Walled-off pancreatic necrosis (WOPN), formerly known as pancreatic abscess is a late complication of acute pancreatitis. It can be lethal, even though it is rare. This critical review provides an overview of the continually expanding knowledge about WOPN, by review of current data from references identified in Medline and PubMed, to September 2009, using key words, such as WOPN, infected pseudocyst, severe pancreatitis, acute necrotizing pancreatitis (ANP), pancreas, inflammation and alcoholism. WOPN comprises a later and local complication of ANP, occurring more than 4 wk after the initial attack, usually following development of pseudocysts and other pancreatic fluid collections. The mortality rate associated with WOPN is generally less than that of infected necrosis. Surgical intervention had been the mainstay of treatment for infected peripancreatic fluid collection and abscesses for decades. Increasingly, percutaneous catheter drainage and endoscopic retrograde cholangiopancreatography have been used, and encouraging results have recently been reported in the medical literature, rendering these techniques invaluable in the treatment of WOPN. Applying the recommended therapeutic strategy, which comprises early treatment with antibiotics combined with restricted surgical intervention, fewer patients with ANP undergo surgery and interventions are ideally performed later in the course of the disease, when necrosis has become well demarcated.

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Key words: Walled-off pancreatic necrosis; Infected pseudocyst; Severe pancreatitis; Acute necrotizing pancreatitis; Pancreas; Inflammation; Alcoholism

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INTRODUCTION

Since the first interdisciplinary symposium on acute pancreatitis in Marseille in 1964 remarkable progress has been gained in creating a uniform classification system for the variable clinical features of this disease. The most important and frequent definitions in terms of pancreatic infection are as follows: (1) Pancreatic infection: the presence of microbes including bacteria or fungi overgrowing the pancreas or the peripancreatic space and causing pathologic changes. Pancreatic infection usually occurs secondary and time-dependently to acute pancreatitis. This definition includes infected necrosis, pancreatic...
abscesses and infected pancreatic pseudocysts; (2) Infected necrosis: intrapancreatic or extrapancreatic necrosis with a positive smear or culture for bacteria or fungi. Usually no major collection of pus is present; (3) Pancreatic abscess: a localized collection of purulent material with little or no necrosis in the region of the pancreas, which is delineated by a wall of collagen and granulation tissue; and (4) Infected pancreatic pseudocyst: a localized collection of infected fluid in the region of the pancreas and, like an abscess, also walled off by a membrane of collagen and granulation tissue. Usually the presence of bacteria or fungi is of no clinical significance and represents contamination only. There may be communication with the pancreatic ductal system; pus or necrosis is generally not found. The term “Walled-off pancreatic necrosis (WOPN)” was first introduced by Connor et al in 2005. This term was officially established later on, on the 2006 Digestive Disease Week during the American Gastroenterological Association Clinical Symposium, “Problems and Pitfalls of Atlanta Classification for acute pancreatitis: American Gastroenterological Association, American Pancreatic Association and International Association of Pancreatology to revisit,” chaired by Dr. Peter Banks. WOPN, formerly known as pancreatic abscess is uncommon and usually occurs in the setting of pancreatitis, usually in complicated cases of pseudocysts or sterile pancreatic necrosis. Infections outside this setting are extremely uncommon but have been reported to occur with perforation of the bowel into the pancreas or splenic parenchymal involvement. It embodies a quite late complication of pancreatitis, chronic or acute, commonly, after the formation of pseudocysts. In pancreatitis, enzymes can be walled off by granulation tissue, by developing pseudocysts or via bacterial seeding of pancreatic or peripancreatic tissue, leading to development of WOPN. Even if WOPN constitutes 1%-9% of all acute pancreatitis complications, it still remains a lethal surgical entity, which can be alleviated through early detection and application of the indicated therapeutic measures. The aim of this article is to review WOPN, its etiology, epidemiology, clinical features, diagnosis and new clues, as they are presented, in the latest articles of the literature.

## EPIDEMIOLOGY

In the US, the incidence of pancreatitis is approximately 185,000 cases per year. At least 80% of cases are due to alcohol and cholecystitis, and all the rest are associated with other triggering conditions, as illustrated in Table 1. Acute necrotizing pancreatitis (ANP) is reported by some to occur in approximately 20% of all episodes of pancreatitis. Although sterile necrosis may occur, a variable percentage develops infection of the necrotic tissue. Bacterial contamination of the necrotic pancreas occurs in as many as 70% of cases, and the mortality rate approaches 100% if surgical intervention and drainage are not undertaken for WOPN. A difference in the rate of WOPN formation between men and women has not been clearly demonstrated. WOPN occurs in 1%-9% of the cases of acute pancreatitis, usually 4 to 6 wk after the initial episode and is heralded by pain, fever and chills. The mortality rate of ANP (about 25% of acute pancreatitis) has been reported to be between 10% and 30%.

### ETIOLOGY-PATHOPHYSIOLOGY

ANP is the most severe end of a spectrum of inflammation associated with pancreatitis. During the past decade, significant progress has been achieved in our understanding of the inflammatory response in pancreatitis, see also Table 1. By contrast, very little is known about the mechanisms mediating another major pathologic response in pancreatitis, the parenchymal cell death. In experimental models of acute pancreatitis, acinar cells have been shown to die through both necrosis and apoptosis. The apoptosis/necrosis ratio varies in different experimental models of pancreatitis. Of note, the severity of experimental pancreatitis directly correlates with the extent of necrosis and inversely with that of

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**Table 1 Etiology of pancreatitis**

| Etiology          | Description                                      |
|-------------------|--------------------------------------------------|
| Biliary tract disease | Obstruction of the pancreatic duct at the level of the ampulla of Vater |
| Excessive alcohol consumption | Direct toxic effect |
| Hyperlipidemia | Restricted blood flow (atherosclerotic emboli, hypoperfusion, vasculitis) results in ischemic disturbance to the acinar structures and an increasingly acidic environment |
| Hypercalcemia | Induces pancreatic injury via a secretory block, accumulation of secretory proteins and possibly activation of proteases |
| Hereditary | Cationic trypsinogen mutations |
| Trauma | Acute release of toxic factors (resulting from inflammatory response) into the systemic circulation |
| Ischemia | Similar to hyperlipidemia |
| Pancreatic duct obstruction | Similar to biliary tract disease |
| Viral infections | Mumps or cytomegalovirus |
| Scorpion venom | Direct toxicity |
| Idiopathic | Develops without readily identifiable cause |
| Drugs | Frequently |
|  | 6-Mercaptopurine |
|  | Azathioprine |
|  | Corticosteroids |
|  | Synthetic estrogens |
|  | Furosemide |
|  | Mesalamine |
|  | Methyldopa |
|  | Sulphonamides |
|  | Tamoxifen |
|  | Occasionally |
|  | Asparaginase |
|  | Chlorothiazide |
|  | Cisplatin |
|  | Hydrochlorothiazide |
|  | Interferon-α |
|  | Sulindac |
|  | Tetracycline |
|  | Valproic acid |

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apoptosis[26]. Inflammation causes cell death with resultant devitalized tissue, which is likely to become infected. The amount of necrotic tissue is the strongest predictor of mortality in ANP. After pancreatic necrosis occurs, 3 potential outcomes exist, resolution, pseudocyst, or WOPN. Pseudocysts may result in prolonged abdominal pain, rupture leading to acute peritonitis, fistula formation, and erosion into vessels with acute hemorrhage[27,28]. Pancreatic ascites or pleural effusion may be developed. Pseudocysts or WOPN may also cause hollow viscus obstruction by compression of surrounding structures, including the colon, stomach, duodenum and the common bile duct. The role of proinflammatory cytokines in this process is being vigorously examined[27]. WOPN forms through various mechanisms, including fibrous wall formation around fluid collections, penetrating peptic ulcers, and secondary infection of pseudocysts. A pseudocyst arises as a local complication of ANP. Over a period of 3-4 wk, sequestration of necrotic tissue occurs, forming a fibrous capsule without an epithelial lining. At any point after the initial injury in ANP, infection of necrotic tissue may occur, leading to WOPN development. When this occurs prior to the formation of the fibrous wall, it is termed infected necrosis. WOPN can be located in single or multiple locations and vary greatly in size[3]. Of note, pseudocyst formation is directly related to the degree of necrosis present. Approximately 3% of patients with acute pancreatitis develop WOPN. Baltazar and Ranson’s radiographic staging criteria predict the formation of pseudocysts and, therefore, WOPN development. Grade A: normal pancreas; Grade B: focal or diffuse enlargement; Grade C: mild peripancreatic inflammatory changes; Grade D: single fluid collection; Grade E: two or more fluid collections or gas within the pancreas or within peripancreatic inflammation. In grade A, B, C, or D, the probability of WOPN development is less than 2%. With grade E disease (2 or more collections of peripancreatic fluid), the probability rises to 57%/39. WOPN should be distinguished from infected necrosis in that little or no necrotic material is present. WOPN also typically appears later in the course of pancreatitis, often 4 wk or more after the start of the attack[34].

PRESENTATION
Diagnosed pancreatitis with an unexpectedly prolonged course, hemodynamic instability, fever, failure of medical therapy, or the presence of fluid collections on a computed tomography (CT) scan all point to the possibility of necrosis and, potentially, WOPN later in the course. Abdominal pain with or without a mass on palpation of the epigastrium is suggestive of parietal peritoneal irritation. Classic physical examination findings, such as Grey- Turner sign or Cullen sign, are supposedly characteristic of pancreatitis but rarely are noted in clinical practice. Other physical findings are nonspecific and include abnormal vital signs consistent with sepsis, abdominal guarding, and rebound tenderness[31]. Peripancreatic fluid encased in a fibrinous capsule defines pseudocysts. Superinfection of pseudocysts is one way that WOPN may be developed, even if pseudocysts are not a prerequisite. Evidence suggests that colonic translocation of bacterial flora accounts for many cases of local infected fluid formations[32]. The most typical organisms isolated from infected necrosis and abscesses are gut flora-associated and Candida spp[33].

DIAGNOSIS
No specific hematologic studies define WOPN. A persistently elevated white blood cell count with a left shift and positive blood cultures is suggestive of this diagnosis. The degree of pancreatic enzyme elevation does not directly indicate the degree of necrosis[34]. The presence of air in necrotic tissue in a pseudocyst on imaging studies is also specific for infection. Abdominal CT scan with IV contrast; ultrasound, either endoscopic or transabdominal; and magnetic resonance imaging (MRI) (with gadolinium) are potential modes for imaging pancreatic necrosis or abscess[35]. MRI is becoming the imaging study of choice because of concerns regarding the use of iodinated contrast, which is said, by some, to devitalize marginal tissue, increasing the burden of necrotic tissue. The current criterion standard for initial evaluation is contrast-enhanced CT scan, which may reveal ischemic pancreatic tissue as evidenced by the lack of uptake of contrast. Contrast-enhanced CT scan (and in particular a contrast-enhanced thin-section multidetector-row CT scan) is the best imaging technique to exclude conditions that masquerade as acute pancreatitis, to diagnose the severity of acute pancreatitis, and to identify complications of pancreatitis[35-37]. MRI may be of some additional benefit in the acute evaluation of ANP; gadolinium does not cause a worsening of ischemia in experimental models[38]. Demonstrable necrotic tissue in the pseudocyst may exist. Typically, this develops more than 3 wk after the initial bout of pancreatitis[39]. The presence of either bacterial or fungal flora in pancreatic fluid collections usually aspirated via CT-guided needle biopsy is the sine qua non of WOPN. The presence of organisms either on Gram stain or culture is essential for WOPN.

TREATMENT
Generally, medical care is supportive, with attention paid to blood pressure and volume status. Patients frequently are transiently bactereemic, so antibiotics are routinely administered. The choice of antibiotics is thoroughly guided by the likely flora and degree of antibiotic penetration into the locations of WOPN and the other necrotic tissue. The most commonly isolated bacteria in WOPN are gut flora, by means of translocation[40]. The most common pathogens are Escherichia coli, Klebsiella pneumoniae, Enterococcus faecalis, Staphylococcus aureus, Pseudomonas aeruginosa, Proteus mirabilis and Streptococcus spp[41]. In
several trials, imipenem has been shown to have good penetration into pancreatic tissue, and it has a good activity against all likely pathogens. Other antibiotics that have been shown to be efficacious in ANP include cefuroxime and a regimen of cefazidime, amikacin and metronidazole. It must be emphasized that the ultimate treatment for WOPN is complete removal by surgical resection or drainage. Primary drainage is the treatment of choice for WOPN. Cases of WOPN have been reported of treatment, in which death has not resulted; however, the standard of care is drainage involving an open procedure. Case series have been reported of WOPN patients, who have been treated with CT-guided drainage tube placement, but these seemed to show inferior results to open drainage. Recent advances in endoscopic treatment using endoscopic ultrasound (EUS) have made guided transgastric treatment of the complications of ANP possible. EUS-guided necrosectomy has been promising to date. The introduction of formal widespread pancreatic and peripancreatic necrosectomy with a following procedure to manage the peripancreatic space, allowing continued drainage and debridement, has markedly decreased the mortality associated with infected necrosis. In specialized centers, this is rapidly becoming the treatment of choice. CT-guided drainage has a role in some patients, who cannot tolerate an open procedure. EUS with trans-gastric drainage is another option. Consideration can be given to medical management of nonsurgical candidates until their clinical status improves. Other forms of aspiration, including endoscopic drainage of WOPN, are currently being investigated, with controversial results. Surgical drainage of WOPN is the procedure for cure. Placement of indwelling drains after the initial procedure may be necessary for complete resolution. Nil per os or a jejunal feeding tube is initially recommended for ANP; however, no contraindication for enteral feeding exists if the pancreatitis has resolved. If the course is prolonged, the institution of total parenteral nutrition can be of benefit. Antibiotics are the primary medical therapy in WOPN, used for the control of bacteremia and sepsis. Supportive care with fluids is needed, and the use of vasopressors may be required, in hemodynamically unstable patients. Overall, it can be presumed that WOPN is an entity that can lead to several complications such as fistula formation, recurrent pancreatitis, bowel obstruction or death. Studies, including the present review based on retrospective observations, have demonstrated that non-operative management has been associated with a favorable outcome in patients with this dreaded complication. If bacteremia and sepsis can be restrained with prolonged antibiotic therapy along with antifungal agents, the need for necrosectomy associated with high morbidity and mortality in these patients can be avoided. Applying the recommended therapeutic strategy, which comprises early application of antibiotics combined with restricted indication for surgical intervention, fewer patients with ANP undergo surgery, and the interventions are performed later in the course of the disease, ideally when necrosis has become well demarcated. Endoscopic sphincterotomy plays a role in patients with a dilated common bile duct from an impacted stone at risk of impending cholangitis. Surgery in acute pancreatitis is used for cholecystectomy in the patient with gallstone pancreatitis, as well as for infected pancreatic necrosis, WOPN, pseudocysts and traumatic pancreatitis with a ruptured duct system.

CONCLUSION

Today, treatment of acute pancreatitis is mainly conservative and surgery is on the retreat. Infection of pancreatic necrosis is still the main risk factor of morbidity and mortality in the course of necrotizing disease. A prophylactic treatment with antibiotics can reduce both infectious complications and mortality. Thus, antibiotics should be administered in severe pancreatitis. If pancreatic infection is suspected, fine needle aspiration should be performed. Today, WOPN is a well accepted indication for open surgery, when minimal invasive treatment is not efficient. Natural orifice transluminal endoscopic surgery (NOTES) has emerged as an innovation in endoscopic access that allows incisionless surgery. Integral techniques used in NOTES have developed in part through advances in endoscopic retroperitoneal access to pancreatic pathology over the past 2 decades. In 2004, Kalloo et al. described peroral endoscopic access to the peritoneal cavity for a liver biopsy, reporting a new access technique for surgical procedures. In actuality, transluminal endoscopic access by Kozarek et al. was well documented as early as 1985 for the treatment of pancreatic pseudocysts. A study reviewing the senior author’s (Gary C Vitale) 15-year experience with natural orifice transluminal endoscopic retroperitoneal access for the drainage of pancreatic abscesses showed that the optimal approach to pancreatic abscess drainage has yet to be studied by a randomized controlled trial, but the literature demonstrates that endoscopic therapy has greatly reduced morbidity and mortality rates compared with surgery.

The natural orifice transluminal approach to pancreatic fluid collections has evolved to address complicated cases that previously would have necessitated surgery. The development of EUS has expanded the safety and efficacy of this modality by allowing one to access and drain more challenging fluid collections. The aim of the surgical procedure is to remove the septic focus by debridement of the infected pancreatic and peripancreatic necrosis. The optimal timepoint for the surgical intervention is when necrotic tissue is well demarcated. Therefore bleeding complications and removal of vital tissue can be avoided. Today, surgical procedures should combine the necrosectomy with a postoperative method to continuously remove necrosis and debris. This is the case with the following 2 techniques: postoperative continuous lavage and closed packing. Fulminant acute pancreatitis is a rare subgroup of acute pancreatitis,
characterized by a rapidly progressive multiple organ failure in the first days following the onset of the disease with a high probability of death despite intensive care unit therapy. There is a poor outcome with both, surgical and conservative therapies. Thus, surgery should only be performed as a last resort[6]. If left untreated, WOPN precipitates to sepsis and death. Adequate drainage of a pancreatic pseudocyst may help prevent some cases of WOPN. However, in many cases the disorder is not preventable[46]. Until now, there are no official established guidelines for the treatment of WOPN. That is a major consideration for the future.

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