal CT with IV contrast is to be performed in the first 24 hours en those cases with an uncertain diagnosis. For an accurate assessment of pancreatic necrosis, the best option is to perform the CT between 48 and 72 hours from the onset of the outbreak. **Strong grade of recommendation (1), moderate quality of evidence (B).**

Recommendation 17. MRI is a good alternative to CT in patients who are allergic to iodinated contrast or who suffer from renal insufficiency. **Weak grade of recommendation (2), moderate quality of evidence (B).**

Diagnosis of infected necrosis. PAAF.

Recommendation 18. If there is a suspicion of pancreatic necrosis, infection and/or of pancreatic collections abdominal fine needle puncture should be performed for diagnostic purposes, directed by either ultrasound or CT. **Strong grade of recommendation (1), moderate quality of evidence (B).**

Recommendation 19. Given that there is a 10% risk of false negatives with the use of FNA, it should be repeated if the clinical suspicion of infection persists. **Weak grade of recommendation (2), low quality of evidence (C).**

Percutaneous drainage. Acute fluid collections / pseudocysts.

Recommendation 20. We advise drainage (internal-external endoscopic drainage or percutaneous drainage) in the following cases: a) Acute fluid collections or infected pseudocysts, b) if there is clinical pain or biliary obstruction. The choice of one or another technique is based on the anatomical characteristics of the collections, the availability of personnel to perform the technique and experience in performing it. **Strong grade of recommendation (1), low quality of evidence (C).**

Recommendation 21. We recommend the drainage of infected collections only. **Strong grade of recommendation (1), moderate quality of evidence (B).**

Infected Necrosis.

Recommendation 22. In patients with high surgical risks, a percutaneous drainage of infected necrosis is recommended prior to surgery. The main objective of percutaneous drainage is control of the sepsis. It is considered a technical "bridge" until a more permanent treatment can be administered, because it can be beneficial for patients whose severe condition prevents them from having any type of necrosectomy. It is also worth mentioning that up to 50% of patients with infected necrosis who have been treated with percutaneous drainage survive without the need for subsequent surgery. **Weak grade of recommendation (2), moderate quality of evidence (B).**

7th Question: Antiproteases and Continuous Arterial Regional Infusion.

Is the continuous intravenous administration of protease inhibitors useful in the treatment of SAP?

In the 1960s the aprotinin protease inhibitor was widely used for the treatment of SAP, without demonstrating any clinical efficacy in three randomized clinical trials (RCTs) ([89]).

Since 1990, and particularly in 1995, the study of the effectiveness of the inhibitor synthetic of the gabexate mesylate (GM) protease began, but a meta-analysis ([90]) of four RCTs on the use of GM and the inhibitors of pancreatic secretion (octreotide, somatostatin) did not show a reduction in the frequency of surgical intervention or mortality, although the incidence of complications was reduced. The RCT by Chen et al ([91]), whose results were published in 2000, showed that continuous intravenous administration of gabexate mesilate (2400 mg / d) for 7 days significantly reduced the frequency of complications and mortality rate. Subsequently Seta et al ([92]) and Heinrich et al ([93]) reached two opposing conclusions on the use of antiproteases in AP, although the mortality was reduced in the AP subgroup.

Therefore, the clinical utility of protease inhibitors in SAP, administered intravenously to reduce the incidence of complications and mortality, is currently unknown and controversial. Furthermore, we must take into account that drugs can not easily reach the pancreas intravenously due to ischemia or impaired microcirculation ([94]).

Studies show conflicting results and its use is only recommended by Japanese authors (39), although from 2006 to 2010 the level of recommendation in its guidelines (JPN guidelines) has dropped from B to C1 (Adapte methodology).

Is regional intra-arterial infusion of protease inhibitors and antibiotics to reduce mortality and frequency of infectious SAP complications useful?

As the initial event in the development of AP is trypsin intracellular activation, agents that prevent the activation of trypsin (protease inhibitors) have been used to treat both acute pancreatitis and as a form of prevention of post Pancreatitis -ERCP (PPC). The antiproteases used include gabexate, ulinastatin, nafamostat and aprotinin. In practice, gabexate and ulinastatin agents are common in Japan and China for the prevention of PPC.

Continuous regional arterial infusion (CRAI) of protease inhibitors and / or antibiotics in the early stages of the SAP ([95], [96], [97], [98]) reduces mortality of SAP with necrosis and the incidence of infectious complications, but controlled studies are required to define its exact role, since the studies performed are of low quality (non-randomized, non-double-blind, too few patients).

Yasuda et al ([99]) employ a CRAI of a protease inhibitor known as nafamostat mesilate (NM), an inhibitor of synthetic serine protease: 150 mg / d through the celiac artery + 100 mg / d for the superior mesenteric artery for 5 - 7 days, and antibiotics (imipenem: 0.5 g / d through the celiac artery + 0.5 g / d through the superior mesenteric artery, for 5-7 days) associated with nutrition (NE and / or NPT) to prevent infection. When checking the pancreatic necrosis infection surgery was performed. In conclusion, continuous regional arterial infusion of a protease inhibitor + antibiotics + NET may improve the clinical course SAP, BY reducing infection and avoiding pancreatic surgery. These authors caution that this study is difficult to assess due to significant biases and influence of the EN. The NM has a very short average life but longer than that of MG (55 s for MG vs. 23 min for NM) and it is used in patients with disseminated intravascular coagulation (DIC) and during hemodialysis, due to its potent anticoagulant effect.

Ino et al ([100]) explains more than techniques and, in view of how complicated it is to routinely catheterize the pancreatic artery, we believe that the burden of treatment is too great to be recommend. This study has limitations similar to previous studies.

Piaścik et al ([101]), designed a randomized controlled trial to determine whether the CRAI of a protease inhibitor and antibiotics reduces SAP mortality. For this purpose 78 patients were covered in the trial:

- 39 patients who were administered a continuous regional arterial infusion (CRAI) in the arm of nafamostat mesylate 240 mg / d + Imipenem 1 g / d for 5 days through the pancreatic artery + Imipenem 0.5 g / 8 h iv for 9 days;
- As compared to the other 39 patients who were only administered 0.5 g / 8 h iv imipenem for 14 days (non-CRAI group).

The analysis of the data shows that mortality in the CRAI group was 5.1% compared with 23.1% in the non-CRAI group. Moreover, urgent surgery was required in 10.3% of the CRAI group compared to 33.3% of the non-CRAI group. It has obvious limitations: the small number of patients and it was not double-blinded. It would be necessary to define which of the two drugs administered through the arteries plays a fundamental role in the prevention of septic complications and reduces mortality.

Although the efficacy of CRAI of a protease inhibitor and the best time to administer it is still being debated, it has a C recommendation in the Japanese guidelines. The usefulness of CRAI of a protease inhibitor should be studied further.

Are protease inhibitors / NSAIDS useful for the prevention of post-ERCP pancreatitis (PPC)?

For years more than 35 drugs for preventing have been studied without conclusive results. The antiproteases are used for the prevention of PPC. In practice, the studies come from Japan and China, especially with ulinastatin and gabexate for preventing PPC. Chen et al ([102]) selected studies of patients treated with ulinastatin. Seta y Noguchi ([103]) selected 18 studies covering a total of 4966 patients. This meta-analysis does not support the use of these agents for the prevention of PPC. Even assuming that the protease inhibitors were effective, the number of inhibitors needed for treatment (NNT = 34.5) to prevent a PPC episode of PPC is very high.

Based on the results of meta-analyzes of protease inhibitors, the latest European guidelines on PPC prevention of ([104]) discourage the use of protease inhibitors. JPN guidelines 2010 ([105]) indicate that administration of protease inhibitors does not prevent CFP, and its use should be limited to high-risk patients, and the costs and safety issues should be taken into consideration.

In this respect, the PPC prophylaxis is also achieved with nonsteroidal antiinflammatory drugs (NSAIDs). Elmunzer ([106]) recently conducted a clinical, multicenter, randomized, double-blind trial with 602 patients who were divided into two groups: one composed of 295 patients who received ERCP after a dose of indomethacin, while the rest received a placebo. 9.2% of the treated group (27 patients) underwent PPC, whereas complications occurred in 16.9% (52 patients) in the placebo group. It concludes that treatment with rectal NSAID indomethacin is sufficient for reducing pancreatitis among high risk patients following ERCP. Furthermore, indomethacin is cheap, accessible and easy to administer. High-risk patients are defined as follows:

- Those who have an Oddi sphincter dysfunction or previous history of postCPRE pancreatitis.
- A pancreatic sphincter is performed on them.
- A precut pancreatic sphincter is performed on them.
- Eight attempts of cannulation are performed on them.
- A pneumatic dilation of an intact biliary sphincter intact is performed on them.
- An ampullectomy is is performed on them.
- Two or more of the following criteria are presented: female and less than 50 years old, a history of reoccurring pancreatitis (2 or more episodes), three or more injections of contrast into the pancreatic duct with at least one of them up to the pancreatic tail, excessive contrast injection into the pancreatic duct, resulting in opacification of the pancreatic acini or pancreatic duct brushing to obtain the cytology.

Are continuous regional arterial infusion and decompression by laparotomy in the SAP with ACS useful?

This is a very novel alternative for treating the patients (11%) with SAP by means of a ACS and it has a mortality rate of between 30% and 60%.

This therapeutic mode is based on retrospective studies and its role in the treatment is not exactly known. In the study of Deng et al ([107]), a new system is applied during the surgical decompression procedure in 8

patients. In addition to the abdominal decompression and the placement of large caliber drains for continuous postoperative irrigation catheter, a drug delivery system catheter is added (Drug Delivery System) that was inserted in the peripancreatic artery for continuous postoperative regional arterial infusion. The following were administered: ulinastatin (100 000 U), antibiotics (imipenem / cilastatin 0.5 g) and octreotide (0.3 mg) dissolved in saline (48 ml) and continuously infused through the catheter for this purpose, twice every day. The concentration of drugs in the tissue of pancreatic inflammation increased and improvements in the biochemical indices of inflammation and survival were observed.

Recommendation 23. Intravenous administration of protease inhibitors in PSAP may reduce mortality and complication rates, though we do not recommend its widespread use. **Weak grade of recommendation (2), moderate quality of evidence (B).**

Recommendation 24. Local intra-arterial administration of protease inhibitors and antibiotics in the early phase of PSAP may lead to a decrease in mortality and infectious complications. Nowadays more studies are needed to confirm its efficacy. **Weak grade of recommendation (2), moderate quality of evidence (B).**

Recommendation 25. Intravenous administration of protease inhibitors does not prevent post-ERCP pancreatitis (PPC). **Strong grade of recommendation (1), high quality of evidence (A).**

Recommendation 26. We recommend the administration of indomethacin rectally after ERCP in high risk patients. **Strong grade of recommendation (1), moderate quality of evidence (B).**

8th Question: Control of PIA and approaches to ACS.

Concept. IAP is the pressure within the abdominal cavity. Its normal value in noncritical patients is subatmospheric (<0 mmHg) and it is < 12 mmHg critical patients. An increase in IAP or in intra-abdominal hypertension (**IAH**) (PIA ≥ 12 mmHg) was detected more than a century, and it has been known to cause alterations in the functioning of the organism. In 1876 the increase in IAP was associated with renal dysfunction. Since then, and especially during the last decade, there have been countless references to this issue, how to measure it and its consequences ([108], [109], [110], [111], [112]).

In 2006 an international committee of experts defined **ACS** as IAP ≥ 20 mmHg, which was maintained and associated with new organ dysfunctions, regardless of the etiology ([113], [114]). The currently available literature regarding the value of the IAP in PSAP, whether it is SAP or CAP, is based on observational studies and case series, by associating the increase of AIP with MOD and the mortality rate ([115], [116], [117, 118], [119], [120]). AIP values of which predict OF and mortality, and recommendations for optimizing both the medical and surgical treatment of ACS ([121], [122], [123], [124]) have even been established.

The conference of experts on ACS establishes the intravesical measure as a standard measuring method for AIP (instilling a maximum of 25 ml of isotonic saline), every 6-8 hours, with the patient in a supine position, at the end of expiration and expressing the amount in mmHg (114). This conference recommends that both the AIP values and the abdominal perfusion pressure (**APP**) should be considered, by taking into account that APP = MAP – IAP, when MAP is the average arterial pressure. The objective is to achieve an AAP of 50-60 mmHg, and ACS is diagnosed below this figure if it is associated with organ dysfunction.

Treatment. Inasmuch as our goal is to achieve a correct APP (50-60 mmHg) we can act by improving the mean arterial pressure (MAP) and / or reducing the IAP (115).

The improvement in MAP is achieved initially by volume replacement (28), while bearing in mind that an excessive volume can worsen ACS (47, 115,[125],[126]) and, after replacement has been completed and, if necessary, we will initiate vasoactive amines .

The reduction of the AIP will be achieved by non-surgical techniques and / or surgical techniques.

As for *non-surgical techniques* the aspiration of gastric contents and / or rectal probing; the administration of prokinetics (metoclopramide, erythromycin oral or IV, neostigmine); sedation and relaxation and a reduction of the third space with diuretics and / or techniques renal replacement (115) will be considered.

If attempts to reduce and optimize AIP are unsuccessful and optimize APP, surgical management should be considered. Among the *surgical techniques*, percutaneous drainage should be considered (only in those cases where there is a lot of free intraabdominal fluid) (115, [127],[128]) and/or decompressive laparotomy (107, 115, 121, 123, [129], [130]). If decompressive surgery is performed and there is no suspicion of infected necrosis it is important that no necrosectomy be performed to prevent infected necrosis from occurring.

Recommendation 27. IAP should be measured in all the patients with PSAP. PSAP is to be measured when the patient is in a supine position at the end of expiration every 6-8 hours and through the urinary bladder by instilling a maximum of 25 ml of isotonic saline and this will be measured in mmHg. IAH is considered when the IAP ≥ 12 mmHg is sustained or repeated and ACS will be considered when IAP ≥ 20 mmHg is sustained and associated with SDMO *de novo.* In the case of IAH episodes and SCA development, our objective will be to achieve an APP of 50-60 mmHg. **Strong grade of recommendation (1), moderate quality of evidence (B).**

Recommendation 28. ACS treatment of in PSAP should consist of increasing MAP or reducing IAP in order to improve APP. **Strong grade of recommendation (1), low quality of evidence (C).**

Recommendation 29. Among the non-surgical therapies used to reduce AIP aspiration of intestinal contents by means of a gastric and/or rectal probe, the administration of prokinetics (metoclopramide, erythromycin, neostigmine), sedation and relaxation and a reduction of the third space with diuretics and / or renal replacement techniques should be considered. **Strong grade of recommendation (1), low quality of evidence (C).**

Recommendation 30. Among the surgical therapies used to reduce AIP percutaneous drainage and/ or decompression laparotomy should be considered. The pancreatic area should only be treated when it is infected. **Strong grade of recommendation (1), low quality of evidence (C).**

9th Question: Pain Control and Sedation.

Pain. Pain is the most common symptom of AP and the main reason for patient consultation. Pain has an intense and persistent character, contributes to AP pathophysiology, can cause anxiety and other deleterious effects (greater hemodynamic instability, respiratory distress ...), so a fast and adequate control is one of the basic principles of treatment.

The mechanism of pain remains unknown but its pathogenic factors are presumed to be a perineural inflammation, an increase of ductal system pressure and parenchyma, parenchymal ischemia, an increase of abdominal pressure, feedback mechanisms, mediators such as substance P and calcitonin gene. Also, local complications (pseudocyst formation, an obstructed bile duct, duodenal stenosis) or pharmacological

side effects (alteration of intestinal dysmotility) may aggravate the pain. The first consideration for pain relief is a comprehensive assessment to identify possible surgery that may reduce the progression of pancreatic damage or complications.

Patients with hypovolemia produced by vascular redistribution may experience pain secondary to ischemia. Proper fluid resuscitation can optimize pain control.

There is no choice analgesic regimen based on the evidence. Frequently, the oral route is not optimal due to the presence of nausea, vomiting, ileus or pain intensity. The administration of pyrazolones (metamizol) and / or opioids (morphine, fentanyl, meperidine, tramadol, etc.) administered endovenously are the most widely used.

There is insufficient evidence to demonstrate the superiority of one type of analgesia. Studies have shown the superiority of a fentanyl transdermal patch ([131]), rectal indomethacin ([132]) and continuous procaine infusion of ([133]) versus a placebo. The superiority of some opioids such as pentazocine administered endovenously ([134]) and continuous buprenorphine infusion ([135]) versus continuous procaine infusion has been observed. Its superiority in comparison with opioids, such as buprenorphine versus intramuscular meperidine ([136]) has not been observed. In a study of 16 patients' metamizol administered endovenously did not significantly achieve faster pain control than morphine administered subcutaneously.

Published studies regarding analgesic treatment of AP are scarce. Meperidine was historically preferred to morphine, because some studies show that the morphine produced an increase in the ODDI sphincter pressure and in the amylase. However, no clinical studies suggest that morphine adversely affects and can worsen or cause an AP or cholecystitis. There is no evidence that this increase in the ODDI sphincter pressure has any impact on the development of AP. It is important to know that *meperidine* has a shorter average life and that repeated doses may result in building up its metabolite normeperidine, which causes neuromuscular irritation and infrequent seizures. Meperidine has a possible minor impact on the bile and pancreatic ducts ([137],[138],[139]), without any benefits being demonstrated and at the expense of increased toxicity (neurotoxicity, nausea, vomiting, dizziness, vertigo ...) (136, [140], [141], [142], [143], [144]).

For adequate pain control of *endovenously administered opioids* are often required. *Morphine and fentanyl endovenously administered* can be used to relieve pain in AP. The use of fentanyl is increasing due to its better safety profile. The administration of opioids should be monitored closely, controlling the level of consciousness and oxygen saturation should be closely monitories, and the patient's needs should be adjusted daily. Side effects should be monitored.

Patient-controlled analgesia by means of a pump is a good choice when the pain is particularly intense ([145], [146], [147], [148], [149], [150], [151]). Opioids can be administered *endovenously* as a bolus, with a continuous infusion and by means of patient-controlled analgesia (PCA). The latter is useful in the conscious patient and partner, when the pain is severe or postoperative ([152], [153], [154]) and allows for self-administration of opiates up to a set limit. The drugs used in our environment are morphine and fentanyl.

The administration of opioids, local anesthetics or the combination of both by injecting structures to control pain of pancreatic origin, such as the epidural space, allows for a smaller dose of opiate (145). This method could be very useful in critically ill patients, as it would reduce systemic doses and, as a result, the

adverse effects of opioids, and increase its beneficial effects, as an improvement in gas exchange and intestinal motility. Experimental studies have shown that epidural administration of bupivacaine has a beneficial effect on pancreatic microcirculation by preventing necrosis and the development of systemic complications ([155]).

Sedation. The patient with AP has *sedation needs* similar to those of other nosological entities. This patient may require sedation primarily in three situations: a) as an adjunct to analgesia, b) as an adjunct to mechanical ventilation, and c) in the event of an alcohol withdrawal syndrome (145). The drugs most frequently used in our environment are midazolam and propofol.

There are few studies on analgesia and sedation in patients with AP. Delving into the different aspects of the recommendations made and suggesting new therapies may improve AP treatment.

Alternatives. Adjuvants in analgesia with opiates could optimize treatment. Antidepressants, such as tricyclic antidepressants or selective inhibitors for recovering serotonin and norepinephrine, and anticonvulsants such as pregabalin ([156], [157]) could play a role in certain forms of pancreatitis.

We do not have sufficient experience with the use of drugs with a potential use. Ketamine or clonidine may be useful in some circumstances (151).

Locoregional analgesia already has a place in epidural treatment. The interpleural route has been used in the treatment of postoperative and upper abdominal visceral pain. Intrathecal infusion pumps may be another alternative ([158]).

Celiac plexus ([159]) and celiac plexus neurolysis blockage guided by imaging ([160], [161], [162]) is a temporary or permanent option (respectively) in patients for whom this locoregional analgesia could not be performed or when it has not been effective..

Endoscopic therapy reduces pain ([163]). Pancreatic duct decompression when required by means of ERCP with the resolution of obstruction, pancreatic duct dilation, stenting, sphincterotomy or pseudocyst drainage.

Enzyme supplements ([164]) , somatostatin analogs such as octreotide ([165], [166], [167]), or lanteotrido ([168], [169]), and antioxidants ([170], [171], [172]) are studied therapies with potential benefits but without sufficient scientific evidence to recommend its use in AP.

Recommendation 31. Analgesia is essential in the treatment of AP. **Strong grade of recommendation (1), low quality of evidence (C).**

Recommendation 32. A comprehensive assessment must be performed to identify potential for surgery that may reduce the progression of pancreatic damage or complications. **Strong grade of recommendation (1), low quality of evidence (C).**

Recommendation 33. There is no analgesic guideline to choose from that is based on evidence. Drugs ranging from non-opioid analgesics to opiates should be chosen, depending on the intensity of the pain. **Strong grade of recommendation (1), moderate quality of evidence (B).**

Recommendation 34. Patient-controlled analgesia (PCA) by means of a pump is a good option when pain is particularly intense in the postoperative stage. **Strong grade of recommendation (1), low quality of evidence (C).**

Recommendation 35. In the case of uncontrollable pain with opioids administered intravenously, loco-regional epidural analgesia can be a good alternative. **Strong grade of recommendation (1), low quality of evidence (C).**

Recommendation 36. Sedation can be used as an adjunct to analgesia, mechanical ventilation or treatment of the alcohol withdrawal syndrome. There is no scientific evidence in this regard. **Strong grade of recommendation (1), low quality of evidence (C).**

Recommendation 37. There may be other methods of analgesia and sedation control. More studies on analgesia and sedation in patients with PA are needed. **Strong grade of recommendation (1), low quality of evidence (C).**

10th Question: Volemia replacement and hemodynamic monitoring. In critically-ill patients with or without mechanical ventilation (MV). In general wards and ICUs.

In patients with PSAP early administration of fluids is recommended, mainly during the first 72 hours, during which the first 24 hours are the most important ([173], [174]). Progressive, controlled and monitored administration of fluids is probably more beneficial than the aggressive administration of fluids, which is widely recommended in most clinical guidelines, primarily in patients with PSAP whose condition is unstable and who show signs of hypoperfusion (ScvO 2 <70% or SvmO2 <65%, lactate> 4 mmol / l, oliguria) (28), as well as associated comorbidities (patients with heart, kidney and / or liver disease) ([175]).The administration of more than 3-4 liters of fluids in the first 24 hours seems to be related to a poor prognosis due to an increased rate of acute respiratory failure and a greater need for admission to intensive care units, either because of the deleterious direct effects of fluid infusion, or because it involves a patient with complicated AP (47, 175, [176]).

Regarding the type of fluid to be administered, crystalloid versus colloid, there is no general recommendation for AP, although balanced crystalloid solutions (Ringer Lactate) have been observed to control SRIS in PSAP, as well as CRP levels when compared to physiological saline serum (50, [177]).

With respect to colloids, since there is no specific recommendation for patients with AP, using hydroxyethyl starch (HEAS) with a molecular weight ≥ 200kDa and / or grade of substitution> 0.4 in patients with severe sepsis is not currently recommended, as well as those patients at risk for acute renal dysfunction, a situation in which there is a significant proportion of patients with PSAP ([178], [179], [180]).

The administration of intravenous fluids is the first-line treatment in patients with unstable PSAP. It is important to remember that the need for fluid administration will be determined by signs of hemodynamic instability and OF. We must continuously ask ourselves if we should continue with fluid resuscitation, while exercising special care for the patient's needs and the potentially dangerous effects of fluid infusion.

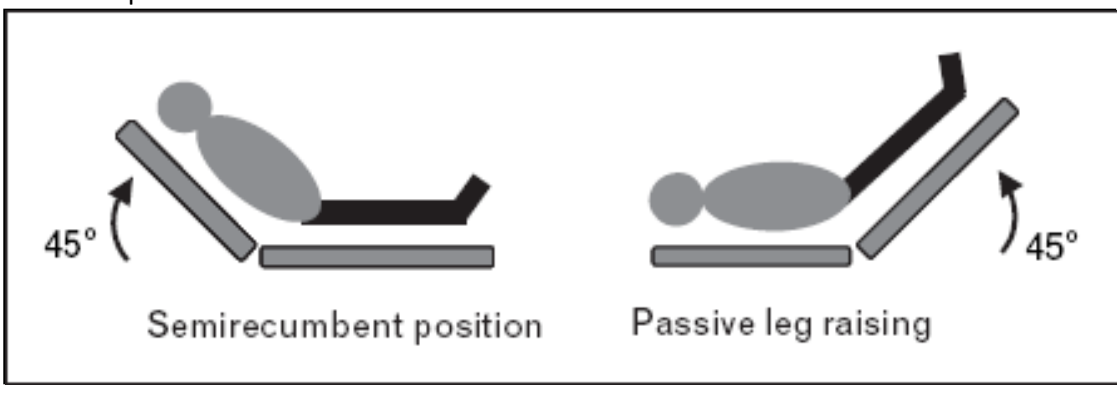
The expected hemodynamic response to fluid infusion is the increase in systolic volume. Today we have tools to assess different parameters related to preload, according to the Frank-Starling mechanisms, in critically ill patients including those with PSAP.

The *classic standard static parameters* for assessing preload related to filling pressures, such as central venous pressure and the average mean arterial pressure, fail to predict the response to a volume of critically ill patients with suspected septic shock and need to be interpreted carefully when this type of patient is assessed ([181], [182]). Static parameters that directly assess intrathoracic volumes, such as the index of intrathoracic blood volume (IIBV), has been assessed as a more reliable parameter for fluid management in this type of patient when compared with the static parameters of pressure ([183]).

Functional hemodynamic parameters are based on the cardiopulmonary interaction in patients undergoing positive pressure mechanical ventilation and uniquely reflect the position on the Frank-Starling curve of each patient by assessing cardiovascular performance. Different hemodynamic parameters can be automatically obtained through various devices. The pulse pressure variation (PPV), stroke volume variation (SVV) and the variation of the pressure wave by pulse oximetry plethysmography (ΔPplet), are among the most frequently found in the literature to be safe in predicting the response to the volume in mechanically ventilated patients ([184]).

It is important to note some limitations in interpretation, such as the presence of cardiac arrhythmias, spontaneous breathing, low tidal volumes (<8 ml / kg), high respiratory rates and right ventricular dysfunction ([185], [186], [187], [188]). In these circumstances, when there are limitations to the assessment of functional hemodynamic parameters (PPV, SVV, ΔPplet), the evaluation can be performed by means of echocardiography or different functional maneuvers (passive lifting leg maneuver, occlusion maneuver at the end of expiration ([189], [190], [191]).

The passive leg raising maneuver (PLR) of Monnet and Teboul (introduced in 2005 and updated in 2008), has been proposed as an alternative to predict the patient's response to a volume load. The test consists of elevating the lower members to a 45 ° angle from a patient position of 45 ° while measuring the systolic volume and cardiac output with transthoracic echocardiography (TTE) prior to lifting and one minute after the maneuver. This maneuver mobilizes approximately 300 ml of blood from the MMII to the intra thoracic compartment and reproduces the effects of volume expansion. It is reversible and avoids the risks of volume expansion.



The EPP test is the only exploration that has repeatedly proven to be reliable in predicting response to volume in spontaneously breathing patients, however, it is important to note that for a proper assessment it is necessary to use a continuous hemodynamic monitoring device or a rapid response for the timely detection of hemodynamic changes induced during the maneuver.

Interpreting these parameters in *patients with intra-abdominal hypertension*, which must be performed fairly frequently with SAP or CAP patients, merits special mention. Pulse pressure variation (PPV), stroke volume variation (SVV), systolic pulse variation (SVP) and the overall volume at the end of diastole can be

considered useful parameters for assessing IAH patient response to fluids, when taking into account that the response thresholds that distinguish responders from nonresponders can be increased ([192], [193]). It is also important to bear in mind the difficulty of interpreting the response to fluids after the maneuver for the passive elevation of the legs of mechanically ventilated patients with intra-abdominal pressures above 16 mmHg has been performed ([194]).

Recommendation 38. We recommend early administration of fluids in patients with PSAP, who are in unstable condition and show signs of hypoperfusion (central venous O2 saturation <70% or mixed venous saturation O_2 < 65%, lactate > 4 mmol/l, diuresis < 0,5 ml/kg/h). **Strong grade of recommendation (1), low quality of evidence (C).**

Recommendation 39. Balanced crystalloids in the amount not exceeding 4.3 liters in the first 24 hours are preferable. Special care must be taken with reviving patients with more severe pancreatitis and / or more comorbidities. **Strong grade of recommendation (1), low quality of evidence (C).**

Recommendation 40. We recommend not using hydroxyethyl starch with a molecular weight> 200kDa and / or degree of replacement > 0.4 in cases of shock and / or renal dysfunction. **Strong grade of recommendation (1), low quality of evidence (C).**

Recommendation 41. Monitoring the administration of fluids in patients with PSAP, mainly in the first 72 hours, is important. Accurate prediction of the response to fluids before volume expansion is crucial. Classic static parameters for monitoring and assessing response to fluids, such as central venous pressure (CVP), pulmonary artery occlusion pressure (PAOP) and average arterial pressure (MAP) should therefore be interpreted with caution in patients on either mechanical ventilation or spontaneous breathing. **Strong grade of recommendation (1), low quality of evidence (C).**

Recommendation 42. Monitoring dynamic parameter measures the cardiac response to changes in preload. Systolic volume variation (SVV) and the pulse pressure variation (PPV) have proven useful as predictors of response to volume in mechanically ventilated and sinus rhythm patients. **Strong grade of recommendation (1), low quality of evidence (C).**

Recommendation 43. Numerous studies have demonstrated the usefulness of the maneuver of leg elevation as a predictor of response to volume (increase ≥ 10% in cardiac output during the first 60-90 seconds of its initiation) in spontaneously breathing patients in critical condition. **Strong grade of recommendation (1), low quality of evidence (C).**

Recommendation 44. The presence of intra-abdominal hypertension, which is common in this type of patients, requires carefully interpreted static and dynamic parameters in patients on mechanical ventilation or those who are spontaneously breathing. **Strong grade of recommendation (1), low quality of evidence (C).**

11th Question: Nutritional and specialized metabolic support of critically ill patients with PSAP

Since this topic was last reviewed ([195]) a few, but highly valuable, contributions have been made. PSAP and its evolutionary forms, SAP and CAP, produce a SIRS which leads to a highly catabolic, hyper-metabolic and hyper-dynamic stress situation ([196], [197]). The previous nutritional status of the patient

will be a determining factor in patient recovery, so chronic alcohol intake and obesity are factors that do not depend on severity.

Currently, the classic concept of treating PSAP, consisting of bowel rest and implementing total parenteral nutrition which was limited to reversing the catabolic situation, has changed. Several studies show increased morbidity and mortality risk with this traditional approach ([198], [199]).

A recent study of several intestinal functionalism markers concluded that intestinal barrier dysfunction appears early in the course of PSAP and that it is associated with pancreatic necrosis infection, the onset of MOF, and the severity of the pancreatitis with an increase in mortality ([200]).

Therefore, emerging data suggest that the route, time, quantity and composition of artificial nutrition aim to reduce pancreatic secretion, treat and/or prevent malnutrition associated with a situation of severe metabolic-catabolic stress, modulate inflammatory response and prevent the development of local and systemic infections ([201], [202], [203], [204]). Nutritional support has become one of the most important elements in the management of PSAP patients.

What are the indications for nutritional support in patients with PSAP?

In PSAP there is an indication for specialized nutrition from admission, since the patients are sick and they will not resume food intake in the following 5-7 days and there is a maximum degree of hypercatabolism.

The need for surgery or the development of local complications associated with pancreatitis does not modify the indication for nutritional support, which must continue to be based on the severity level and the intake efficiency to meet the calculated nutritional requirements.

Enteral nutrition vs. parenteral nutrition in patients with PSAP?

Following well known experimental studies ([205]).the absence of enteral stimulus causes gastrointestinal mucosal atrophy, bacterial overgrowth, increased intestinal permeability and bacterial translocation. This is demonstrated by a study in patients with SAP in which the effect of jejunal vs. NE NPT on the intestinal barrier has been assessed. After 7, 14 and 21 days of treatment plasma concentrations of endotoxin, diamine oxidase and urinary excretion of lactulose / mannitol ratio were significantly lower in the EN group, with a better effect on the intestinal barrier ([206]).

The latest meta-analyzes (**¡Error! Marcador no definido.**, **¡Error! Marcador no definido.**, [207], [208]) conclude that EN shows significant benefits on TPN for reducing mortality, MOF, systemic infection and surgery. In addition, it is associated with a trend toward decreased hospital stays, local septic complications and all at a lower cost.

TPN indication will be based on the impossibility of obtaining an appropriate enteral approach, if there is intolerance to EN or when the clinical and laboratory signs of SAP worsen when initiating EN ([209]).

When following the criteria of TPN indication in critically ill patients, we believe that TPN should be initiated in patients requiring nutritional support, if it has not been initiated enterally or total nutrional support is not achieved in the first 48 hours from admission. Some authors recommend delaying the start for at least five days until SIRS has been overcome according to studies not performed in PSAP. In our view there is no evidence for postponing the start of TPN beyond the initial resuscitation phase ([210], [211]).

Regarding the composition of the TPN, there are no data to recommend specific amino acid patterns or certain lipid formulations in PSAP. No formulation has been proven to be superior to another. It is important to note that lipid emulsions are not contraindicated in patients with PSAP and therefore the energy contribution must be mixed (carbohydrate / fat) (208). The hypertriglyceridemia and hyperglycemia values should be mandatorily and closely monitored.

In patients receiving TPN it may be convenient to simultaneously supply a minimum amount of enteral diet. The aim of the EN, although from a theoretical point of view, would maintain the trophic effect of intraluminal nutrient intake on the intestinal mucosa ([212], [213]).

When to start enteral nutrition?

It seems that bacterial colonization and infection of pancreatitis occur within hours of the start of the AP. A reduction in mortality has been observed in different series when nutritional support is initiated within 48h from its development (204, [214], [215]). The existence of prior malnutrition (as in the case of PSAP cases due to alcohol consumption) is another reason to start early EN.

Studies assessing the effect of EN on systemic inflammatory response in patients with PSAP also show a faster reduction in APACHE II and inflammatory markers (200, 203, 207).

There is an ongoing study trying to establish which is the best time to start EN ([216]), but at this point, if we consider that EN, when initiated as early as possible, improves the course of the disease process, we recommend early NE in PSAP in the first 24-48 hours from admission, after the initial resuscitation phase (198, 200, 202, 203, 205, 207, 214).

How should enteral nutrition be administered?

There are studies on PSAP where exocrine secretion in response to cholecystokinin and other secretagogues has been seen to be markedly reduced ([217]).Furthermore, the EN distal flow to the Treitz ligament minimally stimulates pancreatic secretion while respecting the "rest pancreatic".

Most of the randomized controlled studies on EN versus TPN are performed with the administration of EN in jejunum, while showing no secondary complications in that location, so it is concluded that the use of *jejunal nutrition* (202, 204, 207) is PSAP is safe. The use of a double-lumen catheter, which allows for jejunal perfusion during gastric decompression, while monitoring the quantity and the aspect of debit gastric, facilitates the tolerance and handling of EN in those patients.

In recent years several studies have appeared where the administration of EN in gastric chamber appears safe and well tolerated in PSAP, and in comparison to the jejunal route it shows similar results; however these studies are questionable because they include less severely-ill patients where the location of the probe remains unclear ([218], [219]) and the initiation of the diet is performed late from the beginning of clinical treatment ([220]). Randomized studies with greater statistical power are needed to recommend its routine use.

What is the most recommended type of formula?

Enterally or parenterally nutrient supply, in the absence of indirect calorimetry, will be performed on the basis of recommendations for specialized nutritional and metabolic support of critically ill patients. SEMICYUC-SENPE Consensus 2011: 25-30 calories Kcal / kg / d, without exceeding an intake of > 4 g / kg / d of glucose, lipid intake of 0.7-1.5 g / kg / d 1 to 1.8 g protein intake / kg / d ([221]).

The last metaanalysis ([222]) on the formulations used in pancreatitis concludes that semi-elemental and polymeric diets can be used in PSAP, since there are no significant differences between feeding tolerance, infectious complications or mortality. Only one study on pancreatitis where the objective was to assess the type of diet administered concludes that both the oligomeric diets and the polymeric diets are well tolerated in patients with pancreatitis. This study includes a small number of patients with acute pancreatitis, where the time of NST placement lasts more than 7 days with a high calorie intake ([223]).

What specific nutrients are shown in PSAP?

There are few clear recommendations regarding the prognostic benefits of the administration of enriched diets with specific pharmaconutrients in patients with PSAP.

If we talk about enteral farmaconutrition in PSAP, scientific evidence is scarce and the corresponding recommendations are ambiguous. In published studies, the benefits with scientific significance refer to improvements in biochemical markers of inflammation ([224]) and they suggest positive prognosis for patients with PSAP to whom pharmaco-enriched nutrition is administered ([225], [226]), although there is not considered to be sufficient evidence for recommendation as a result of the design of these studies (202, 207, 209, [227]).

Studies with the administration of glutamine parenteral and enteral supplementation in PSAP patients receiving TPN, have provided positive prognosis with the reduction of hospital stays, infectious complications and the need for surgical intervention, as well as better glucemic control and more rapid improvement in biochemical markers of inflammation (204, [228], [229]).

With respect to the administration of *probiotics and prebiotics* in patients with PSAP and after analyzing the data obtained from relevant studies (199, 200, [230], [231], [232]), no recommendations can currently be made for its use because the evidence in the bibliography is very contradictory. The same microorganisms have not always been used and the doses used have also been different. Even probiotics are considered hazardous in these severely ill patients ([233]) and should not be administered in PSAP ([234]) and there is still a long way to go.

There are few studies on the parenteral or enteral administration of oligoelements and antioxidant micronutrients in patients PSAP ([235], [236]).

Recommendations:

Recommendation 45. Specialized nutritional support in potentially severe acute pancreatitis, in its SAP and CAP forms, should be started early, within the first 48 hours after initial resuscitation. **Strong grade of recommendation (1), moderate quality of evidence (B).**

Recommendation 46. Enteral jejunal nutrition is preferable to parenteral nutrition. **Strong grade of recommendation (1), high quality of evidence (A).**

Recommendation 47. Parenteral nutrition is indicated if enteral nutrition cannot be administered, if there is intolerance to this nutrition or if it results in an exacerbation of pancreatitis. **Strong grade of recommendation (1), moderate quality of evidence (B).**

Recommendation 48. Enteral or parenteral nutritional intake shall be achieved on the basis of recommendations for specialized metabolic and nutritional support of critically ill patients. SEMICYUC-SENPE (2011) Consensus: caloric intake of 25-30 Kcal/kg/d, without exceeding an intake

of > 4 g/kg/d of glucose, lipid intake of 0,7-1,5 g/kg/d and protein intake of 1-1.8 g/kg/d. **Strong grade of recommendation (1), moderate quality of evidence (B).**

Recommendation 49. Polymeric and elemental diets are equally recommendable. **Weak grade of recommendation (2), moderate quality of evidence (B).**

Recommendation 50. Assessing the possibility of maintaining a minimum supply of jejunal nutrients, even in patients with impaired jejunal nutrition who are being treated with parenteral nutrition, is suggested. **Weak grade of recommendation (2), low quality of evidence (C).**

Recommendation 51. The use of glutamine in patients with severe acute pancreatitis who receive parenteral nutrition is recommended. **Strong grade of recommendation (1), moderate quality of evidence (B).**

Recommendation 52. The use of prebiotics or probiotics in patients with potentially serious acute pancreatitis is not recommended. **Strong grade of recommendation (1), moderate quality of evidence (B).**

12th Question: Role of Endoscopy / Digestive Endoscopy in Critical, Severe, and Acute Pancreatitis.

Role of Endoscopic retrograde pancreatic cholangiography and Endoscopic sphincterotomy (ERCP-EE) in Biliar AP

Most acute pancreatitis (AP) cases are of a biliary origin due to a transient or permanent obstruction of the pancreatic and bile duct ([237]). Numerous studies have attempted to clarify the role of endoscopic retrograde pancreatic cholangiography (ERCP) in this regard.

The existence of AP and cholangitis is accompanied by a high rate of complications. There is now a broad consensus on recommending that ERCP be performed as soon as possible in this subgroup of patients ([238]).

The usefulness of early ERCP in patients with biliary AP without cholangitis has been the subject of several randomized trials ([239], [240], [241], [242], [243]) and meta-analysis (93, 147, [244], [245], [246], [247], [248]). While there is an agreement that early ERCP in predictably mild AP does not seem to be beneficial, the results differ from those of the AP group with severity criteria and those with data suggesting biliary obstruction ([249], [250]). This is probably related to the different criteria for selecting the patients, mainly in regard to the exclusion of cholangitis, and the criteria used to predict the severity of AP. In a recent Cochrane review (250), including 5 randomized trials, the strategy of performing early ERCP showed no reduction in mortality or complications related to AP regardless of the prediction regarding AP severity.

A strategy based on the performance of a magnetic resonance cholangiopancreatography (MRCP) or endoscopic ultrasonography (EUS) could probably better define patients who would benefit from performing ERCP.

In critically ill patients, or those for whom ERCP with sphincterotomy cannot be performed, or when ERCP, "transhepatic percutaneous drainage of the gallbladder (TPDG)" is a good therapeutic option for patients with signs of PAG cholangitis or obstruction of the bile duct. Wenkui Yu, et al (243), who compared TPDG with ERCP with endoscopic papillotomy in biliar SAP, obtained equally favorable results in the two arms that were compared, with a complication rate similar for both groups. The work is well designed, prospective, randomized, with 101 patients, so the degree of recommendation and scientific evidence is high.

Biliar AP with cholelithiasis is an indication for cholecystectomy. A cholecystectomy should ideally be performed during admission and, if this is not possible, no later than four weeks after discharge, in order to prevent further episodes of PA (147, 150, [251]), except in cases where there are peripancreatic collections or pseudocysts that are expected to require surgery ([252]). In patients who are not candidates for surgery or who reject this technique, endoscopic sphincterotomy is a valid alternative ([253], [254]).

Role of endoscopy in the management of pancreatic pseudocysts.

The drainage of pancreatic pseudocysts is necessary only at the onset of symptoms and does not depend on the initial size of such collections. Situations that can benefit from drainage are the pseudocyst infection and the condition of neighboring structures that can appear in the symptoms resulting from compression of the gastrointestinal or biliary tract or due to the condition of surrounding vessels ([255], [256], [257]).

There are three possible forms of drainage: the radiological, surgical and endoscopic. With respect to other modes of drainage, the endoscopic form is the most more physiological ([258], [259]). There are no comparative studies between radiological and endoscopic drainage, but in regard to the latter, it consists of an internal drainage, thus avoiding the appearance of cutaneous fistulas ([260], [261]). It also allows for multiple prosthesis and also enables nasochistic drains to be placed in different places and debridement of necrotic debris to be performed ([262]).Comparative studies between surgical and endoscopic drainage show similar figures of success with lower morbidity and costs of the drainage performed with endoscopy ([263]).

There are two possible forms of endoscopic drainage: the transmural and transpapilar. At present, performing transmural drainage with EUS guided is recommended whenever available. The use of endoscopic ultrasonography limits the appearance of technical complications and allows for the drainage of pseudocysts in complicated or atypical situations, in patients with portal hypertension and it is more accurate than CT in differentiating pseudocysts from cystic pancreatic tumors ([264], [265], [266]).

The drainage route is mormally transmural. It is indicated when there is complete pancreatic ductal obstruction or the pseudocyst is greater than 6 cm. The endoscopic approach is feasible when the distance between the pseudocyst and gastric or duodenal wall is less than 1 cm.

Transpapillary drainage by means of ERCP is recommended when the pseudocyst and pancreatic duct are in contact, especially there is only one point of contact, it is smaller than 6 cm and it is separated from the gastric or duodenal wall.

It requires a joint transpapilar and transmural approach only in cases of rupture, stricture or pancreatic duct stones (266, [267]).

Interventionist endoscopy. Role of endoscopy in the management of infected pancreatic necrosis.

Infected pancreatic necrosis is a complication that usually appears from the second week of evolution and it is associated with high morbidity and mortality. The treatment should be administered as late as possible (not before the third week) to stabilize the patient, reduce the inflammatory process and resolve organ failure (147). Until recently, the standard treatment was surgery, but a more conservative approach is currently recommended at the beginning, by combining medical treatment, percutaneous and endoscopic drainage and, resorting to surgery only if there are no improvement after such treatments (5). Recent studies show the effectiveness of endoscopic necrosectomy, which is an effective technique, but it should be performed only in specialized centers because it presents complications ([268]), which are equal to or greater than surgical complications; the level of safety is acceptable ([269]).

Both the guided drainage of pancreatic collections by conventional endoscopy such as endoscopic ultrasound-guided methods can be considered first-line drainage collections which lead to extrinsic compression. However, endoscopic ultrasound-guided drainage must be the first choice in those cases in which there is no extrinsic compression.

Direct endoscopic necrosectomy of organized pancreatic necrosis may be a technique that, in experienced hands, is effective and has an acceptable level of safety compared to surgery. Endoscopic transmural drainage is a perfectly valid option for patients who cannot undergo surgery or any other drainage technique using large collections or who suffer from necrosis and / or suspected infection. In an unorganized infected necrosis, however, surgery is still the preferred option.

Recommendation 53. **ERCP-EE.** When confronted with biliary AP having cholangitis data, ERCP should be performed urgently (within 24 hours) with biliary drainage. **Strong grade of recommendation (1), moderate quality of evidence (B).**

Recommendation 54. When confronted with biliary AP having an obstruction of the biliary duct, performing ERCP (ERCP-EE) with early (first 72 hours) cleaning of the bile duct may prove beneficial. **Strong grade of recommendation (1), moderate quality of evidence (B).**

Recommendation 55. In patients with biliary AP and predictors of severity, performing urgent ERCP is controversial if no cholangitis or biliary obstruction data is available. **Weak grade of recommendation (2), moderate quality of evidence (B).**

Recommendation 56. In patients with mild or moderate biliary AP without cholangitis or persistent biliary obstruction, performing ERCP does not significantly reduce the risk of complications or death. **Strong grade of recommendation (1), high quality of evidence (A).**

Recommendation 57. In centers where ERCP is not available in the first 48-72 hours and the patient shows signs of cholangitis or obstructive jaundice, the patient should undergo percutaneous transhepatic drainage of the gallbladder or biliary surgery within this timeframe. **Strong grade of recommendation (1), high quality of evidence (A).**

Recommendation 58. Performing ERCP with endoscopic sphincterotomy is an alternative to cholecystectomy as a prophylaxis for new episodes of biliary AP in patients with high surgical risk or who have refused to undergo surgery. **Strong grade of recommendation (1), moderate quality of evidence (B).**

Recommendation 59. Only symptomatic pseudocyst drainage is considered suitable. **Strong grade of recommendation (1), low quality of evidence (C).**

Recommendation 60. The endoscopic drainage route is usually the first choice. **Strong grade of recommendation (1), low quality of evidence (C).**

Recommendation 61. The use of ultrasound endoscopy limits the development of complications resulting from this technique and it is useful for differential diagnosis with other pancreatic cystic lesions. **Strong grade of recommendation (1), moderate quality of evidence (B).**

Recommendation 62. Infected or symptomatic pancreatic necrosis indicates the need for treatment. The approach should be performed in stages with medical treatment, radiological drainage or endoscopic or surgical or endoscopic debridement. **Strong grade of recommendation (1), high quality of evidence (A).**

Recommendation 63. The ideal time to perform this treatment for an infected or symptomatic pancreatic necrosis is at least 3 or 4 weeks from the onset of pancreatitis. **Strong grade of recommendation (1), low quality of evidence (C).**

Recommendation 64. Direct endoscopic necrosectomy is an alternative to surgical debridement when performed in specialized centers. It offers acceptable levels of efficacy, although it is not free of morbidity and mortality. Therapeutic / interventional ultrasound endoscopy (USE) shall be considered an option for the management of pseudocysts and / or symptomatic or complicated abscesses, as well as for performing necrosectomies in patients with infected necrosis whose baseline counter indicate the surgical option. We wish to point out that if this therapeutic option is chosen, it should be performed in centers that are especially "devoted" to this pathology and which have multidisciplinary team composed of expert endoscopists, surgeons and interventional radiologists. **Strong grade of recommendation (1), moderate quality of evidence (B).**

13th Question: Antibiotic prophylaxis in PSAP.

Prophylactic antibiotics in acute pancreatitis.

Prophylactic antibiotherapy in SAP patients is defined as the prescription of antibiotics without any clinical evidence of infection, in order to avoid pancreatic necrosis (NP) infection.

Prophylactic antibiotherapy originated in the 80's after the Discovery that the principal cause of mortality in SAP patients was (NP) infection. It is striking that antibiotic prophylaxis was found effective in previous studies of low quality up to 2002, in, so it was included in several guides.

In 2004 the German School published a double-blind study with ciprofloxacin plus metronidazole ([270]), where the antibiotherapy was not shown to be beneficial in preventing pancreatic necrosis infection and advocated early antibiotherapy.

In 2003 ([271]) a multicenter, double-blind, randomized clinical trial began with a placebo, using meropenem in SAP with NP. It is the study with the most patients with NP. The overall mortality rate was 20% in the meropenem group and 18% in the placebo group (p = 0.799). In conclusion, this study showed that there is no statistically significant difference between treatment groups for pancreatic or peripancreatic infection, mortality or the need for surgical intervention, and does not support the early use of prophylactic antimicrobials in patients with severe necrotizing pancreatitis.

The latest study ([272]), is a non-double blind, randomized, controlled, and multicenter trial on the effectiveness of prophylactic imipenem in severe pancreatitis. Mortality, MOF, the number of surgical interventions, and the need for intensive care (ICU) and the hospital stay did not differ between the two groups. It recognizes that the ICU and early antibiotherapy have reduced the incidence of infection and delayed surgery until the 3rd and 4th week, but with an economic cost of 20,465 with imipenem compared to half that cost in the control group, 10,221. This study has methodological weaknesses that are identical to those studies performed prior to 2002. It is not strong enough and it was terminated due to slow recruitment. Severe pancreatitis was diagnosed by clinical and laboratory criteria, based on PCR. A small proportion of patients (23%) developed a pancreatic necrosis exceeding 30%, and a third of the patients had absolutely no necrotizing SAP.

Does antibiotic treatment play an important role in the treatment of AP?

There is no doubt that prolonged randomized trials are needed to clarify the crucial question (41). Does the reduction of NP infection reduce mortality? However, a new trial would have to consider the reclassification of AP and the real rate of infected NP is 20% in patients with more than one third of glandular necrosis, and not 40-70% as suggested in the past. To demonstrate a significant reduction of 10% in infected NP between 240-400 patients must be included in this trial. To actually demonstrate that the reduction of infected necrosis reduces mortality from 20% to 10%, more than 3000 patients must be included in the trial.

Despite the recommendation not to use prophylactic antibiotics in SAP (24, 26, [273]) they are still being used. In the EPIC-2007 study ([274]).most patients admitted to an ICU with SAP required antibiotics (112/159), and about a third of them received antibiotic prophylaxis (38 of 159 patients, 23, 9%). This practice of antibiotic prophylaxis, although not supported by scientific evidence, is still widely used.

Since the last update of this topic in 2008 there have been several studies on antibiotic prophylaxis in AP. Most do not have a sufficient sample size, with non-double-blind design ([275], [276]). These studies, and another with a double-blind design ([277]), do not show that there are any advantages in the use of prophylactic antibiotics. In conclusion, we can establish a strong recommendation not to use antibiotic prophylaxis in AP patients with a necrosis greater than 30%, although the evidence is of moderate quality.

All these studies have been included in several meta-analyses: Jafri et al ([278]), Pezzilli et al ([279]), Bai et al ([280]) y De Madaria et al ([281]), with the conclusion that antibiotic prophylaxis has no advantages. Other recent meta-analyses show very similar results ([282], [283], [284], [285]).

Does AP with intraabdominal fungal infection (IFI) offer a worse prognosis than intraabdominal bacterial infection (IIB)?

Vege et al (29) reviewed data from 207 consecutive patients hospitalized with SAP between 1992 and 2001 with the primary objective of comparing mortality and other secondary aspects of intraabdominal fungal infection (IFI, 30 patients) with abdominal bacterial infections (ABI, 78 patients) and pancreatitis without intraabdominal infection (NII, 99 cases). It defines a primary fungal infection as those infections for which there have been no previous abdominal operations; secondary infections were those that developed after earlier surgery. 52% (108/207) of patients had intra-abdominal infection; all these patients developed IAB and in 30 patients (15%) developed concomitant IAH. There were seven cases of primary fungal infections and 23 secondary fungal infections and no differences were observed between these groups. Compared with patients with IAB, IAH patients had longer hospitalization stays (63 vs. 37 days, $p < 0.01$) and the need for ICUs (28 vs 9 days, $p < 0.01$) and higher rates of hospital stays and OF (73 vs. 47%, $p < 0.04$), but similar mortality rates (20 vs 17%, $p > 0.41$).

As a general rule the need to administer antifungal prophylaxis early is never raised, unless the patient has previously received antibiotics and present other risk factors; in these cases it is called "*early antifungal treatment*" and defined "when antifungal prophylaxis is initiated from the first week of admission" (25).

The role of "early antifungal treatment" (incorrectly called "antifungal prophylaxis").

In 1995, the first physician to use an antifungal was Luiten ([286]), and he found a reduction in the number of *Candida* infections in SAP due to digestive decontamination with an amphotericin and local antibiotic ([287]). Years later, in 2003, de Waele states that early administration of fluconazole reduces the incidence of fungal infections but not mortality ([288]). A randomized clinical trial of prophylaxis with low-dose garlicina

and fluconazole in SAP resulted in a reduction of fungal infection in both groups and these authors conclude that antimicotic agents in prophylactic dose s may reduce the incidence of fungal infection in patients with SAP ([289]).

Three recent reviews support and justify the possible role of antifungals in SAP. Trikudanathan's ([290]) review and Jan De Waele's review in 2011 ([291]) analyze the rational use of antibiotics and antifungals in patients with SAP. They describe the following risk factors for developing an infectious complication during AP with pancreatic necrosis (IAH): previously administered antibiotics, total parenteral nutrition, endoscopic procedures, prolonged ICU stay, central venous catheter is use for an extended period of time and the age of the patient (elderly <70 years). The third review on the subject (Kochhar 2011) ([292]) concludes that the role of antifungal prophylaxis is unclear and further studies are required. Natural history and especially the treatment of fungal SAP have not been studied and by extension the same criteria apply as in bacterial SAP.

Antifungal administration should be assessed in some high risk cases of fungal infection. Early antifungal treatment may be indicated at bedside in patients with 3 or more points in the "Candida score" ([293]). If the patient is septic, receiving total parenteral nutrition presents multifocal colonization and in the presence of risk factors one should not hesitate to establish empirical antifungal therapy, although with a weak recommendation. Treating drain colonization is not recommended.

Antifungal treatment should be performed early. Fluconazole reaches adequate concentrations in the pancreas, and the dose should have an initial load of 12 mg / kg / d followed 6mg/kg/d. Amphotericin B in the liposomal form has a greater antifungal spectrum and greater penetration in pancreatic necrosis. Echinocandins are also useful.

Whenever no residual infection remains and the patient's condition improve, a 7-14 day duration in early antifungal treatment should be sufficient. Once the fungal infection has appeared in SAP the definitive treatment is surgery.

What is the role of DDS in SAP?

Since 1992 when the first information appeared on the DDS in the SAP and up to the present, following the through the 1999 Luiten trials and Sanchez's report in 2000, it has not been shown to have a favorable impact in these patients ([294]). Luiten's is the only study on DDS and SAP that has shown the decrease of mortality in patients with necrotizing pancreatitis, but from a level of 35% (which is a very high figure and it is currently unacceptable) to 22% ($p > 0.05$), mainly at the expense of late mortality (> 2 weeks), and significant reduction ($p = 0.003$) rates of over infection of pancreatic necrosis by negative Gram. Despite these results, it is not possible to draw firm conclusions regarding DDS.

A comparative study on DDS, using a simple and practical method, should probably be planned. Currently can not be recommended for the systematic use of DDS in SAP for preventing pancreatic sepsis cannot be currently recommended.

What is the next step?

The use of prophylactic antibiotics in patients with acute pancreatitis and NP is an issue that has not been clarified where the development of "large" controlled trials are required (powerful RCTs), by using the new Petrov classification of acute pancreatitis.

The reviews and studies highlight the lack of evidence for the use of antimicrobials in prophylaxis against pancreatic necrosis infection ([295]).

At the present time, there are only two high-quality and powerful trials, those of Insemann et al and Dellinger et al, which provide proof against the use of prophylactic antibiotics, although they do not indicate the ideal number of trials for this type of testing. Both trials clearly support the recommendations described above. Consequently, clinical practice must be influenced by these recommendations.

Recommendation 65. The use of prophylactic antibiotics in PSAP patients with or without pancreatic necrosis is not recommended. **Strong grade of recommendation (1), moderate quality of evidence (B).**

Recommendation 66. The analysis of individual patients may be important for identifying potential candidates who might benefit from antibiotic prophylaxis. **Weak grade of recommendation (2), low quality of evidence (C).**

Recommendation 67. The role of "early antifungal treatment" (misnamed antifungal prophylaxis) with fluconazole is unclear and requires further study. But once the fungal infection appears an antifungal with a greater spectrum than fluconazole should be used as soon as possible and by extension the same criteria used in SAP and CAP with bacterial infection are applied. **Weak grade of recommendation (2), moderate quality of evidence (B).**

Recommendation 68. Empiric antifungal treatment based on clinical findings without microbiological confirmation does not appear to be effective. **Weak grade of recommendation (2), moderate quality of evidence (B).**

Recommendation 69. There is no conclusive evidence at present for recommending the routine use of SDD in PSAP. **Weak grade of recommendation (2), moderate quality of evidence (B).**

14th Question: Hemofiltration in PSAP. Dynamic Approach to Extra - Renal Replacement Techniques: Early Hemofiltration; High-volume hemodiafiltration.

Immunomodulation and therapeutic control attempts in SAP treatment

PSAP and the evolutionary forms of SAP and / or CAP are characterized by the production and disposal into the plasma of elevated concentrations of inflammatory mediators of the remote development of an inflammatory condition and, consequently, although the initial process is local, their consequences rapidly become widespread (SIRS and subsequent development of MOF), as in sepsis, burns, etc. ([296], [297]).

Back in the 70s a group of pioneers suggested a change of strategy in the therapeutic approach of "reducing or mitigating the inflammatory process in the pancreas", by initially using peritoneal lavage. ([298], [299], [300]).

HF has several features that make it suitable for the removal of these proinflammatory substances, although there are conflicting data in the literature regarding the actual effectiveness of HF for removing inflammatory mediators (TNF-alpha, IL 1 , PAF, IL-6 and complementary fractions), because it has not always been possible to demonstrate that this clearing has an impact at the systemic level [301, 302, 303, 304]). However, there are consistent data that support the beneficial effect of HF on the clinical situation and recovery of patients with SIRS or MOF, which contributes especially to the stabilization of the respiratory and hemodynamic systems [305, 306, 307, 308]).

HF in the treatment of SAP: Clinical experience.

Based on the data presented, some authors have considered the possibility of achieving an immunomodulatory effect by using CTDB in patients without ARF, even though, paradoxically, no data were available on preclinical research to support this hypothesis ([309], [310], [311]).

In 2003 starts the application of early HFVVC as an alternative immunomodulatory treatment in SAP without conviction ([312], [313]). The major argument against these sttudies jobs is that they consist of a series of cases and not of controlled studies, and, on the other hand, the initiation of treatment can not be considered early (average delay of 6 days in initiating the treatment).

The most prestigious study ([314]) on HF and SAP with a randomized design was published in 2005. The authors analyzed the evolution of 37 patients with SAP, by comparing HF 1 vs. 4 l / l and early initiation of treatment (48 h) versus a late initiation (96 h). Mortality was significantly lower in the group receiving more doses with a more obvious hemodynamic improvement. The early treatment Group also benefitted in a similar way.

Recently, other authors ([315]) have developed a prospective case and control study of SAP, by distributing the patients into four groups, depending on whether they accepted or not HVHF (high exchange doses) and in the presence or absence of ARF at the time of initiation of HVHF. HVHF was introduced early in the treatment. The authors detected a significant improvement in the severity level of patients undergoing HVHF, as well as a significant reduction in the mortality of this group (an 81.0% survival rate on the 28th in the group receiving treatment vs 57.6% in the control groups. p = 0.026).

HF in SAP treatment: Current recommendations for its use.

From what has been discussed above it follows that the use of CRRT as specific immunomodulating treatment in SAP is based on appealing arguments, such as the positive effect these techniques have on the function of certain organs, the impossibility of immunomodulating impaired inflammatory response, maintaining cellular defense capacity and hindering the development of infections and, finally, the possibility of having a positive impact on the prognosis of these patients. In these cases, the starting time of the treatment, the exchange dose used, and the filter replacement frequency may affect the efficacy of treatment. However, at present we must consider that the accumulated experience is still insufficient, because, although well-designed experimental work has yielded positive results, clinical experience is limited to a small group of case series that are difficult to assess, two case-control studies using a methodology that prevents them from being conclusive, and a randomized study with a small number of patients.

Finally, the indication is based on the concept of a CRRT dynamic approach for AP patients in critical condition; i.e., how and when to dosify (4), when and how to initiate and how to terminate TDE in these critically-ill patients ([316]).

Management of patients with SAP and ARF.

FRA is a major problem in the development of SAP ([317], [318]), and although an isolated appearance might be considered very rare, a relatively high frequency of occurrence within a MOF has been detected. In these circumstances it implies an alarming increase in mortality of 70-80%, compared with 8% in patients without renal involvement, and finally, it becomes necessary to perform a TDE, and in these cases the mortality increases to 90 % ([319]). It shows a beneficial effect from continuous treatment ([320], [321]). Performing HFVVC early with a high exchange dose (HVHF) has shown to have a positive effect on the hemodynamic and / or respiratory condition of patients ([322]), by controlling the so-called "dialytrauma" ([323], [324]), and recommendations on withdrawal ([325]) *(diuresis > 1 ml / kg / h for> 24 hours*, the possibility of

a neutral hydric balance, without reducing the required volume, absence of uremia complications). Finally, we suggest a dynamic approach to therapies, by making a daily "check-list or review" of therapeutic targets (metabolic and fluid management) and adjusting the dose until final withdrawal. If the patient is able to maintain metabolic homeostasis and hydric balance without TCDE the technique could definitely be removed.

On the other hand, if we know that acute renal dysfunction or ARF is common in such critically ill patients with AP and that they will undergo scans with intravenous contrast and will receive potentially dangerous drugs for renal function, we believe that prevention protocols, as well as early detection and treatment of ARF in patients not only with PSAP, should be recommended, according to the validated aspects recently described in the COFRADE study ([326]).

Consequently, given the need for a purification treatment in a patient with complicated SAP with ARF, and considering the results obtained in other related pathologies and extrapolating these results for patients with SAP (in which there are no specifically published data), we have decided to make these recommendations and select the use of a TCDE:

Recommendation 70. At present, with the experimental and clinical evidence accumulated the use of TCDE as immunomodulating therapy as in the Potentially Severe Acute Pancreatitis (PSAP) has a favorable recommendation but it is not conclusive. **Weak grade of recommendation (2), moderate quality of evidence (B).**

Recommendation 71. After considering the possible beneficial effect on patient's immune response and the course of the illness, DTE should preferably be initiated early. **Weak grade of recommendation (2), moderate quality of evidence (B).**

Recommendation 72. A safety renal system for PSAP patients should be provided be means of the creation of a prevention protocol, early detection and ARF handling both in ICUs and general hospital rooms. **Strong grade of recommendation (1), high quality of evidence (A).**

Recommendation 73. If an ARF patient has general and hemodynamic stability, any treatment that currently controls the internal environment (extended or continuous IHD) could be used for this purpose, based on the team and infrastructure experience. **Strong grade of recommendation (1), high quality of evidence (A).**

Recommendation 74. In the cases of acute renal failure in the course of SAP with hemodynamic instability, according to the experience accumulated in other related pathologies (There is no specific data on SAP), TCDE is recommended. Although there is no definitive study on this subject, the use of IHD in hemodynamically unstable patients is not recommended. **Strong grade of recommendation (1), moderate quality of evidence (B).**

Recommendation 75. TCDE should be started early in the course of acute renal failure. **Strong grade of recommendation (1), moderate quality of evidence (B).**

Recommendation 76. Based on the interest of using more cost-effective treatments and with the aim of reducing the complications of this type of therapies, a dynamic approach to these therapies would be very useful, based on the basis of the type of patient and the stage in his/her recovery. **Strong grade of recommendation (1), low quality of evidence (C).**

15th Question: Surgical approach to SAP or CAP with and without Pancreatic Necrosis and Sepsis.

SURGICAL INDICATIONS

Sterile Necrosis

Currently, there is a consensus on the conservative management of patients with AP and sterile necrosis, which is based on the medical treatment. In 1991, Bradley and Allen described a series of patients in whom conservative treatment seemed to have good results. Recent guidelines recommend surgical treatment for those patients where intensive supportive care has failed. A recent national study on patients undergoing surgery ([327]), which had been published, shows that surgery for sterile necrosis is associated with increased mortality, and supports conservative treatment unless a pancreatic or peripancreatic infection is detected.

Current management of AP patients with sterile necrosis is based on conservative treatment. However, after the acute stage, a small number of patients with non-infected necrosis may benefit from surgical treatment:

1. Patients, who after several weeks of conservative treatment, still suffer from fever, lethargy, recurrent abdominal pain, nausea and / or vomiting and hyperamylasemia after attempts to return to an oral diet, typically have large amounts of necrotic tissue and often have concealed retroperitoneal infections in this devitalized tissue that are objectified after debridement ([328]).
2. Patients with postnecrotic rupture of the main pancreatic duct, which is classified as *"disconnected duct syndrome*", with a clinic similar to that discussed above, which are tributaries of surgical treatment (24).
3. Intestinal obstruction or biliary stenosis due to the organization of necrosis.

Infected Necrosis

Contrary to the controversy that erupted regarding the treatment of sterile necrosis, there is virtual unanimity about the concept that patients with infected necrosis are tributaries of surgical treatment.

Some articles have appeared advocating conservative treatment, even in patients with infected pancreatic necrosis ([329], [330], [331], [332]). Most of these studies have been conducted on patients who have refused surgery or have been considered to be at a very high surgical risk. Prolonged antibiotic treatment, occasionally supported by percutaneous drainage of intraabdominal collections, helps to get acceptable results.

Since mortality rates for patients undergoing conservative treatment who had infected pancreatic necrosis were very high, this treatment is not currently advisable unless patients refuse surgery or are considered inoperable due to a high comorbidity ([333]).

However, recent data may question this assertion. Stern et al ([334]) note that FNA bacteriology does not determine either the surgical approach or the clinical status and the parenchymal impact. Invasive options should be increased, and the endoscopic and laparoscopic approaches versus the standard beginning laparotomy should be continued, if the clinical situation permits. Overall, neither does a positive bacteriology imply a surgical indication, nor does a negative bacteriology rule it out (There are no false negatives) and the same is true of the discovery of gas in CT.

In summary, patients with infected necrosis should be treated surgically based primarily on the clinical situation. A positive PAAF or gas in the CT does not appear to be totally synonymous today with surgical treatment if the patient is able to undergo surgery from a clinical standpoint.

SURGICAL TECHNIQUE

The surgical technique for the treatment of AP with infected necrosis is based on a necrosectomy involving extensive debridement of the entire pancreatic and necrotic peripancreatic tissue, while preserving the viable tissue as much as possible in an attempt to prevent secondary pancreatic fistulas and limiting where possible lesions to and / or removal of adjacent organs.

Rau's study ([335]), where he compared the results on mortality published in the literature, between necrosectomy and declining drainage, necrosectomy and lavage by means of a closed and a necrosectomy plus programmed relaparotomy and an open or temporarily closed abdomen, indicated a mortality for different techniques of 42 %, 20% and 21%, respectively.

These techniques have not been studied using well-controlled, randomized studies, so that there is no clear indication of one procedure over another (93, 335). In this case, the experience of the surgical team, the proper management of these patients subjected to an open abdomen, temporary closure or continuous lavage by the nursing team that controls the treatment; provide the principal criteria for selecting one technique or another.

Recently, Bradley (333) reported that open abdomens should be reserved for those patients with acute pancreatitis and infected necrosis who present extensive collections that exceed the pancreatic cell and fill the entire retroperitoneal space behind the colon.

It is probably in these cases where the value of intra-abdominal pressure (IAP) becomes more relevant. The patients that Bradley (333) described are, without doubt, patients with elevated abdominal pressure, who frequently are sick with a universal necrosis that is not confined to the pancreas and who are certainly those who should be treated by means of a temporary closure of the abdomen; proceeding to the conventional closing of the laparotomy is a clear predisposing factor for the development of abdominal compartmental syndrome (ACS) with fatal consequences.

If the patient is stable during pancreatic surgery, cholecystectomy can also be performed. If the condition of the patient undergoing surgery is unstable, and there is a vesicular plastron, the gall bladder should not be operated on and only the necrosectomy should be performed.

TIME FOR THE SURGICAL INDICATION

Pancreatic necrosis is a dynamic process that has two distinct phases, the early and late phases. The conclusive evidence that advised against surgery of sterile necrosis (335, [336]) indicates that the best time to indicate necrosectomy is during the late phase of the disease; i.e., the phase in which the necrosis infection is common (often after three or four weeks from its onset) (24, [337]).

In the early or initial phase (first two weeks after its onset) surgical indication should only be established in the following cases:

a. Cases of MOF and diagnostic doubts between PSAP and mesenteric ischemia or perforation of empty viscera.
b. Cases of intestinal ischemia or a perforation which is secondary to the extension and / or compression pancreatic necrosis produced by pancreatic necrosis, either at the level of small intestine or colon.
c. The appearance of ACS in the early days, by performing decompressive surgery without a necrosectomy.

In all patients with CAP or SAP AIP should be recorded regularly in search of the development of ACS that could make it necessary to perform decompressive surgery.

NEW SURGICAL TECHNIQUES

Minimally invasive pancreatic necrosectomy (MIN) ([338]) has been developed according to two diametrically opposed philosophies. On the one hand, there is a group of surgeons who supports MIN as a complementary method of open necrosectomy, which is useful for the treatment of waste collection after conventional surgical treatment; this form of management has been referred to as "*step-down*" (5).

On the other hand, there is another group of surgeons who support "*step-up*" (5), which relegates open necrosectomy to a secondary option after the failure of a minimally invasive technique.

The transgastric route described by Baron ([339]) is inspired by the classic surgical treatment of retrogastric pancreatic pseudocysts. By using this procedure, it has been possible to successfully debride pancreatic necrosis; however, it requires a specific localization of the necrosis: encapsulation and liquefaction of the necrosis area located in the lesser sac and therefore delimited by the stomach, duodenum and colon transverse: "*walled off pancreatic necrosis*".

The retroperitoneal approach described by Carter's group in Glasgow ([340]) is an adaptation of the classic lumbotomy for debridement of infected pancreatic necrosis basically localized on the left side of the abdomen.

The randomized, controlled study conducted in the Netherlands (5) comparing an *open necrosectomy* to the "*step-up*" technique (percutaneous drainage and, if it is insufficient, minimally invasive retroperitoneal necrosectomy), shows that 35% of patients can only be treated with percutaneous drainage and the remainder require the combination of percutaneous drainage and minimally invasive retroperitoneal necrosectomy. There are fewer complications, 69% for open necrosectomy versus 40% for the "*step-up*"; however, it was not possible to demonstrate a significantly lower mortality, 19% vs. 16%.

The use of radiologically guided percutaneous catheters is considered a "*bridge*" technique until a more definitive treatment can be applied; it can be extremely useful for stabilizing patients whose condition is too serious to tolerate any type of necrosectomy (337). This technique has not been compared to surgical debridement, but in a systematic review of the literature on the usefulness of percutaneous drainage as the sole technique in the treatment of pancreatic necrosis, the use of drainage was found to be sufficient for 55.7% of patients who did not require surgical necrosectomy (85).

A new message has emerged from all these new techniques: *necrosectomy in itself may be less important than achieving proper drainage* (339).

Currently endoscopic techniques, with some exceptions, have failed to demonstrate its superiority over conventional techniques; however, the future of minimally invasive techniques in the treatment of patients with infected pancreatic necrosis is promising, as long as the experience in handling it increases and the new technology needed for obtaining the best results appears. (335, [341]**¡Error! Marcador no definido.**).

CONCLUSIONS:

1. The management of patients with sterile necrosis is conservative.

2. The management of patients with infected necrosis is surgical. If the patient's clinical condition permits, surgery should be delayed as long as possible and it should be preceded by less aggressive approaches.
3. Necrosectomy and lavage and necrosectomy, lavage and scheduled and / or open abdomen laparotomy are the most recommended "classic" techniques.
4. The best time for necrosectomy is in the late stage of the disease.
5. Less invasive surgical techniques make a strong appearance and should be evaluated by means of well-designed studies.

Recomendación 77. Surgery. Indications: Infected necrosis plus clinical deterioration; Intestinal ischemia or perforation secondary to pancreatic necrosis; Intestinal obstruction or biliary stricture due to the organization of necrosis. **Strong grade of recommendation (1), high quality of evidence (A).**

Recomendación 78. Surgery. Technique: Necrosectomy + drainage ± temporary closure. **Weak grade of recommendation (2), moderate quality of evidence (B).**

Recomendación 79. Surgery. Moment of surgery: 3-4 weeks after initiation of the PSAP as long as the patient's condition permits. **Strong grade of recommendation (1), moderate quality of evidence (B).**

Recomendación 80. Surgery. New surgical techniques: Minimally invasive or not combined with percutaneous drainage; Retroperitoneal and transgastric. **Weak grade of recommendation (2), low quality of evidence (C).**

Recomendación 81. In a patient with infected necrosis and organ failure, current indication is surgical necrosectomy. Treatment by means of other options which are less invasive, such as radiological or endoscopic techniques, has yet to be determined. Radiological or endoscopic techniques can be used in a patient with infected necrosis and without organ failure. When the patient's condition does not improve, surgical necrosectomy can be performed. **Strong grade of recommendation (1), high quality of evidence (A).**

16th Question: Costs of managing a PSAP patient in an ICU.

AP is a complex entity where multidisciplinary treatment is necessary. Performing more frequent economic evaluation studies has failed to address, with few exceptions, the pathology that we are assessing. The number of tasks with a pharmacoeconomic approach is small. An economic assessment of overall AP treatment has not been performed as of today, and we only have observational estimates of hospital treatment costs (in Spain, a mean average of € 3,365, an average of 6,488 with a standard deviation of 14 393) ([342]). This treatment, which is expensive, is warranted by the excellent prognosis of these patients after recovering from an acute episode (123) (84% of the patients who had worked the year prior to SAP episode were able to return to work) ([343]).

We can distinguish between two major types of economic studies: the economic study "embedded" in another study (observational, clinical trial, etc…), and purely "economic" study (e.g. decision analysis), whose budgets must be drawn up from studies with the best level of available evidence. For the first type

of economic study a GRADE assessment is simple. For the second type of study, which is more complex, with several assumptions that may influence the results, it may be more complex to label them, especially if they are based on small tasks with little statistic power.

Management of AP from the economic standpoint.

From a general management point of view, implementation of a systematic multidisciplinary algorithm, such as clinical pathways, in patients with acute pancreatitis can result in a reduction of mortality, shortening of the length of stay, and reduction of hospital costs. In a study performed in the USA ([344]), there was a significant improvement in the outcomes of patients with acute pancreatitis after implementation of the algorithm. In particular, the mortality rate was 6.6%declines of these three variables: in 1998 (prior to introduction of the algorithm) as compared with 2.2% in 2009, the mean length of hospitalisation was 9.6 and 7.2 days, respectively, and the mean cost of treatment was $6,186 and $6,160, respectively. The last difference is meaningful taking into account the inflation rate since 1998. At the same time, it is worth mentioning that these findings were derived from a retrospective study and further prospective studies are warranted.

Regarding the management of imaging of acute biliary pancreatitis, we found several interesting tasks.
Gregor ([345]) performs a decision analysis to assess the cost-effectiveness of performing endoscopic retrograde cholangiopancreatography (ERCP) routine in patients with idiopathic PA, versus performing ERCP after a 2nd episode symptomatic. He concludes that performing routine ERCP provides a marginal overall benefit, although the benefits are greater and the option is more cost-effective in the subgroup of patients with higher probability of a hidden choledocholithiasis.
As a result of this study, the patients with "a priori" high probability of choledocholithiasis underwent an performed ERCP before cholecystectomy, whereas if this probability was low cholangiography was performed. Arguedas [(346)] performs a cost-benefit analysis as to whether surgical cholangiography (IOC), ERCP, endoscopic ultrasound (EUS) or colangiopancreatoRM (CPRM) or intraoperative cholangiography (IOC) (these last 2 followed by ERCP) should be performed on these patients. This study rates the different strategies, with AP morbidity and mortality data and the data from each test, with the expected complications of each, and the characteristics of each test (sensitivity and specificity) and the costs. The result is that with a probability of choledocholithiasis <15%, the observation with performing ICO is the least expensive option, if that probability is 15-58% EUS and ERCP if the probability is> 58%. In terms of cost-effectiveness, for a probability of 7-45% of cholelithiasis, EUS is the option of choice, and for greater ERCP values.
A similar approach is followed in a more recent study ([347]), but it can differ depending on the severity of the illness; according to the authors, EUS is the dominant strategy (or it is the strategy of "choice" from the pharmacoeconomic point of view) in acute biliary AP, while in unsevere forms EUS is slightly more expensive although it is associated with less ERCP and fewer ERCP-realted complications.

The nutritional support of these patients is an area of interest.

In a randomized study, albeit a small one ([348]), conducted in the U.S., enteral nutrition (EN) intake by means of a nasojejunal tube or parenteral nutrition (PN) was compared after 48 hours of support with fluids and analgesics. Patients on an enteral diet was on the diet for a shorter time, which involved an average savings of $ 2,300 per patient in diets, and lower rates of metabolic and infectious complications (data consistent with those found in the severe AP subgroup).
These results are similar to those found in an observational and descriptive study in Colombia ([349]), with progressively lower average hospital costs (EN and a mixed PN, $ 38,300; $ 23,200 NP; NE $ 16,000) and less hospitalization (29 days in the 2nd group and 19 in the 3rd).
A small randomized controlled trial (n = 28) compared the efficacy of PN with glutamine supplementation versus standard PN ([350]). No significant changes in measured events or cost variations were observed.
A randomized trial was performed in China (n = 100) comparing NP until the start of an oral diet versus a "more individualized" approach with successive NP, transpyloric NE and, finally, prepyloric EN, phases. In the second group lower rates of complications, secondary infections, intraabdominal infections, length of hospital stay and hospital costs were observed ([351]).

TCRR costs. The support of these patients with continuous renal replacement therapies is very fashionable, but with controversial results. In a study performed in China ([352]), a systematic review on the early initiation of this technique in Chinese patients with severe AP, short-term continuous venovenous hemofiltration (HFVVC) is described as the most cost-effective, with better results than HFVVC long-term peritoneal dialysis, or a combination of short-term HFVVC and peritoneal dialysis. IT also refers to the superiority of high flow techniques. However, the study has some methodological limitations. Therefore, the issue continues to be controversial.

Surgical costs in PSAP. En cuanto al tratamiento quirúrgico activo, encontramos varios aspectos.
An old observational study ([353]), with a short series of 10 AP necrotizing patients, showed the effectiveness of open necrosectomy, with $ 3,214 per year of a life saved, although part of several unrealistic assumptions (100% mortality in the absence of surgery, life expectancy of 75 years); a more recent observational an retrospective study, performed in New Zealand ([354]) did not find any significant differences (-3.8 days in ICU stay, 44 days in a hospital room – or costs -) in performing open minimally invasive pancreatic necrosectomy.
In a recent Dutch randomized study (5), the efficiency of a minimally invasive "Step by Step" approach (percutaneous drainage or endoscopic transgastric, with a video-assisted attempt if the first attempt is not effective) versus an open necrosectomy is assessed. This approach reduces the likelihood of the primary combined end point (multiple organ failure, viscus perforation, enterocutaneous fistula, intra-abdominal bleeding or death), there is no variation in isolated mortality, but there is a significant reduction in costs of up to € 10,800 per patient.

Prevention costs. Finally, we describe at least three actions with preventive objectives:
In Navarra ([355]) the efficacy of somatostatin for preventing post-ERCP AP was studied. The cost of the hormone is much lower than ERCP. Assuming an AP rate of 3% in the somatostatin group and 10% in the control group, the economic benefit with AP rates in the control group of at least 4.2% are described.
In a study performed in the U.S. ([356]) different strategies for placing a pancreatic stent for preventing post-ERCP pancreatitis with Markov decision trees was assessed; the study reached the conclusion that stent implantation in patients with a risk of ERCP is the most cost-effective strategy.

And performing open ([357]), laparoscopic ([358]), or early cholecystectomy, for acute cholelithiasis, can help reduce costs by avoiding hospital readmissions for cholecystectomy-related medical problems, including AP. In fact, although old clinical guidelines (1998) recommend that cholecystectomy be performed in biliar AP within 2 weeks after the acute episode, and even in the same hospital, there is "administrative" resistance to doing it, despite the increase costs involved in a subsequent readmission to perform scheduled surgery. As an important methodological limitation, the two studies are observational and retrospective.

PPC prophylaxis of PPC is also achieved with nonsteroidal antiinflammatory drugs (NSAIDs) and a recent study (106) concluded that rectal treatment with indomethacin is sufficient to reduce pancreatitis among patients at high risk following an ERCP. Moreover, this drug, indomethacin, is cheap, accessible and easy to administer.

Recomendación 82. There are only a few economic assessment studies of patients with AP. Due to a limited number of studies on this topic we do not to make any recommendations on this aspect.

Table 1. Classification of the recommendations (Grade and Evidence) (Guyatt et al. *Chest* 2006; 129; 174-181**)**

Grade of recommendation and Evidence	Benefits as opposed too risks and weight-impact	Methodological quality of support	Consequences
1A. Strong grade of recommendation, high quality of evidence	The benefits clearly outweigh the risks and the workload, or viceversa	RCTs without important limitations, or overwhelming proof from observational studies	Strong recommendation that may be applied without reservations to most patients and under most circumstances
1B. Strong grade of recommendation, moderate quality of evidence	The benefits clearly outweigh the risks and the workload, or viceversa	RCTs with important limitations (inconsistencies regarding the results, methodological defects, indirect or imprecise inconsistencies) or exceptionally solid evidence or observational studies	Strong recommendation that may be applied without reservations to most patients and under most circumstances
1C. Strong grade of recommendation, low quality of evidence	The benefits clearly outweigh the risks and the workload, or viceversa	Observational studies or case series	Strong recommendation that could change when higher quality proof is available
2A. Weak grade of recommendation, high quality of evidence	The benefits are barely balanced by the risks and the workload	RCTs without important limitations, or overwhelming evidence from observational studies	Weak recommendation, a better measurement may vary according to the circumstances, or those of the patients, or those of the social values
2B. Weak grade of recommendation, moderate quality of evidence	Benefits barely balanced by the risks and the workload	RCTs with important limitations (inconsistencies regarding the results, methodological errors, indirect or imprecise inconsistencies) or exceptionally solid evidence from observational studies	Weak recommendation, a better measurement may vary according to the circumstances of the patients or those of the social values
2C. Weak grade of recommendation, low quality of evidence	Uncertainty in the estimates of benefits, risks and workload; benefits, risks and workload are very balanced	Observational studies or case series	Very weak recommendations, other alternatives may be equally reasonable

RCT: Randomized controlled trials

"Con el Aval Científico de la SEMICYUC" En Madrid, 30 de Octubre de 2012. Lista Distribución = **Pancreatitis CC-UCI, 2012-1 y 2**

Appendix 1. Authors / Task Force Members: Group CC – Recommendations PSAP 2012 (To see on-line).

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2nd Question: Classification of Acute Pancreatitis.

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4th Question: Criteria for early admission to an ICU.

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5nd Question: Biomarkers of acute pancreatitis severity. Inflammatory and Infection Markers.

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6th Question: Role of Radiology in AP. Diagnosing of infected necrosis. Percutaneous Drainage.

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8th Question: Control of PIA and approach to SCA.

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10th Question: Volume replacement and hemodynamic monitoring. In critically-ill patients with or without mechanical ventilation (MV). In general wards and ICUs

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12th Question: Role of Endoscopy / Gastrointestinal Ultrasound Endoscopy in severe and critical acute pancreatitis.

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13th Question: Antibiotic prophylaxis in PSAP.

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14th Question: Hemofiltration in PSAP. Dynamic Approach to Extra - Renal Replacement Techniques: Early Hemofiltration; High-volume hemodiafiltration.

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15th Question: Surgical approach to SAP or CAP with and without Pancreatic Necrosis and Sepsis.

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16th Question: Costs of managing a PSAP patient in an ICU.

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