Methods to analyze data from studies with test-negative designs are the focus of considerable ongoing research.[5,7-10] A clear understanding of the assumptions underlying the design, the reasons for using it in practice, and its relative strengths and limitations is essential for readers to critically assess, interpret, and apply the findings in a principled fashion. Researchers who use test-negative designs to investigate Covid-19 vaccine effectiveness can look to the article by Thompson et al. for examples of how to report primary findings and assess the sensitivity of these findings to potential biases that are specific to the test-negative design.

Drs. Dean, Hogan, and Schnitzer contributed equally to this editorial.

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Drainage for Infected Pancreatic Necrosis — Is the Waiting the Hardest Part?

Todd H. Baron, M.D.

Acute necrotizing pancreatitis, which occurs in up to 30% of episodes of acute pancreatitis, can be a devastating, life-threatening disease. For many years, acute necrotizing pancreatitis (the cause of clinically severe pancreatitis) was managed with open surgical necrosectomy. Surgeons eventually realized that necrosectomy was largely not beneficial for patients with sterile necrosis and that delay in surgery to allow for demarcation of the necrotic process from healthy, viable tissue resulted in better outcomes, including lower surgical mortality.[1] The focus then shifted to recognition of and intervention for infected necrosis, as well as determination of the appropriate timing of surgery.

Parallel to the introduction of endoscopic, percutaneous, and less-invasive surgical drainage procedures for pancreatic necrosis, there was a refinement in nomenclature for acute pancreatitis and its consequences. Necrotizing pancreatitis results in defined inflammatory processes that form in and around the pancreatic bed, with some of these processes occurring early after onset and some occurring later. Among the delayed entities is walled-off pancreatic necrosis (initially termed "organized pancreatic necrosis").[2,3] Walled-off pancreatic necrosis is a defined entity that occurs 4 weeks or more after the onset of acute necrotizing pancreatitis. It is an evolution of acute, early pancreatic necrosis or peripancreatic fat necrosis, or both, (Fig. 1A) to a well-circumscribed, demarcated "collection" of both solid (necrotic tissue) and liquid (pancreatic juice, from associated pancreatic ductal disruption) components (Fig. 1B) as shown on cross-sectional imaging (computed tomography

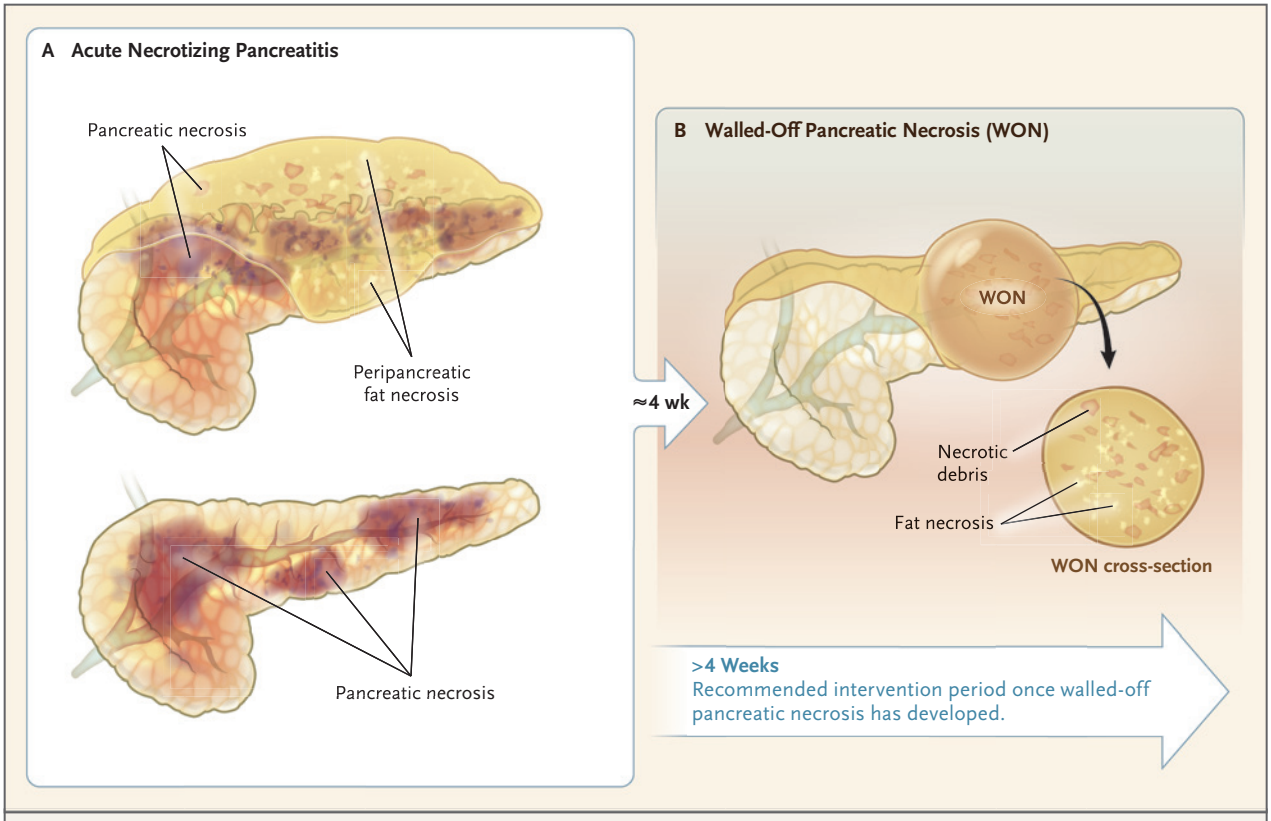

Figure 1. Acute and Walled-Off Pancreatic Necrosis.

Shown are pancreatic and peripancreatic fat necrosis (Panel A, top) and pancreatic necrosis only (Panel A, bottom). Walled-off pancreatic necrosis (WON) contains both solid and liquid components (Panel B). Pancreatic duct disruption is usually present in both acute and walled-off pancreatic necrosis. FT denotes fat necrosis, N necrosis, ND necrotic debris, and P pancreas.

or magnetic resonance imaging). In some cases, this demarcation may occur earlier than 4 weeks after the onset of acute pancreatitis.

Although infected necrosis can be managed medically with antibiotics, some form of drainage is often needed. The Dutch Pancreatitis Study Group previously provided important clinical data showing that initial percutaneous drainage is superior to up-front open necrosectomy for management of infected necrosis and reported on the benefits of endoscopic transluminal drainage.[4-6] For some time, investigators[7] have pondered whether the long-held surgical mantra of delaying surgical necrosectomy until pancreatic necrosis is demarcated[1] applied to nonsurgical (percutaneous and endoscopic) drainage approaches and whether perhaps delaying drainage of infected necrosis resulted in worse outcomes. Thus, Boxhoorn et al.,[8] on behalf of the Dutch Pancreatitis Study Group, sought to determine whether earlier, nonoperative drainage is beneficial for patients with infected pancreatic necrosis. They report the results of this trial in this issue of the *Journal*.

A total of 104 patients with infected necrosis whose onset of acute pancreatitis was within 35 days before randomization were assigned to one of two strategies: immediate (within 24 hours after diagnosis of infection) administration of antibiotics and image-guided (e.g., computed tomography) percutaneous drainage or endoscopic ultrasound-guided transmural drainage; or administration of antibiotics, with nonoperative drainage postponed until development of walled-off pancreatic necrosis. Patients in the postponed-drainage group could undergo drainage before the stage of walled-off necrosis was reached if clinical decompensation occurred.[8]

The mean time after onset of pancreatitis to the first intervention was 24 days in the imme-

diate-drainage group and 34 days in the postponed-drainage group; the first intervention consisted of endoscopic transluminal drainage in 56% of patients in the immediate-drainage group and 67% in the postponed-drainage group. There were no differences between the groups in overall complications from the time of randomization to 6-month follow-up, or in mortality, mean hospital stay, and cost. The mean number of total interventions (surgical and nonsurgical) was greater in the immediate-drainage group. It is important to note that no surgical or nonsurgical intervention for necrosis was needed in approximately 40% of patients in the postponed-drainage group. Even more impressive was the difference in the need for surgical necrosectomy, which was performed in 51% of patients in the immediate-drainage group as compared with 22% of patients in the postponed-drainage group.

This trial adds to the growing volume of high-quality studies guiding evidence-based recommendations.[2,9] The management of acute necrotizing pancreatitis is now predominately nonsurgical. In the early stage (usually the first 1 to 2 weeks), management consists of intensive medical care, institution of enteral nutrition, and withholding of antibiotics.[2,9] Drainage of sterile necrosis does not reduce mortality among patients with acute necrotizing pancreatitis, although subsequent elective endoscopic, percutaneous, or surgical intervention for sterile walled-off necrosis may eventually be needed for patients with intractable symptoms, such as gastric outlet or biliary obstruction, or patients who remain unwell.[2] Differentiating infected necrosis from sterile necrosis with concomitant ongoing systemic inflammatory response within the first few weeks after the onset of pancreatitis may be difficult, but there are established criteria to guide clinicians.[8,10] The distinction between infected and sterile necrosis is essential because infected necrosis is associated with significantly higher mortality, requires initiation of antibiotics that penetrate pancreatic tissue (tailored to available culture data), and often results in percutaneous, endoscopic, or surgical intervention (alone or in combination). As shown in the present study,[8] nonoperative drainage in clinically stable patients is best delayed until the development of walled-off necrosis, which usually occurs 30 or more days after the onset of pancreatitis.

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