Proposed BBUGGSS Guidelines on Severe Acute Pancreatitis (SAP)

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Definition

The term "pancreatitis" was originally used in 1824 by *Dr. George Pearson Dawson* from combining *"pancreas"* and *"itis"*. Pancreatitis is defined as *"inflammation of the pancreas"*.

History

Understanding of Pancreatitis

Historical accounts of the illness suffered by Alexander the Great (323 BC), which led to his demise, could have indeed been acute pancreatitis.[1]

Reginald Huber Fitz (1843 – 1915) was a pathologist at the Massachusetts General Hospital that presented clinical characteristics of haemorrhagic, suppurative and gangrenous forms of pancreatitis.[2] Fitz postulated that management for pancreatitis with laparotomy was *"ineffective... an operation which, in the early stages of the disease, is extremely hazardous"*. He incorrectly assumed that acute pancreatitis was a complication of gastroduodenitis.

In 1896, it was Chiari that proposed that the underlying pathophysiological process of acute pancreatitis was pancreatic autodigestion and stated that the pancreas *"succumbs to its own digestive properties"*.[3]

The autodigestive theory was developed in the 1900's by Eugene Lindsay Opie (1873 – 1971). He developed the "common channel" hypothesis, proposing that a gallstone fixed in the ampulla of Vater could occlude the pancreatic and common bile duct, thereby causing reflux of bile into the pancreatic duct and subsequent activation of pancreatic enzymes leading to pancreatitis.[4] Lerch et al. established obstruction of the pancreatic duct alone can also cause necrotising pancreatitis.[5]

Surgical Management

Throughout history there have been cycles of eagerness alternating between surgery and conservative treatment for pancreatitis.

Initially, upon publication of a paper by Lord Moynihan (1935)[6], surgical intervention was the preferred management option for severe acute pancreatitis (SAP), with Moynihan himself stating *"... certain that recovery from this disease, apart from at operation, is so rare that no case should be left untreated"*.[6]

From the 1930's, a change in approach was observed to conservative therapy after mortality rate as high as 50% - 75% was noted for surgery.[6]

In the 1970's, surgical management was revisited for acute complicated pancreatitis. It was the work of Beger and Bradley, that classified the types of pancreatic necrosis ("infected" vs. "sterile"), differentiated those that benefited most from surgical intervention and also considered the different surgical approaches to drainage ("open" vs. "closed").[7,8]

Current favoured techniques have emerged from randomised controlled trials including 'Step-up' (percutaneous drainage to Video Assisted Retroperitoneal Debridement - VARD) and

endoscopic necrosectomy, however due to the heterogeneity in characteristics and anatomical location of walled-off pancreatic necrosis – WOPN often a single strategy is not suitable in all circumstances.[9-11] Laparoscopic surgical debridement/drainage techniques have shown some success in select group of patients with central, solid, retrogastric/infracolic WOPN.[12]

Epidemiology

- Incidence 56/100,000 population in the United Kingdom[13]
- Prevalence of gallstone pancreatitis is higher in females than males[14]
- 80% of patients will have a mild course of pancreatitis and is self limiting[15]
- Moderately severe/severe pancreatitis (20%) includes patients with organ failure (<48 hours-moderately severe, >48 hours in severe) and/or presence of local complications (necrosis/pseudocyst) and may require referral to a specialist unit for treatment[16]
- Overall mortality rate of between 30% - 50% in severe cases[16]

Pathophysiology

Pancreatitis is characterised by loss of intracellular and extracellular compartments secondary to obstruction of pancreatic secretory transport and activation of pancreatic enzymes resulting in autodigestion of the pancreas.

Biliary Acute Pancreatitis

Pancreatic duct outflow obstruction from an impacted ampullary stone, migrating gallstone or functional obstruction of sphincter of Oddi causes increase in pressure within the pancreatic duct and reflux of secretions. This leads to release of activated pancreatic enzymes, caused by injury to pancreatic duct epithelium, resulting in further damage to pancreatic tissue.[17]

Alcoholic Pancreatitis

The exact mechanism is not fully understood but it is believed that alcohol inhibits the secretion from acini cells, activates transcription of proinflammatory cytokines (TNF-α, IL-6), alters cell permeability, increases lysosomal fragility and enhances necrosis.[18]

Diagnosis

The diagnosis of pancreatitis is confirmed by presence of 2 of 3 criteria:

1. Clinical – sudden onset of epigastric pain radiating to the back, nausea and/or vomiting and pyrexia (>38°C)
2. Serum amylase/lipase >3 times the upper limit of normal
3. Imaging - (computed tomography, magnetic resonance, ultrasonography)

Aetiology

- Most common are gallstones (50%) and alcohol (25%)
- Others include: hypertriglyceridaemia, hypercalcaemia, post ERCP, trauma, medications (Sodium Valproate, steroids, and Azathioprine) rarely hereditary, viral (Mumps, Coxsackievirus B4, COVID-19[19]), pancreatic divisum, autoimmune IgG4 or idiopathic (<10%)

Predictors of severity

Pancreatitis is graded according to its severity into mild, moderate and severe. Scoring systems need reassessment at different time points and none have shown superiority over others. Predicting severity is difficult but important in aiding triage for admission to critical care, assessing need for pancreatic imaging and calculating risk for morbidity and mortality.[20] Some established scoring systems used to predict severity of pancreatitis have been discussed below.

Ranson's Criteria or Glasgow-Imrie score:

Historically, the Ranson's criteria and Glasgow-Imrie Score (abbreviated of Ranson's criteria parameters) have been utilized, although both are poor predictors of severity.[21] These scores are traditionally scored at 48 hours following admission ***(Appendix 1)***. A score is ≥ 3, severe pancreatitis is likely and therefore, referral for consideration of Level 2 or Level 3 care is warranted. The relationship of score with mortality is listed below[22]:

- Score 0 – 2: 2% mortality
- Score 3 – 4: 15% mortality
- Score 5 – 6: 40% mortality
- Score 7 – 8: >90% mortality

Bedside Index of Severity (BISAP):

BISAP score incorporates the systemic inflammatory response syndrome criteria, only has 5 variables and can be used from the time of admission. It has been validated for predicting mortality and probability of admission to intensive care.[21,23,24] A point is given for each of the following criteria and a score of 3 or more indicates a poor prognosis ***(Appendix 2)***.

Serum Markers:

Multiple laboratory markers have been assessed in predicting severity. C-reactive protein (CRP), an acute phase protein has shown most promise in predicting outcomes in pancreatitis.[25] CRP ≥ 150 mg/dL at 48 hours is associated with a worse prognosis.[26-28] A Cochrane review has shed caution on studies assessing serum markers (CRP, procalcitonin, lactate dehydrogenase) highlighting paucity of data as well as methodological deficiencies.[26]

Early Warning Score (EWS):

EWS is a tool that uses six physiological measurements including pulse, systolic blood pressure, respiration rate, oxygen saturations, temperature and level of consciousness to create a score which helps determine the patient's clinical state. Patients that are acutely unwell will score highly.[29]

When compared with APACHE II, Imrie, CT grading and Ranson criteria, EWS was found to be the best indicator for adverse outcome (measured at 24 hours) and mortality (measured on day 3).[30-32]

Modified CT severity index (MCTSI):

Balthazar CT grading of pancreatitis has been superseded by MCTSI. It is an extension of the CT severity index that was developed by Balthazar and colleagues in 1994 for distinguishing mild, moderate and severe pancreatitis by CT imaging. Scores are generated by estimating pancreatic inflammation and necrosis giving a score out of 10 ***(Appendix 3)***. There is evidence of correlation between MCTSI score and outcomes.[33]

Harmless Acute Pancreatitis Score (HAPS):

The HAPS is a scoring algorithm that has been developed to identify patients that would follow a non-severe or mild course of acute pancreatitis.[34] Its components constitute 3 parameters:-

- Absence of rebound tenderness or guarding
- Normal hematocrit
- Normal serum creatinine

Systemic inflammatory response syndrome (SIRS):

Persistent (>48 hours) SIRS is associated with multi-organ failure and mortality in acute pancreatitis (25% - persistent SIRS versus 8% - transient SIRS).[35] Similar to EWS, examining for SIRS is pragmatic, simple and easily repeated.[36]

Classification

Revised Atlanta Classification for Acute Pancreatitis:

Formulated in 2012, the revised form is an update of the 1992 Atlanta classification and is by consensus an approved international classification of severe acute pancreatitis (SAP).[37]

The classification system is based on local and systemic determinants of severity (mild, moderate, and severe):

Revised Atlanta Classification of Acute Pancreatitis: Definition of Severity
Mild pancreatitis (80%) • Absence of organ failure • Absence of local complications
Moderate pancreatitis (one or both of the following) • Organ failure resolving within 48 hours • Local or systemic complications (sterile/infected)
Severe pancreatitis • Persistent organ failure (>48 hours): single or multiple

There is distinction between **two clinical periods** of SAP:

- Early (1st week): severity is based on the absence or presence of systemic organ failure.
- Late (> 1 week): severity is based on the presence of local complications or persistent systemic organ failure.

The Atlanta Classification also divides SAP into two basic types:

- Interstitial Oedematous Pancreatitis (IOP): IOP is acute inflammation of pancreatic and peripancreatic tissue without necrosis. IOP is divided according to time from onset into acute pancreatic fluid collection (APFC) (< 4 weeks) and pseudocysts – an encapsulated fluid collection with an inflammatory wall (>4 weeks).
- Necrotising Pancreatitis (NP): NP is classified according to time from onset into acute necrotic collections (ANC) (< 4 weeks) and WOPN – an encapsulated collection of pancreatic and/or peripancreatic necrosis with an inflammatory wall (>4 weeks). The pattern of necrosis is sub-divided into: parenchymal necrosis, peripancreatic necrosis or most commonly combined type (peripancreatic and parenchymal necrosis).
- ANC/WOPN or APFC/pseudocysts may be **sterile** or **infected with or without symptoms**.

Natural course of pancreatic collections (WOPN/Pseudocyst):

- IOP will progress to APFC in between 30 and 40% of patients within 4 weeks from the onset of SAP.[37-40] Some 90% of these collections resolve without intervention and the remainder persist to form pancreatic pseudocysts (10%).
- Early studies postulated that the size of pseudocyst was an important factor in deciding on intervention, with the "Rule of 6" commonly being utilised (cysts >6cm and/or duration >6 weeks should be treated).[43] Recent studies have disputed the rule and in today's clinical landscape, other factors such as a disrupted/disconnected pancreatic duct, onset of symptoms (i.e. abdominal pain, visceral compression causing vomiting or jaundice) and persistence of pseudocyst during close surveillance are used to determine drainage (Figure 1).[44]
- Early (<4 weeks) pancreatic necrosis develop into ANC in 90-100% patients, which then progress into WOPN in 60% (> 4 weeks) and resolve in 25%.[45] WOPN can be single or multiple, and its commonest location is retrogastric (bulging into lesser sac), although it can develop anywhere in the retroperitoneum. The variability in location and occasional presence in multiple sites adds to the difficulty in achieving drainage and clearance. About a half of patients with WOPN are symptomatic and 30% become infected.[37] Spontaneous resolution of WOPN is most commonly seen in patients with <30% necrosis and without pancreatic duct involvement.

Investigations

Liver Function tests (LFT)

- LFT's: An elevated Alanine Transaminase (ALT) >150U/L has a positive predictive value of 85% for gallstones. LFT's should be measured in the first 24 hours from admission.
- CRP and other predictive indicators are mentioned above.

Imaging:

- Ultrasound (US): US is used to assist in determining if acute pancreatitis is secondary to gallstones and should be performed in the first 24 hours of admission. Early detection can help plan urgent cholecystectomy to prevent recurrent attacks of

pancreatitis. US can also demonstrate dilated common bile duct (CBD), which could indicate an impacted CBD stone, or presence of pancreatic pseudocyst.[10]

- Contrast-enhanced Computerised Tomography (Ce-CT): Indications for Ce-CT are in diagnostic uncertainty, confirmation of severity, clinical deterioration after initiation of conservative treatment, suspicion of a pseudo-aneurysm or when planning for intervention. Ce-CT is ideally performed > 72 hours after onset of symptoms (unless it is to confirm diagnosis), at which point complications of severe pancreatitis can be identified. Surveillance CT scans are useful in monitoring progression or resolution of SAP before or subsequent to intervention.[10] Ce-CT scoring systems are not superior to others in predicting severity and therefore evidence suggests early inappropriate use of Ce-CT leads to increased length of hospital stay without improving clinical outcome.[47] The risk of contrast allergy or nephrotoxicity should not be underestimated.
- Magnetic resonance imaging (MRI): Commonly in the form of a magnetic resonance cholangio-pancreatography (MRCP). Allows assessment of the biliary tree, ductal stones, and comprehensive evaluation of full spectrum of pancreatic pathologies including the presence of a pancreatic divisum, pancreatic duct stricture, disruption or disconnection.[10] Secretin stimulated MRCP is recommended following a negative EUS to identify any rare morphological abnormalities of the pancreas. T2 weighted MRI images of the pancreas are advised to differentiate between solid and liquid components of a pancreatic collection (pseudocyst Vs WOPN).
- Endoscopic Ultrasound (EUS): Provides detailed images of the pancreas, including the duct and parenchyma. It is recommended as the first line following negative investigations for biliary aetiology (right upper quadrant US) for detection of micro calculi. It has a diagnostic yield of 88% for detection of biliary sludge, CBD stones, pancreatic neoplasms and chronic pancreatitic.[48] EUS also plays an important role in the management of SAP by way of drainage of collections by deployment of lumen apposing metal stents (LAMS) via the posterior stomach wall.[47,48] Endoscopic transluminal pancreatic necrosectomy can be performed through the LAMS when the collections are dominantly solid.[47,48]

Genetic counseling

- Genetic counseling should be considered following a second attack of idiopathic acute pancreatitis.

Management

Medical:

Early resuscitation:

- Patients with SAP often develop hypovolaemia due to third space losses and vomiting. They may also have concomitant hypotension secondary to a SIRS response and goal directed intravenous fluids is required for preservation of organ function.[47]
- Consensus guidelines from the International Association of Pancreatology and American Pancreatic Association (IAP/APA) recommend the use of Ringer's Lactate (Ringer's Lactate is similar to Hartmann's Solution in the UK) for the initial resuscitation phase.[47] Goal-directed fluid therapy should be used at 5-10 ml/kg/h initially until resuscitation goals are met through utilisation of key observations (heart rate; <120 beats/minute and blood pressure; mean arterial pressure 65-85 mmHg) and urine output (0.5-1 mL/Kg/hour).[47]

Antibiotics:

- Prophylactic antibiotics has been studied extensively in patients with SAP, however a Cochrane review studying 7 randomised controlled trials (RCT's) found no evidence to support their use in terms of reducing rates of systemic infection, infections in WOPN and mortality.[49,50]
- In the presence of confirmed necrosis or pancreatic collections, the use of antibiotics is warranted based when infection is clinically suspected. Antibiotic therapy should be guided by sensitivity of cultured organisms when available and by duration and severity of septic symptoms.

Pain Relief:

- Severe pain leads to impairment of respiratory function by restriction of abdominal wall movement. Providing effective analgesia is critical in preventing respiratory dysfunction.

Nutrition

- Mild pancreatitis – early oral feeding can be restarted on improving abdominal pain and inflammatory markers.
- SAP – enteral tube (NG/NJ) feeding should be primarily used in those that require nutritional support. Parenteral nutrition should only be considered when enteral (NG/NJ) options fail.

Specialist Referral:

- Referral to a specialist pancreatitis center is required when interventional radiological, endoscopic or surgical intervention is needed. A specialist center is defined by IAP/APA as a unit with high volume experience, ICU facilities including organ replacement therapy and 7-days a week access to intervention.[47]

Approaches to Drainage of Pancreatic Collections (WOPN/Peudocyst):

- It is imperative that all cases are discussed at a dedicated multidisciplinary team meeting
- Intervention is delayed and if possible beyond 4 weeks to reduce the risk of morbidity and mortality. After 4 weeks, urgent intervention is required in those patients with clinical signs of infection, new onset organ failure or intra-peritoneal rupture of infected pancreatic collection ***(Figure 1)***. In these acute pathologies a lifesaving procedure is performed and the decision for the type of intervention should be favored towards the approach which allows for, if possible single-staged drainage. In a proportion of cases single-staged clearance will not be possible due to limitations from patient critical state and/or anatomical location of collection. If not achievable, then the modality which would achieve the least number of interventions possible should be selected ***(Figure 2)***.
- The approach to drainage depends on several factors ***(Figure 2)***
    - Timing of need for intervention
    - Onset of infection/symptoms
    - Anatomical location
    - Characteristics of collection (solid/liquid)
    - Patients critical state (ITU/HDU, need of ventilatory/circulatory support)
    - Presence of pancreatic duct disruption/disconnection
- Open surgery has a high risk of morbidity and mortality[32] and if possible minimally invasive approaches should be selected.

Endoscopic:

Endoscopic Retrograde Cholangio-Pancreatography (ERCP)

- Urgent ERCP (<24 hours) should only be utilised if concomitant ascending cholangitis is present with biliary pancreatitis.[47]

Endoscopic transluminal pancreatic necrosectomy ***(Figure 2)***

- Endoscopic transluminal pancreatic necrosectomy is offered in centers with appropriate experience and setup. It has advantages in critically ill patients where risk to patient is significantly increased by the added stress of surgery.
- The procedure is preferred in collections which are retrogastric with or without pancreatic duct disruption.
- EUS guided drainage via cystgastrostomy with a LAMS can be successful in liquid-dominant collections. However, when placed in cavities that have a dominant solid necrotic element, there are limitations to the availability of endoscopic instruments to achieve satisfactory single-staged clearance of necrosis.[51]
- Endoscopic drainage is not possible, when collections are not adjacent to the stomach. In these circumstances percutaneous drainage or surgery can offer an alternative approach to treatment.[52]

Radiological ***(Figure 2)***:

- The step-up approach (PANTER trial) has been shown to improve patient outcomes through utilisation of an initial percutaneous radiological drain, stepping up to either larger drains or VARD if initial drainage is unsuccessful.[9,16]
- This approach is possible when collections are maturing out to the flank and therefore accessible for percutaneous approach.

Surgical ***(Figure 2)***:

Necrosectomy – either laparoscopic or open

- A group of patients will either develop an early infection during the initial presentation needing urgent debridement/drainage, and another group will present with symptoms/latent infection during surveillance in the outpatient setting. It is important to differentiate the two groups, as the latter group are in a more stable physiological and nutritional state, therefore increasing the likelihood of achieving a definitive surgical option when opting for infracolic necrosectomy.
- Open necrosectomy traditionally performed via a rooftop incision with open, closed packing or continuous postoperative lavage[53]. This approach is sometimes necessary but recognized to have a high risk to morbidity and mortality.
- Minimally-invasive (laparoscopic) necrosectomy has the advantage of clearing majority of solid collections at a single sitting. Superior view at laparoscopy, access and fine but effective instruments all contribute in achieving complete debridement and clearance of cavities.
    - Transgastric necrosectomy is reserved for retrogastric solid collections
    - Infracolic necrosectomy is utilised for infracolic, centrally located collections.[54]
- The drawback of the infracolic approach is the risk of forming a pancreatic fistula in context of a concomitant pancreatic duct disruption or disconnection. Patients that develop infection in the index admission are often critically ill and therefore performing a Roux-en-Y cystjejunostomy is not possible due to the high chance of failure from anastomotic leak. An interval Roux-en-Y fistula tract-jejunostomy can be performed at 6 months following development of a pancreatic fistula.
- As mentioned above single-staged laparoscopic infracolic necrosectomy and Roux-en-Y cystjejunostomy is reserved for patients under close surveillance in the outpatient setting that have persistent collections (WOPN/Psuedocyst) or suddenly develop symptoms/latent infection.
- Laparoscopic pancreatic necrosectomy with Roux-en-Y cystjejunostomy with concomitant cholecystectomy + common bile duct exploration video: https://www.youtube.com/watch?v=OG9pdRO5DaU

Follow-Up and Surveillance

It is reported that 17% - 22% of patients will have recurrent pancreatitis and 8% - 16% will develop chronic pancreatitis.[55,56]

Around two thirds of patients with acute pancreatitis develop pancreatic exocrine insufficiency (PEI) during index admission and a third during follow-up. This was significantly higher in those who developed SAP.[57] Thirty nine percent of patients with SAP can develop diabetes and therefore patients should be checked for diabetes annually.[58]

Asymptomatic/sterile WOPN/Pseudocyst should be monitored with interval scans to delineate progression of collections. Persistent, symptomatic or collections (initially sterile) with latent infection can be treated following discussion at a specialist benign pancreatitis MDT with percutaneous, surgical or endoscopic approaches described.

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Appendix 1 – Glasgow Score

Parameter	**Value**
PaO_2	< 7.9 kPa
Age	> 55 years
White Cell Count	> 15 x 10^9/L
Calcium	< 2 mmol/L
Urea	> 16 mmol/L
LDH	> 600 IU/L
Albumin	< 32 g/L (serum)
Blood Glucose	> 10 mmol/L

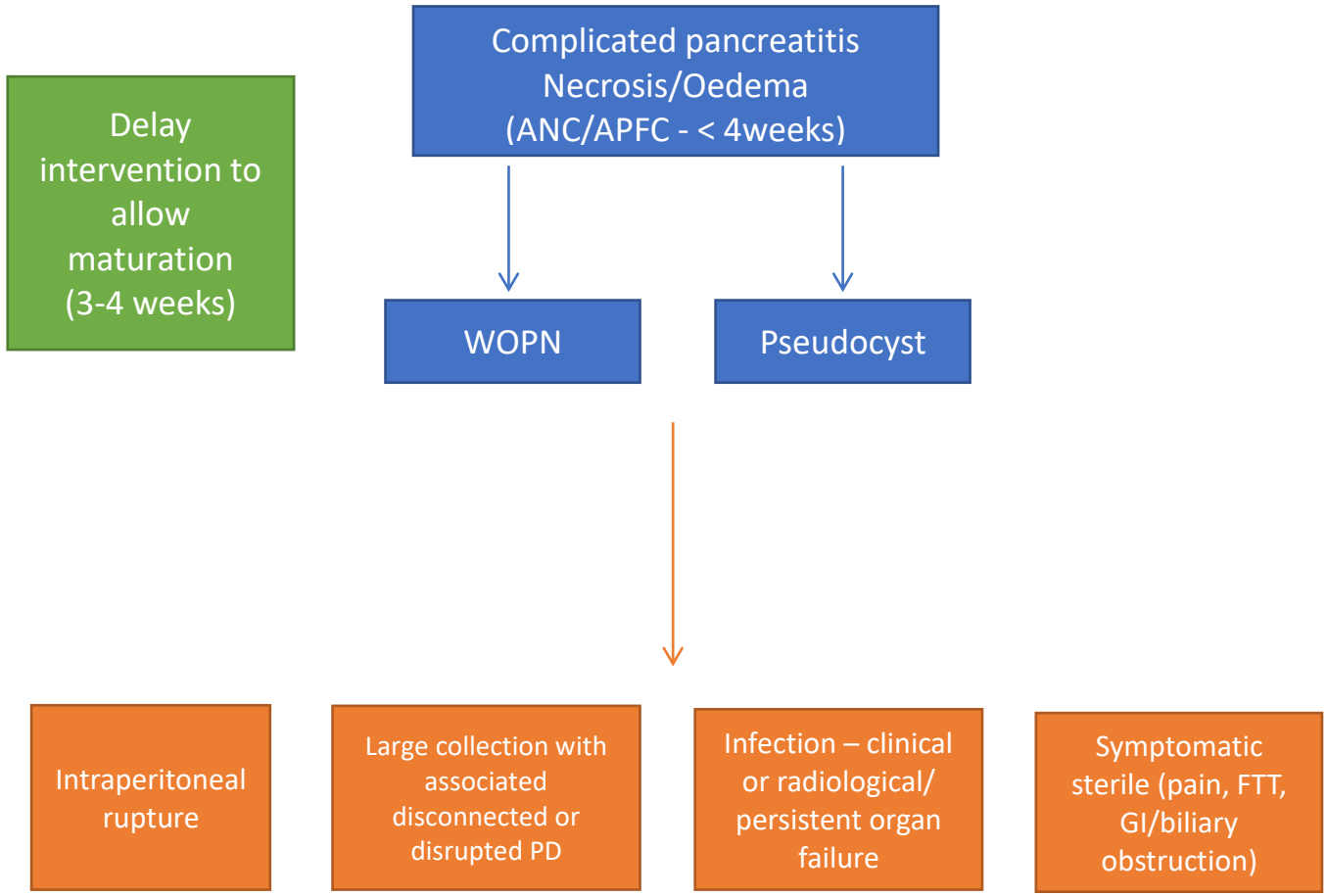
Appendix 2 – BISAP Score

Parameter	**Value**
Blood Urea Nitrogen	> 8.9 mmol/L
Impaired Mental Status	Present
Systemic Inflammatory Response Syndrome (SIRS)	Present
Age	> 60 years
Pleural Effusion on Chest Imaging	Present

Appendix 3 – MCTSI Score

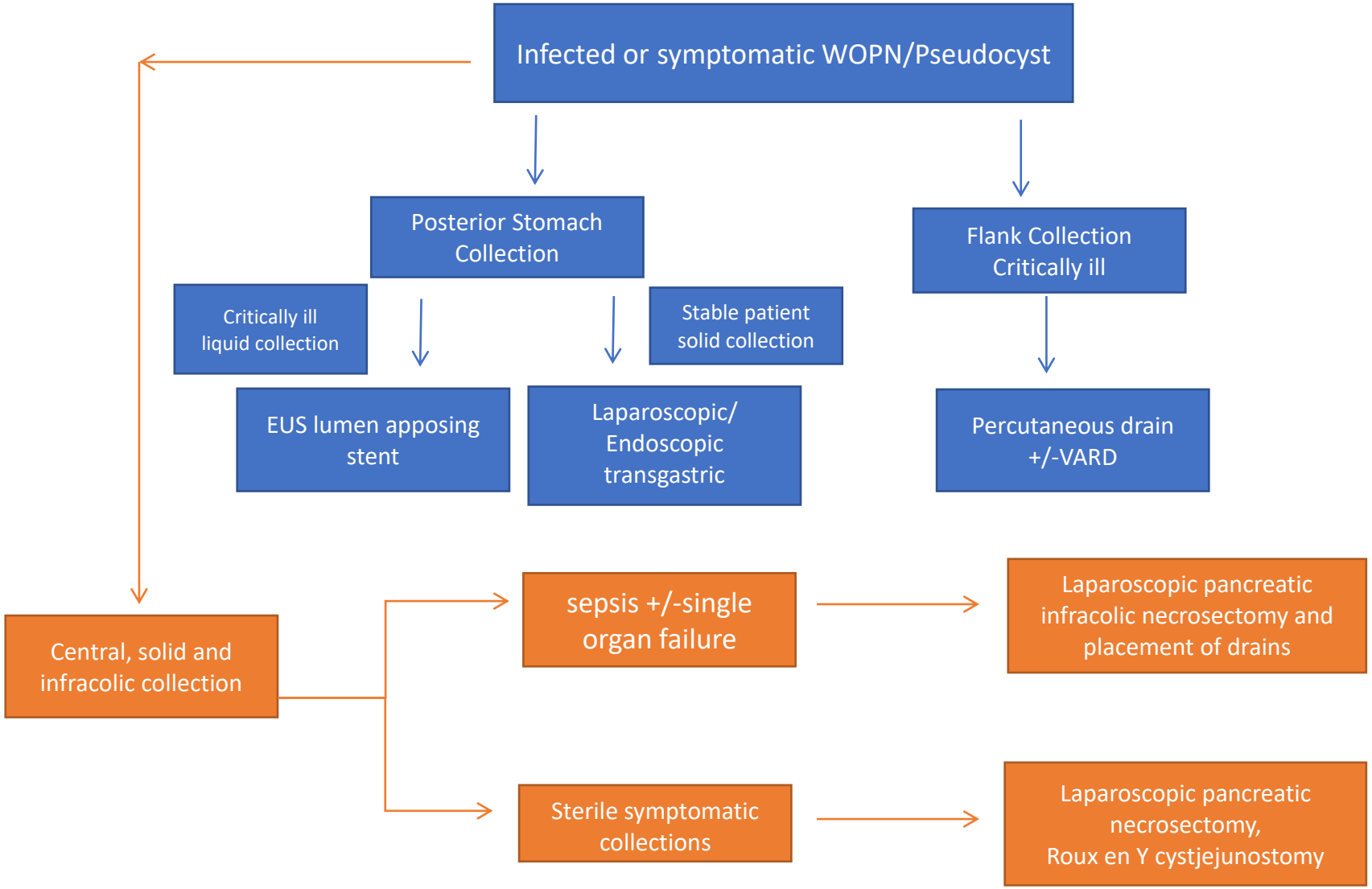
Parameter	**Value**
Pancreatic Inflammation	• 0: Normal pancreas • 2: Intrinsic pancreatic abnormalities with or without inflammatory changes in the peripancreatic fat • 4: Pancreatic or peripancreatic fluid collection or peripancreatic fat necrosis
Pancreatic Necrosis	• 0: None • 2: 30% or less • 4: More than 30%
Extrapancreatic Complications	• 2: One or more of: pleural effusion, ascites, vascular complications, parenchymal complications, and/or GI involvement
Score	• 0-2: Mild • 4-6: Moderate • 8-10: Severe

Figure 1



Natural history of severe acute pancreatitis (blue boxes) and indications for pancreatic intervention (orange boxes). ANC – Acute necrotic collection, APFC – Acute pancreatic fluid collection, WOPN – walled-off pancreatic necrosis, EUS – endoscopic ultrasound, FTT – failure to thrive, PD – pancreatic duct

Figure 2



Preferred intervention pathway for Infected/symptomatic pancreatic collections pseudocyst/WOPN >4 weeks. Critically ill are patients with organ failure supported with inotropes and intubated in ITU. In such patients general anaesthesia and laparoscopy is not possible and less invasive techniques should be considered.