

# Managing the Patient with Acute Pancreatitis in Medical Intensive Care Unit

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## INTRODUCTION

Majority of patients hospitalized with acute pancreatitis (AP) will develop mild AP caused by bile duct obstruction or excessive alcohol consumption. Less common causes include hyperlipemic AP or hypercalcemia. Idiopathic and iatrogenic AP (after endoscopic retrograde cholangiopancreatography (ERCP)) represent minority of AP. In cases of abdominal or thoracic trauma, clinical and laboratory signs of AP should be actively searched for.

Severe AP will develop in less than 20% and is characterized by concomitant organ failure (e.g., respiratory, circulatory, liver, renal, coagulopathy). Rather than concentrating on different scoring systems, clinicians should focus on risk factors associated with the development of AP (age, co-morbidities, presence of systemic inflammatory response syndrome (SIRS), sepsis, presence of pleural effusions, elevated hematocrit, increased body mass index (BMI), altered mental status). Vast majority of patients with AP will present to the emergency department with no organ failure or pancreatic necrosis. Those that initially present with symptoms lasting > 48 hours and have C-reactive protein > 150 are classified as having severe pancreatitis. It is of

utmost importance to initially recognize patients with severe AP and admit them to intensive care units (ICU) or high dependency units for close observation. The use of Ranson's criteria has limited value, and its use is discouraged. Acute Physiology and Chronic Health Evaluation (APACHE) II was developed for ICU use and is not discriminatory enough to use in early phase of AP. Its use in emergency department is not validated.

It is not possible to predict which patient will develop severe AP so closed monitoring with daily inflammatory, renal, pancreatic markers and arterial blood gasses (ABG) with arterial lactate is imperative.

Patient with AP developing or already with septic shock, acute respiratory insufficiency (ARI), multiple organ failure (MOF) should be admitted to ICU for close monitoring. Arterial line, central venous line, Foley catheter, nasogastric tube (or orogastric in intubated patients) should be placed. Arterial blood pressure should be monitored invasively; arterial catheter allows blood to be drawn for ABG analysis and lactate determination. Urine output should be assessed hourly.

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The course of severe AP typically shows two mortality peaks, first within the first week due to SIRS and MOF and second after 14 days due to (septic) complications. If not already performed within 24 hours of admission, ERCP with papillotomy and stent placement should be performed in patients with AP and concurrent cholangitis.

## DIAGNOSTIC PROCEDURES

Abdominal ultrasound to evaluate for cholelithiasis, dilated bile and pancreatic duct should be performed on all patients with AP regardless of their initial blood chemistry. Abdominal US can show potential pleural effusion, peripancreatic fluid, peripancreatic tissue involvement and additional abdominal pathology. It is readily available, non-invasive and cheap.

Contrast-enhanced CT is not an imaging method of choice in early course of AP as it does not add any diagnostic value to abdominal US, laboratory and clinical findings. It should be performed however after 72 hours if abdominal symptoms continue and patient deteriorates. CT is invaluable in later course of the disease (not discussed here).

## FLUID BALANCE

In acute phase fluid resuscitation is often required with volumes up to 6 L during initial 24 hours. After each fluid bolus (30 mL/kg ideal body weight) fluid responsiveness should be reassessed using invasive methods (stroke volume variation, global end-diastolic blood volume index (GEDV), velocity time index (VTI)) or non-invasively (vena cava diameter). Measuring central venous pressure to determine the volume status is obsolete method and should be abandoned. Haemoconcentration (assessed by hematocrit) must be avoided. Balanced crystalloids share numerous advantages over non-balanced ones. Use of colloids in AP setting, especially starches (HES), regardless whether balanced or not, is contraindicated (FDA, EMA) and should be avoided. Of note, early aggressive fluid administration is most beneficial within the first 12–24 hours, and may have little benefit beyond.

## ANALGESIA

Adequate analgesia blunts pro-inflammatory response during AP, suppresses sympathetic drive, has favorable effect on respiratory and physical therapy. Multimodal analgesia is recommended with opioid (tramadol, piritramide, fentanyl, sufentanil), paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs) if not contraindicated in combination. Special attention must be paid for patients with renal failure in which opioids accumulate, and long-acting compounds such as piritramide are not optimal choice. In the same setting, NSAIDs are contraindicated as well. Rectal application of NSAIDs has shown to have favorable effect after ERCP.

Smaller studies consistently showed that thoracic epidural analgesia (TEA) with epidural catheter placed between 6<sup>th</sup> and 9<sup>th</sup> thoracic vertebra, enables opioid-sparing analgesia, secures adequate analgesia with improvement of gut motility, pancreatic and splanchnic arterial perfusion and seem to decrease mortality in patients with AP. We are still waiting for definite results from multicentre trial (EPIAN study). Hypotension should not be retained as a contraindication for TEA during AP since it is manageable by fluid administration or pharmacological interventions. Standard contraindications for epidural catheter apply, with notion that increased C-reactive protein does not automatically mean sepsis and should be interpreted in accordance to other variables.

## NUTRITIONAL SUPPORT

Early enteral nutrition via (oro)gastric route is not feasible in all patients with AP but should be heavily encouraged though. Early trial with minimal nutrients delivery (20 mL/hour) with standard high protein enteral formula should be used initially. Immunomodulatory formulas containing arginine, glutamine, and omega-3 fatty acids should be avoided. Gastric residues should not be monitored at regular predetermined intervals (e.g., every six hours). There is still no consensus among clinicians what is still acceptable residue or whether to return or discharge aspirated residue. In case of gastric passage blockage or lack of peri-

stalsis, positioning of enteral tube is recommended. Commercially available tubes include weighted tubes and Tiger tube specially designed to anchor into distal duodenum pass the Treitz ligament enabling direct enteral feeding. Some tubes have additional lumen enabling feeding into gut while venting through the gastric opening.

Routine use of prokinetic agents demonstrated no benefit; however, clinicians report regular use of metoclopramide (10 mg every 8 hours), neostigmine (0.5 mg every 8 hours) together with colonic enemas. To reverse opioid-induced constipation due to opioid analgesia use of methylnaltrexone (Relistor) is indicated. Parenteral nutrition should be avoided during first week and administration tailored individually (partial parenteral nutrition in combination with enteral or complete). Use of prokinetics is indicated in elevated intra-abdominal pressure (IAP). Enteral or parenteral erythromycin (500 mg every 8 hours) is indicated when metoclopramide and neostigmine are ineffective.

Extensive research has been done on enteral supplementation of prebiotics and probiotics in patients with AP. Results were mostly inconclusive (strain of bacteria from the same species, different species, number of colony-forming units, etc.) while some studies demonstrated increased mortality due to septic complication including endocarditis and bowel perforation. As for now, the use of pre- and probiotics in patients with AP is contraindicated.

## ANTIBIOTIC COVERAGE

Routine use of prophylactic antibiotics in patients with severe AP and sterile necrosis is not recommended. Up to 25% of pancreatic necroses will however eventually get infected, causative agents being enteric Gram negative bacteria (*E. coli*, *P. aeruginosa*) and anaerobes (*Bacteroides* spp.) and *Candida* spp. In one third the infection is polymicrobial. In patients with infected necrosis, antibiotics known to penetrate pancreatic necrosis with anaerobic coverage (e.g., meropenem) may be useful in delaying percutaneous or surgical intervention, thus decreasing morbidity and mortality. Other classes include fluoroquinolones with metronidazole or high dose cephalosporins. Material for microbiological must be

obtained, and antibiotic therapy should be adequately tailored (targeted). Prophylactic use of anti-fungal agents is contraindicated. Material for microbiology cultivation should be obtained as soon as possible using US- or CT-guided fine needle biopsy. In case of open surgery, material should be obtained and sent for microbiology as well.

## PROTON PUMP INHIBITORS

Ulcer prophylaxis with proton pump inhibitors does not have direct favorable effect on the course of AP. Its use should be individually tailored.

## DEEP VENOUS THROMBOSIS PROPHYLAXIS

Prophylaxis for deep venous thrombosis in AP is recommended in all patients with severe AP. Surge in procoagulant inflammatory mediators, stasis, vessel spasm, and mass effects from the surrounding inflamed pancreas all contribute to splenic or portal vein thrombosis which occurs in up to 20%. Once the diagnosis is confirmed, therapeutic heparin treatment should begin. Standard unfractionated heparin has certain advantages over low molecular weight heparin, being cheaper, dosing easily adjustable, with predictable kinetics and available antidote.

## RESPIRATORY SUPPORT

SIRS, pleural effusions, decreased compliance of abdominal and thoracic wall because of volume loading and capillary leak all increase the work of breathing, inevitably leading to ARI. AP is one of the most common causes of acute respiratory distress syndrome. Non-invasive ventilation via face mask or helmet should be the initial approach. High-flow oxygen therapy is easy to use and can be applied in step down units as well in ICU. In comparison to non-invasive ventilation, high-flow oxygen therapy enables moisturizing and heating the delivered gasses. If non-invasive ventilation fails, invasive mechanical ventilation with strict adherence to protective ventilation principles should be applied.

## INTRA-ABDOMINAL HYPERTENSION

IAP monitoring via dedicated gastric tube (Nutrient) or measuring probe attached to Foley catheter is simple, non-invasive method that should be part of basic monitoring in every patient with AP that requires urinary catheterization or gastric tube placement. More than 60% of patients with AP will develop intra-abdominal hypertension (IAH) during the course of disease. Failure to recognize increase in IAP (> 12 mmHg) leads to end-organ failure. Factors that contribute to IAH are among others decrease in abdominal wall compliance, increase in intra-luminal contents, capillary leakage or fluid resuscitation. Pressures greater than 12 mmHg are consistent with IAH, and pressures > 20 mmHg together with new onset organ dysfunction is consistent with abdominal compartment syndrome (ACS).

Some authors recommend maintaining abdominal perfusion pressure (APP) greater than 60 mmHg; however, WSACS 2013 consensus management statement could make no recommendations for the use of APP in the resuscitation or management of patients. The majority of authors urge clinicians to implement techniques towards normalizing IAP and not on maintaining APP over predetermined value.

### Physiological derangements due to intra-abdominal hypertension

Increase in IAP leads to increased jugular venous pressure which in return impairs cerebral venous drainage and contributes to increased intra-cerebral pressure (ICP). Compression to inferior vena cava decreases right heart venous return and decreases cardiac output. Peripheral venous stasis, especially in lower extremities can compromise arterial flow. Combination of fluid resuscitation and increased IAP lead to increased central venous pressure (CVP) which in turn decreases visceral perfusion pressure leading to gut ischemia, bacterial translocation, and end-organ failure. Increased CVP impairs renal perfusion pressure leading to activation of renin-angiotensin-aldosterone system which additionally impairs mesenteric perfusion. IAH impairs lung functional residual capacity, increases ventilation/perfusion mismatch. Multiple organ

failure development often leads to acute respiratory distress syndrome.

Non-surgical interventions to reduce IAP include insertion of decompression gastric and rectal tube, initiating prokinetic agents, administering enemas, performing colonoscopic decompression when indicated and discontinuing enteral nutrition. Repositioning the patient in supine position (no head elevation) can be tried as an IAP lowering technique. The use of diuretics and renal replacement therapy with fluid removal can have favorable effect but is time-consuming. Especially in patients that already have intravascular volume depletion, diuretic use leads to acute kidney injury. The use of deep sedation and analgesia, or even neuromuscular blockade, may transiently improve abdominal wall compliance and reduce IAP while more durable treatments are being pursued. Applying high positive end-expiratory pressure (PEEP) seems to have little or no impact on IAP measurement. PEEP should be set to counterbalance IAP.

### Surgical decompression

Once a diagnosis of ACS is suspected or definitively made and conservative approach to reduce IAP failed, there should be rapid progression to surgical decompression. Although modern management of uncomplicated pancreatitis emphasizes avoidance of surgical intervention, surgical decompression may improve renal or respiratory function. Early surgical decompression is associated with reduced mortality in patients with severe acute pancreatitis, early multiple organ dysfunction syndrome, and abdominal compartment syndrome.

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