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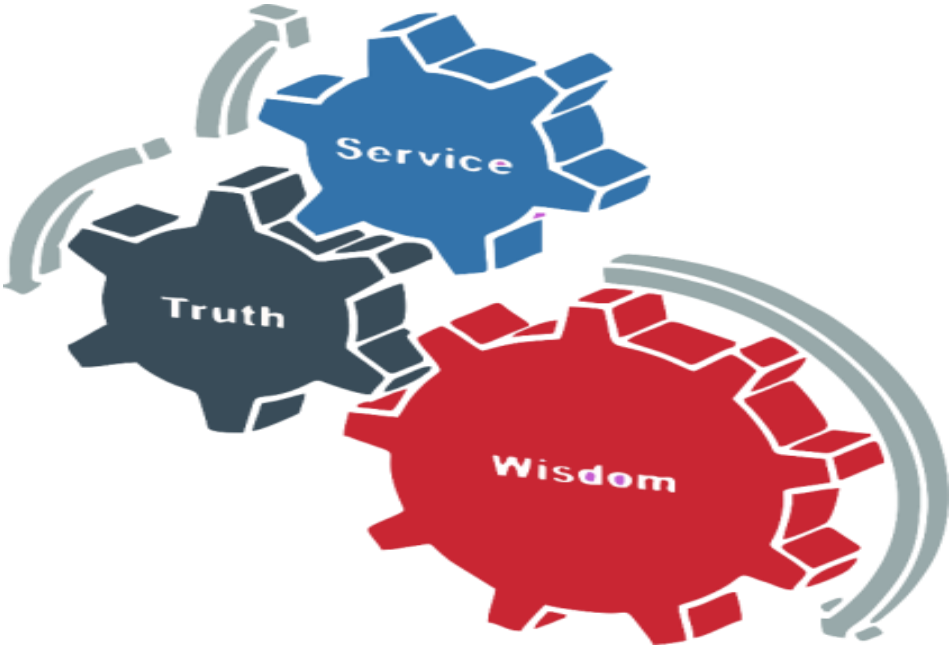

VISION

To Impart Evidence Based Research Oriented Medical Education.

To Provide Best Possible Patient Care.

To Inculcate the Values of Mutual Respect & Ethical Practice of Medicine.

Title: **Evidence Based guidelines for management of Acute Pancreatitis in RMU & Allied Hospitals**

These are Evidence based recommendations for management of acute pancreatitis in Rawalpindi Medical University and Allied Hospitals. RMU acute pancreatitis severity criteria is based on the results available from pilot study data conducted in 2019-20 in RMU allied hospitals.

Expert Panel

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Convener	Dr. Tanveer Hussain
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Patron in Chief Message

Institutional new criteria for assessment severity of acute pancreatitis is one of the most exciting initiative that Rawalpindi Medical University has formulated on its own admitted patients in RMU allied hospitals.

I also want to express my sincerest congratulations and heartfelt gratitude to all those involved in the preparation of this protocol and their commitment during the preparation process.

Professor Muhammad Umar
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Acknowledgement

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Contents

Acute Pancreatitis

Introduction:

Acute Pancreatitis severity scoring index: Prospective study to identify determinants in Pakistan

Acute pancreatitis (AP) is characterized by inflammation of the exocrine pancreas, associated with acinar cell injury, a local and systemic inflammatory response. AP range in severity from self limiting, mild pancreatic oedema, to severe systemic inflammation with pancreatic necrosis, organ failure and death.

Epidemiology and Aetiology

The incidence of acute pancreatitis is increasing worldwide due to increased rates of obesity and gallstones. AP has a mortality rate of 1%–7% which increases to around 20% in patients with pancreatic necrosis[2]. The mortality rate is influenced by severity of the disease with several prognostic factors. The presence of persistent organ failure is associated with the highest mortality, which is as high as 60% in some series[3]. Gallstone pancreatitis is more common in women over the age of 60, especially among those with microlithiasis, while alcoholic pancreatitis is more frequent in males[4]. Several aetiological factors have been described for AP although in up to 30% of cases an aetiological factor cannot be identified (termed idiopathic pancreatitis)[5]. The presence of microlithiasis accounts for 80% of idiopathic pancreatitis.[6]The most common cause worldwide is alcohol consumption but in our study gallstone is leading cause[52].

TABLE 1

Aetiology and pathogenesis of acute pancreatitis

Pathogenesis of acute Pancreatitis	Aetiology
Ductal obstruction	Gallstones
	Alcohol
	Post endoscopic retrograde Cholangiopancreatography
	Malignancy
	Mucinous tumours
	Pancreas divisum
	Sphincter of Oddi dysfunction
Acinar cellinjury	Alcohol
	Trauma
	Ischaemia
	Drugs (eg, corticosteroids, azathioprine and thiazides)
	Viruses
Defectiveintracellular	Alcohol
transport	Hereditary
	Hypercalcaemia
	Hypertriglyceridaemia
	Autoimmune

Diagnosis:

The diagnosis of AP should be considered in any patient presenting with severe upper abdominal pain. History and examination may be indicative of AP but two out of the following three criteria should be met for diagnosis:

- Typical history.
- Elevated serum amylase or lipase (>3 ULN).
- Imaging(Ultrasound, CT or MRI) consistent with acute pancreatitis.

Prognostication:

Several prognostic scores have been developed or adapted to predict disease severity. According to the International Association of Pancreatology and American Pancreatic Association (IAP/APA) guidelines, the presence of a systemic inflammatory response syndrome (SIRS) at admission and persistent SIRS at 48 hours both predict severe AP[26]. Persistent SIRS was associated with a mortality of 25% compared with 8% for transient SIRS.[27] The sensitivity of persistent SIRS for predicting mortality is 77%–89% and specificity 79%–86%[27–29]and at admission 100% and31%, respectively[28]. Other scoring systems such as APACHEII, Ranson and modified Glasgow score are not superior or inferior to (persistent) SIRS at predicting mortality[30] .

The rationale of this study was to compare different parameters used in Ranson's, BISAP, APACHE-II, and MCTSI for the severity of acute pancreatitis and design new criteria to assess the severity of AP at the local population because the etiology of acute pancreatitis is different as compared to western population, that may be cost-effective and more simple[17,18].
Our new proposed criteria has higher sensitivity and relativity close specificity to BISAP, APACHE II and Ranson[52].

Materials and Methods:

This prospective pilot study was conducted at Rawalpindi Medical University allied hospitals from August 2019 to December 2019. All patients with a diagnosis of acute pancreatitis were included in the study. Different scoring parameters were entered into standardized proforma.

100 patients were included in the pilot study. Among 24 parameters from APACHE-II, Ranson's, BISAP, and MCTSI, only 11 parameters, Pleural effusion (PE), Pancreatic necrosis (PN), LDH, serum Calcium (Sca++), Pulse, GCS, MCTS1, Base deficit, PO2, BUN-24 and BUN-48 were significantly related(at 10% level of significance) with the severity of acute pancreatitis. Similarly out of 24, 10 parameters AST, LDH, Serum Ca++, Pulse, PE, PN, Base deficit, MCTS1, PO2, and BUN 48were significantly covered more than 50% of the area in AUC analysis. Our proposed criteria based on 9 parameters LDH, Serum Ca++, Pulse, PE, PN, Base deficit, MCTS1, PO2, and BUN 48which were blowing by the two methods (ANOVA and ROC). The sensitivity and specificity were higher with our proposed criteria 93.1% and 60.6%respectively as compared to the Ranson's, modified Ranson, BISAP, and APACHE-II criteria.

Comparison of different criteria with the proposed criteria (RMU) for measurement of severity of acute pancreatitis

Criteria	Cut off point	Area	p-value	Sensitivity	Specificity
Ranson's	5.5	0.501	0.988	31%	76.1%
M.Ranson's	3.5	0.524	0.713	48.3%	54.9%
BISAP	5.5	0.711	0.001	62.1%	74.6%
APACHE II	9.5	0.636	0.033	62.1%	66.2%
Proposed criteria (RMU)	3.5	0.848	0.000	93.1%	60.6%

Data Synthesis

The evidence was synthesized from values entered in proforma of patients admitted with acute pancreatitis in RMU allied hospitals.

Formulation of new Criteria (RMU)

Criteria for severity of acute pancreatitis was formulated on the basis of pilot study result strength on patients admitted with acute pancreatitis in RMU Allied Hospitals.

Future plan

Final (RMU) criteria for severity of acute pancreatitis will be formulate after the result of full original study.

Way Forward

After the results of final study, our plan will be to collaborate with other Universities for application of this new criteria at their hospitals to consolidate the (RMU) criteria. This new criteria based on our own population etiology and outcome of acute pancreatitis.

Treatment

The main aim of initial treatment is to alleviate symptoms and prevent complications by reducing pancreatic secretory stimuli and correction of fluid and electrolyte abnormalities. Initially, patients should be fluid resuscitated and kept nil by mouth with bowel rest when nausea, vomiting or abdominal pain are present. Supportive care continues until pain is resolved and diet restarted. The majority of patients will improve within 3–7 days of conservative management. Patients with organ failure or poor prognostic signs should be assessed for admission to a high dependency unit[26].

Immediate Management

- Ensure patent airway
- Oxygen – target 94-98% saturation (88-92% if COPD)
- Intravenous fluids**(**Isotonic crystalloids)
- Administer 30ml/kg for hypotension or
- lactate≥4mmol/l , 5-10mls/kg/h first 24 hours until goals met

Goals

- Heart rate <120/min
- Mean arterial pressure = 65-85mmHg
- Urine output = 0.5-1ml/kg/h
- Hourly urine output monitoring & consider urinary catheter

Urgent Senior & ITC team review if any of below

Clinical signs

- Airway not maintained
- Resp. rate >35/min paO_2<6.7kPaHR<40 or >150/min
- Systolic blood pressure <80mmHg, MAP <60mmHg
- Diastolic blood pressure >120mmHg, Anuria, Coma (GCS <8)

Blood Tests

- pH <7.1 or >7.7
- Sodium <110 or >170mmol/l, Potassium <2.0 or>7.0mmol/
- Calcium >3.75mmol/l, Glucose >44.4mmol/l

Consideration of HDU involvement

- Persistent SIRS >48h

- Elderly (aged >70yr
- Obese (BMI>35)
- Moderately severe pancreatitis

Presence of SIRS on admission is a predictor of Severe pancreatitis and requires senior review and discussion with ITC team

Organ failure definitions:-

Cardiovascular	Hypotension requiring inotropes
Respiratory	Type 1 or 2 respiratory failure
Renal	Oliguria or creatinine>177umol/L
Hepatic	INR >1.5
Hematological	Platelets <100 (10*9/L)
Neurological	Impaired consciousness

Severity Assessment (ATLANTA classification) Assess at admission, 24 hours and 48hours.

Severe:	Persistent (>48 hrs) organ failure. local complications (e.g. necrosis, peripancreatic fluid collections, pseudocyst, splenic & portal vein thrombosis) or Exacerbation of coexistent disease
Moderately severe:	As above but transient only (<48 hours)
Mild:	No organ failure, local complications or exacerbation of coexistent disease

NB: **If SIRS or organ failure present at admission then classify as SEVERE. If resolved at 48 hours can be reclassified as moderately severe.**

Initial Resuscitation

Resuscitation with intravenous fluids, analgesics and anti emetics should be part of the initial treatment even before the diagnosis of acute pancreatitis is made. Goal directed rehydration with Ringer's lactate solution (or Hartmann's) is recommended[31] at rate of 5–10 mL/kg/ hour until resuscitation goals are reached[26]. A urinary catheter should be inserted in severe AP to record accurate fluid balance. Aggressive hydration leads to increased rate of sepsis, need for more mechanical ventilation and higher mortality[33 34] , therefore infusion rates should be carefully tailored according to age and comorbidities of individual patients. Adequate early fluid resuscitation is the single most important aspect of medical management that reduce organ failure and in hospital mortality[35]. Effective pain control is important to prevent diaphragmatic splinting, thereby reducing the risk of respiratory complications. The most commonly used drugs are opiates (morphine or fentanyl) either for breakthrough pain or as patient controlled analgesia. Monitoring of arterial oxygenation, acid base balance and blood glucose should be carried out.

Severe pancreatitis

The treatment of severe pancreatitis should be delivered in a high dependency unit. Insulin should be administered to maintain strict glucose control as this has been associated with reductions in morbidity and mortality in critical illness[36]. Hypocalcaemia and hypomagnesaemia should be identified and treated to avoid the development of cardiac arrhythmias.

Antibiotics in acute pancreatitis

The use of antibiotics in non infected pancreatitis is not currently recommended as there is no clear evidence of benefit. Prophylactic antibiotics have not been shown to reduce mortality, extra pancreatic infections or need for surgical intervention[37]. Antibiotic use should be restricted to patients in whom infection is strongly suspected[38].

Antibiotics should be recommended in following conditions:

Extra pancreatic infection (e.g. pneumonia, urinary tract infection)
Suspected cholangitis
US proven cholecystitis
Suspected infected pancreatic necrosis

Extra pancreatic infection

Treat according to source of infection as local antimicrobial guidelines

- Cholangitis /cholecystitis
  (Local antibiotics guidelines)
- Infected Pancreatic Necrosis
  (Meropenem IV 1g 8hourly)

Collections in severe pancreatitis

The2012 revised Atlanta criteria discern four types of peripancreatic fluid collections in acute pancreatitis depending on the content, degree of encapsulation and time (figure 1).

Indications to drain pancreatic collections include infection, symptomatic sterile necrosis and persistent asymptomatic collections can be observed. WON typically occurs >4 weeks after the onset of AP[39]. Infected pancreatic necrosis can be diagnosed on clinical signs, presence of gas on imaging but fine needle aspiration is not routinelyrequired[26]. The choice of intervention depends on individual patient factors including anatomy of the collection and may involve endoscopic or radiological approach. Open (surgical) necrosectomy is no longer recommended in necrotizing pancreatitis following the landmark PANTER trial[40]. Many patients are candidate for a 'step-up' approach, starting with conservative management, to either percutaneous drainage or endoscopic transluminal drainage. Patients who do not respond to initial percutaneous or endoscopic drainage may require either upsizing to larger or more numerous percutaneous drains or endoscopic necrosectomy in those with an endoscopically placed lumen apposing metal stent (LAMS). A recent meta-analysis has indicated that patients with WON drained endoscopically with LAMS may do better than those drained with plastic stents[41].

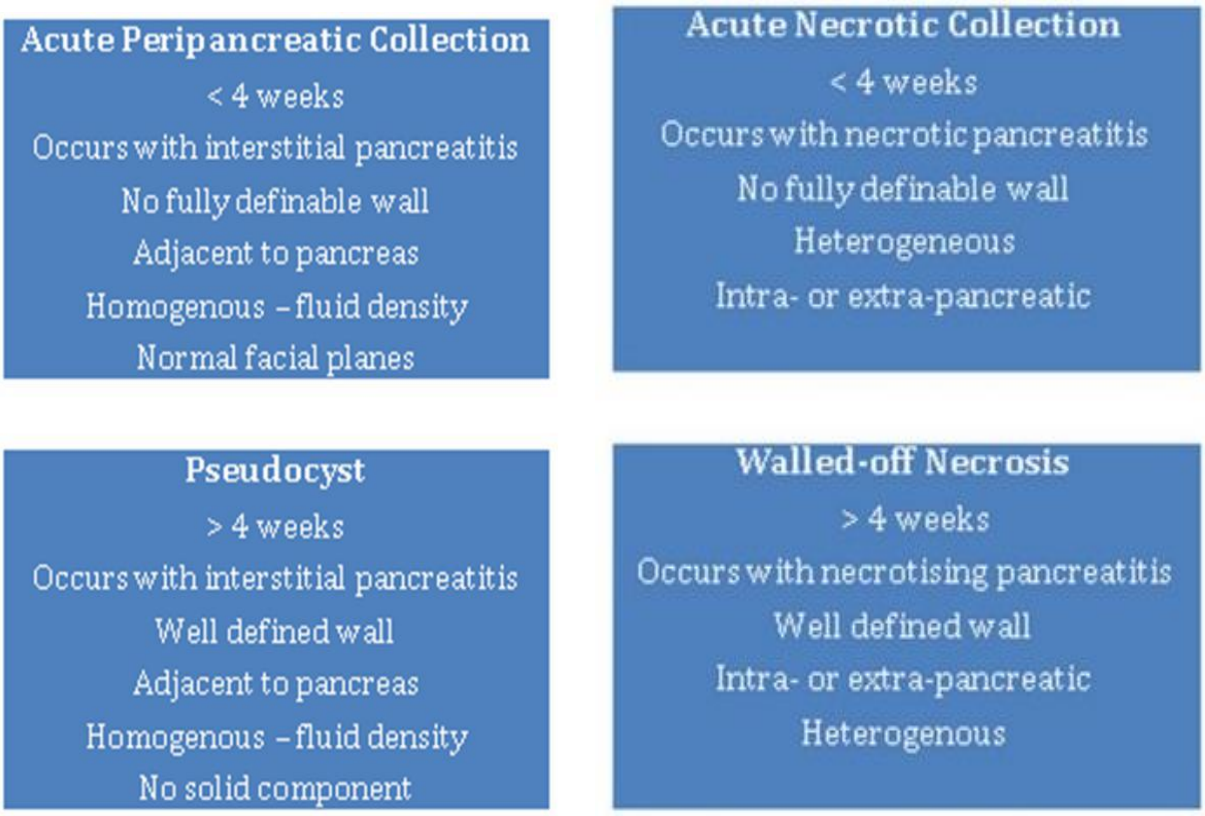


Figure 1 Atlanta 2012 classification of pancreatic fluid collections[39].

Pseudocysts may resolve spontaneously but drainage required in complications (infection, biliary or duodenal obstruction) or if patients symptomatic with pain. Endoscopic cystogastrostomy with multiple plastic pigtail stents is the preferred drainage option although percutaneous drainage can be considered in unfavorable anatomy. The use of LAMS for the drainage of pseudocysts is well described for ease, but the risks, clinical benefit and cost implications have not yet been studied. The timing and choice of approach requires multidisciplinary collaboration.

Nutrition

In mild pancreatitis, enteral nutrition should be recommenced as soon as abdominal pain has subsided[44]. In severe pancreatitis, patients should be kept nil by mouth until fully resuscitated, usually after 48 hours, enteral diet (if tolerated) or enteral tube feeding can be commenced[26]. Enteral nutrition, compared with parenteral nutrition, decreases sepsis, organ failure, need for surgical intervention and mortality[45,46]. Post pancreatic feeding is no longer recommended unless there is mechanical gastric outlet obstruction or patient is unable to tolerate nasogastric tube feeding[47]. Parenteral nutrition should be reserved for patients who are unable to reach nutritional goals with Nasogastric/Nasojejunal feeding. Pancreatic enzyme supplementation should be prescribed for patients with symptoms of pancreatic exocrine insufficiency[48].

Gall stone pancreatitis

All patients with gallstone pancreatitis should be considered for cholecystectomy when they are fit to undergo surgery. In mild biliary pancreatitis, cholecystectomy should ideally be performed during index admission or within 2 weeks of discharge, as interval cholecystectomy is associated with a significant risk of readmission with recurrent biliary events[26],[50]. In severe gallstone pancreatitis, cholecystectomy can be delayed until collections have improved, patient is well enough for surgery and gallbladder is some distance from the collection[26]. In surgically unfit or frail elderly patients, ERCP with biliary sphincterotomy can be considered as definitive treatment although risks of sphincterotomy should be balanced against the risk of recurrent biliary events[51].

Use of ERCP and PTC for biliary drainage

Inpatient biliary drainage by ERCP or PTC (Percutaneous transhepatic cholangiopancreatography) should be considered for:

1) Severe gallstone pancreatitis with cholangitis (URGENT)
2) Gallstone pancreatitis with obstructing common bile duct stone where surgical bile duct exploration not considered appropriate.
3) Gallstone pancreatitis with non-obstructing common bile duct stone where surgical bile duct exploration not considered appropriate

Outpatient

Elective biliary drainage with ERCP should be considered for:

Gallstone pancreatitis with non obstructing common bile duct stone where ERCP not technically achievable during index admission due to pancreatic swelling and surgical bile duct exploration not considered appropriate.

Definitive treatment for gallstone pancreatitis where patient not surgically fit.

Alcohol induced pancreatitis

Patients with alcohol induced pancreatitis may need alcohol withdrawal prophylaxis. Benzodiazepines, thiamine, folic acid and multivitamins are used. Dedicated outpatient follow up visits are advised to prevent recurrence[49].

All patients require assessment of harmful drinking and alcohol dependence. For acute alcohol related pancreatitis treat according to above pathway.

For chronic alcohol related pancreatitis, diagnosis require patient symptoms.

. Imaging to determine pancreatic structure (CT scan first line investigation)
. Tests of pancreatic exocrine and endocrine function
. If steatorrhoea or poor nutrition, consider for pancreatic enzyme supplements (e.g.Creon)
. If pain only symptom, no enzyme supplements
. Offer surgery if large duct (obstructive) pancreatitis

. Offer celiac plexus block, splanchnicectomy or surgery if small duct (non obstructive) chronic pancreatitis and pain poorly controlled.

Idiopathic pancreatitis

If gallstones and alcohol have been excluded as AP cause, investigate other possible causes such as:

- Metabolic causes (such as hypercalcaemia or hyperlipidaemia)
- Drugs
- Microlithiasis
- Hereditary causes
- Autoimmune pancreatitis
- Ampullary or pancreatic tumours
- Anatomical anomalies (Pancreas Divisum)

In patients where no aetiology has been identified, the following investigations should be performed in sequential order:

- Repeat abdominal US (at 6weeks)
- If no gallstones then for IgG4 – to exclude autoimmune pancreatitis
- If above normal then for MRCP
- If above normal then for endoluminal ultrasound(EUS)
- If above normal consider hereditary causes through genetic testing

Prognosis

Most patients with AP will improve within 1 week of conservative management and well enough for discharge. The aetiology should be identified and a plan to prevent recurrence should be initiated before hospital discharge. Long term prognosis is based on the aetiological factor and patient compliance to life style modifications. AP generally resolves and leaves pancreatic function intact. Many patients progress to recurrent AP or chronic pancreatitis and the risk is higher among smokers, alcoholics and men.

Summary of Recommendations

Diagnosis

The diagnosis of AP is established by two of the three following criteria:

(i) abdominal pain consistent with the disease,

(ii) serum amylase and/or lipase greater than three times the upper limit of normal,

(iii) characteristic findings from abdominal imaging

(strong recommendation, moderate quality of evidence).

Contrast enhanced computed tomographic (CECT) or magnetic resonance imaging (MRI) of pancreas should be reserved for patients in whom diagnosis is unclear or who fail to improve clinically within the first 48–72 h after hospital admission

(strong recommendation, low quality of evidence).

Etiology

Trans abdominal ultrasound should be performed in all patients with acute pancreatitis.

(strong recommendation, low quality of evidence)

In the absence of gallstones or history of significant alcohol use, serum triglyceride considered the etiology if> 1,000 mg/dl.

(conditional recommendation, moderate quality of evidence).

In patients above 40 years, pancreatic tumor should be suspected as possible cause of acute pancreatitis.

(conditional recommendation,low quality of evidence).

Genetic testing may be considered in young patients (< 30 years old) if no cause is evident and family history of pancreatic disease is present.

(conditional recommendation, low quality of evidence).

Initial assessment and risk stratification

Hemodynamic status should be assessed immediately on presentation and resuscitative measures begun as soon as possible.

(strong recommendation, moderate quality of evidence).

Risk assessment should be performed immediately to stratify patients into higher and lower risk categories to assist triage.

(conditional recommendation, moderate quality of evidence).

Patients with organ failure should be admitted in intensive care unit or HDU whenever possible.

(strong recommendation, low quality of evidence).

Initial management

Aggressive hydration(defined as 250-500 ml per hour of isotonic crystalloid solution) should be given to all patients, unless cardiovascularor renal comorbidites exist.

Early aggressive intravenous hydration is most important in first 12–24 h and may have little benefit beyond.

(strong recommendation, moderate quality of evidence).

In patients with severe volume depletion (hypotension and tachycardia), more rapid repletion (bolus) may be needed.

(conditional recommendation, moderate quality of evidence).

Ringer Lactate solution can be preferred over isotonic crystalloid fluid.

(conditional recommendation, moderate quality of evidence).

Fluid requirements should be assessed at frequent intervals within 6 h of admission and for the next 24–48 h.

The goal of aggressive hydration should be decrease blood urea nitrogen.

(strong recommendation, moderate quality of evidence).

ERCP IN Acute Pancreatitis

Patients with AP and concurrent acute cholangitis should undergo ERCP within 24 h of admission.

(strong recommendation, moderate quality of evidence).

ERCP is not needed in patients with gallstone pancreatitis who lack laboratory or clinical evidence of ongoing biliary obstruction.

(strong recommendation, low quality of evidence).

In absence of cholangitis or jaundice, MRCP should be used to screen for choledocholithiasis if highly suspected.

(conditional recommendation, low quality of evidence).

Antibiotics

Antibiotics can be given forextrapancreatic infection, such as cholangitis, catheter acquired infections, bacteremia, urinary tract infections or pneumonia.

(strong recommendation, high quality of evidence).

Prophylactic antibiotics in patients with severe acute pancreatitis is not recommended.

(strong recommendation, moderate quality of evidence).

Antibiotics in sterile necrosis to prevent the development of infected necrosis is not recommended.

(strong recommendation, moderate quality of evidence).

Routine administration of antifungal along with prophylactic or therapeutic antibiotics is not recommended.

(conditional recommendation, low quality of evidence).

Nutrition in Acute Pancreatitis

Mild AP, oral feedings can be resumed immediately if nausea, vomiting and abdominal pain has resolved.

(conditional recommendation, moderate quality of evidence).

In mild AP, initiation of feeding with a low-fat solid diet appears as safe as a clear liquid diet

(conditional recommendations, moderate quality of evidence).

Severe AP, enteral nutrition is recommended to prevent infectious complications. Parenteral nutrition avoided unless enteral route is not available, not tolerated, or not meeting caloric requirements.

(strong recommendation, high quality of evidence).

Nasogastric and nasojejunal delivery of enteral feeding comparable in efficacy and safety.

(strong recommendation, moderate qualityof evidence).

Role of surgery in Acute Pancreatitis

In mild AP, due to gallstones in gallbladder, cholecystectomy should be performed before discharge to prevent a recurrence of AP.

(strong recommendation, moderate quality of evidence)

In necrotizing biliary AP, to prevent infection, cholecystectomy is to be deferred until active inflammation subsides and fluid collections resolve or stabilize.

(strong recommendation, moderate quality of evidence).

Asymptomatic pseudocysts and pancreatic or extrapancreatic necrosis do not warrant intervention, regardless of size, location or extension.

(strong recommendation, moderate quality of evidence).

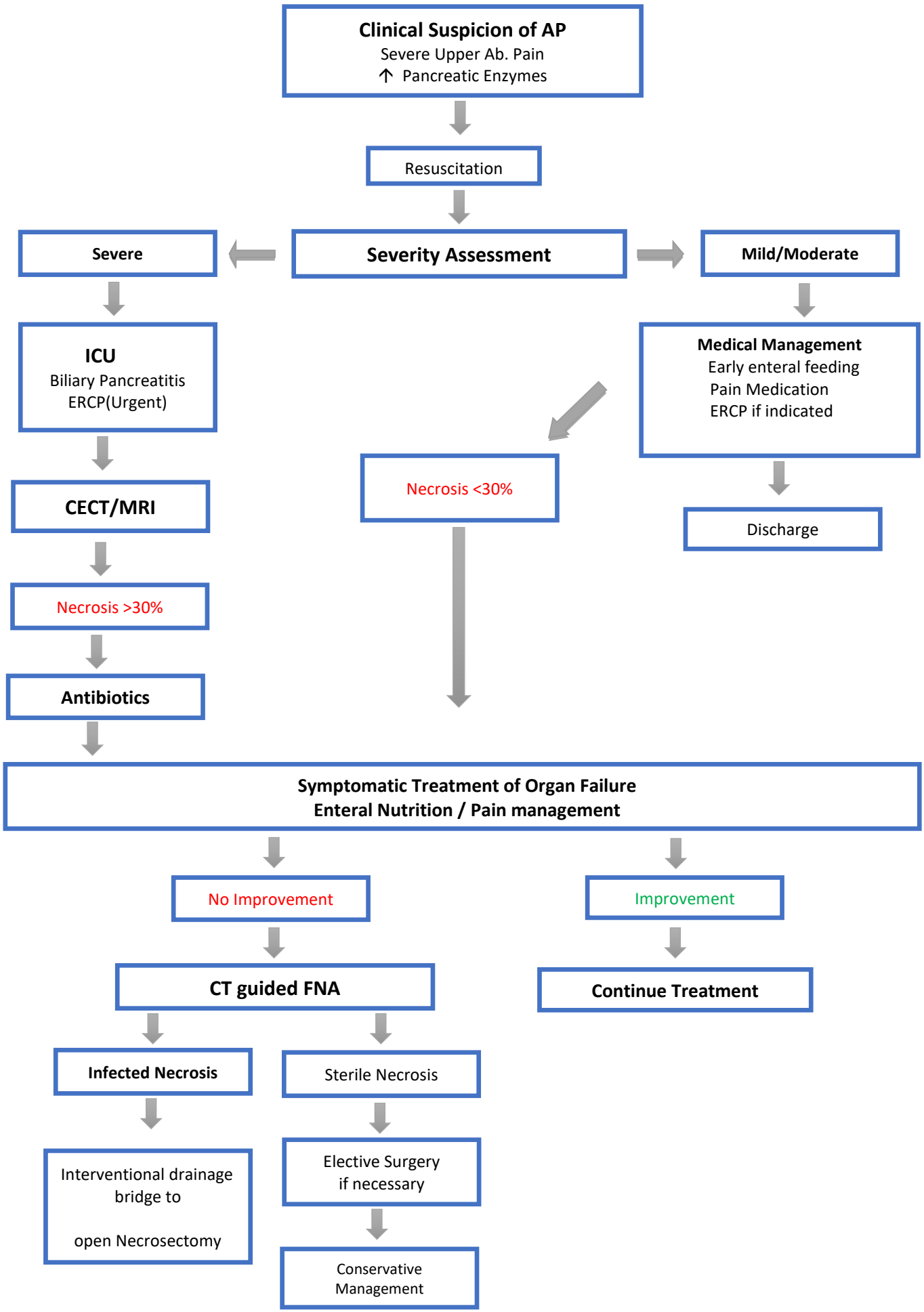
In stable patients with infected necrosis, surgical, radiologic or endoscopic drainage can be delayed preferably for more than 4 weeks to allow liquefication of the contents and development of fibrous wall around the necrosis (walled-off necrosis).

(strong recommendation, low quality of evidence).

In symptomatic patients with infected necrosis, minimally invasive methods of necrosectomy are preferred to open necrosectomy.

(strong recommendation, low quality of evidence).

Acute Pancreatitis Algorithm



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