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Management of infected acute necrotizing pancreatitis

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Abstract

Necrotizing or severe pancreatitis represents approximately 10%-20% of acute pancreatitis. 30%-40% of patients with acute necrotizing pancreatitis (ANP) will develop debris infection through translocation of intestinal microbial flora. Infected ANP constitutes a serious clinical condition and is complicated by severe sepsis with high mortality rates of up to 40% despite progress in current intensive care. The timely detection of sepsis is crucial. The Quick Sequential Organ Failure Assessment score, procalcitonin levels > 1.8 ng/mL and increased lactates > 2 mmol/L (> 18 mg/dL), indicate the need for urgent management. The escalated step-by-step management protocol starts with broad-spectrum antibiotics, percutaneous drainage or endoscopic management, and ends with surgical management if needed. The latter includes necrosectomy (either laparoscopic or traditional open surgery), peritoneal lavage and extensive drainage. This management protocol increases the chance of survival to approximately 60% in patients with otherwise fatal cases. Any treatment choice must be individualized, and the timing is critical.

Key Words: Pancreas; Acute abdomen; Acute pancreatitis; Necrotizing pancreatitis; Sepsis; Septic shock

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Core Tip: Infected acute necrotizing pancreatitis requires multidisciplinary management and multiple interventions that must be individualized. Early recognition of sepsis and prompt step-by-step individualized management for timely debridement and intensive care are imperative to improve outcomes.

TO THE EDITOR

We read with great interest the recent paper by Xiao *et al*^[1], and we would like to express our satisfaction and congratulations for their excellent work. It is a well-written comprehensive opinion review presenting the current data on the serious condition of infected necrotizing pancreatitis (INP). I agree absolutely with the proposed step-by-step management. We would like to reiterate that the timely detection of sepsis is crucial. Despite intensive care efforts, ongoing deterioration of the clinical picture is a strong indicator of great relevance, especially during the first 7-14 d from the onset of acute pancreatitis. The Quick Sequential Organ Failure Assessment score (at least two of the following three clinical indications are present: Tachypnea ≥ 22 /min, low level of consciousness, and arterial pressure ≤ 100 mmHg) for sepsis is a bedside prompt for identifying patients with suspected severe infections and poor outcomes^[2]. Therefore, it has significant value for treatment decision-making when facing INP^[3].

The necrotizing form represents approximately 10%-20% of patients with acute pancreatitis, with an overall mortality of up to 15%^[3,4]. However, 30%-40% of patients with acute necrotizing pancreatitis (ANP) will develop debris infection through translocation of intestinal microbial flora. Infected ANP is complicated by severe sepsis, with high mortality rates up to 40% despite progress in current intensive care^[2,5,6]. The escalated step-by-step management consists of endoscopic management, interventional methods and surgical approaches. The timing of interventional application is still under debate^[1,3,4,6]. However, early recognition and timely debridement are crucial. Thus, reliable predictive factors of infected debris are essential for proper management of high-risk and potentially fatal cases^[5,7].

C-reactive protein (CRP) levels above 150 mg/dL predict severe ANP on admission. Procalcitonin (PCT) above 0.5 ng/mL is a predictor of ANP from the first twenty-four hours. Serial assessment of changes in PCT reflects the course of the disease. Levels above 1.8 ng/mL are an indication of infected ANP^[5]. Lactate levels greater than 2 mmol/L (> 18 mg/dL) indicate severe sepsis^[2].

An Acute Physiology and Chronic Health Evaluation II score ≥ 14 on admission, early persistent systemic inflammatory response syndrome (SIRS) within the first forty-eight

hours and multiple organ dysfunction syndrome (MODS) within two weeks after admission constitute prognostic factors of higher mortality after operative necrosectomy^[5].

A predictive model, based on CRP, albumin, creatinine and alcohol abuse as the etiology of AP, has been developed for the distinction of infected and noninfected ANP^[7]. Microbial culture and metagenomic next-generation sequencing of pancreatic fluid aspirate under computed tomography (CT) guidance have been proposed for a more accurate and timely diagnosis of a suspected ANP infection^[8]. Obesity [body mass index (BMI) > 30] has a negative effect on both the development and course of ANP. The possibility of infected ANP and MODS is higher in obese individuals than in nonobese individuals, and early interventional drainage is required. Increased mortality is associated with increasing BMI^[9].

The immune response that is expressed by an early increase in anti-inflammatory cytokines [tumor necrosis factor soluble receptors, interleukins (IL)-10, IL-1 receptor antagonist] is of great research interest^[5]. Another interesting predictive novel biomarker of ANP is the gut microbiome on admission. *Enterococcus faesium* and *Finnegolia magna* have been postulated as potential predictors of NP and INP^[10]. Infected ANP is indicated by the presence of extraluminal peripancreatic gas bubbles on imaging and can be confirmed by positive microbial culture on fine needle aspiration by imaging guidance. However, the latter has been used less often in clinical practice^[3]. The step-by-step management protocol starts with broad-spectrum antibiotics, percutaneous drainage or endoscopic management, and ends with surgical management if needed^[3,11].

Ultrasound-guided percutaneous management, either transgastric or transabdominal drainage, for infected fluid collections is the first-choice method, with success rates ranging between 50% and 75%^[12-14]. Transgastric debridement and drainage are not technically applicable early within the first 2-4 wk before the cyst wall matures, in lesser sac locations or in walled-off cysts at distant sites from the stomach. Transabdominal drainage is an alternative option for sepsis control^[4]. For fluid removal and

debridement, adequate drain placement is needed. Double pig-tail plastic stents or esophageal fully covered self-expandable metal stents have been used^[4,11,15-17]. Percutaneous direct endoscopic necrosectomy is feasible despite technical difficulties, but the technique requires relevant experience^[4]. Failure of the procedure ultimately requires surgical necrosectomy^[3,18]. A randomized study of long-term follow-up showed that there was no superiority of endoscopic over surgical management in terms of major complications and mortality in infected ANP. The only difference found in favor of endoscopy was fewer pancreatic fistulas requiring reoperation^[19].

Laparoscopic management of infected pancreatic necrosis or peripancreatic infected fluid collection is feasible, safe and effective; it encompasses extensive necrosectomy, detailed irrigation of the peritoneal cavity (lavage) and placement of drain catheters. The retroperitoneal approach is another alternative access route^[20]. Indocyanine green-guided video-assisted retroperitoneal debridement has been used for clear surface separation of debris in the management of infected ANP. This method is safe and avoids the risk of vascular and healthy pancreatic parenchymal injury resulting in persistent fistula^[21].

Traditional open surgical debridement, irrigation and drains, leaving open the abdomen (for example, vacuum-assisted closure) for planned reinterventions have been limited to critically ill patients^[3]. The novel effective application of nanotechnology in diagnosis and treatment is a promising evolution^[22]. Serum pancreatic enzyme assessment and imaging for early detection of the disease course may be useful. Nanoparticles have been used as drug carriers and could be valuable for the application of both antibodies and antibiotics. Nanotechnology could be used to possibly overcome the resistance of microbes to antibiotics. In addition, it has been postulated that gene therapy may be more effective than drug therapy in severe acute pancreatitis^[22].

In addition to what has already been mentioned above, novel future directions include nanotechnology, the application of hydrogen peroxide (H₂O₂) in necrosectomy, 3-dimensional CT (3D CT) cinematic, and anti-inflammatory monoclonal antibodies. The preliminary use of H₂O₂ in endoscopic necrosectomy of walled-off necrosis showed

excellent outcomes. Thus, prospective randomized controlled trials are necessary to precisely establish its role^[23,24].

The novel volumetric 3D CT and cinematic rendering may improve further diagnosis and prognosis by precisely identifying infected necrotic tissue and local complications^[25]. To date, there has not been etiopathogenic management of severe sepsis and septic shock consequences, despite the current considerable progress, unless patients undergo surgery and supportive intensive care. In infected pancreatic necrosis, proinflammatory factors, mainly TNF- α but also IL-6, IL-8 and monocyte chemotactic protein, activate the body's defense response to inflammation, causing SIRS, which is called sepsis. If this initially beneficial reaction is not balanced by the compensatory anti-inflammatory response syndrome, then it will become uncontrolled and excessive, which leads to disseminated cell damage causing MODS and ultimately death^[22,26]. Thus, the regulation of this balance by the use of antibodies or molecules against the most important inflammatory mediator of the cytokine cascade, TNF- α , would be crucial. The levels of TNF- α were increased within 1-2 h of endotoxin injection in an experimental model^[26].

In conclusion, the current step-by-step, timely and individualized management of infected ANP is essential and improves patient outcomes. Percutaneous catheter drainage is the first step. Endoscopic debridement usually requires an elapsed time of three to four weeks. Transgastric debridement (laparoscopic or open) is suitable for central retrogastric collections. Laparoscopic transperitoneal debridement is suitable for isolated collections at the root of the mesentery. Open transperitoneal debridement is only performed when a collection is inaccessible to all other methods of drainage or after the step-up approach has failed.

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