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EDITORIAL

Persisting Early Hypotension: Is This Why Necrosis Gets Infected in Acute Pancreatitis?

James H. Grendell

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Acute pancreatitis is a disease with a striking range of severity. Most patients have a relatively mild course and are eating within a few days and out of the hospital in less than a week. Nevertheless, other patients will endure a long and complicated course that may involve persisting organ failure, infection, a long intensive care unit stay, and multiple diagnostic tests and therapeutic interventions, which on occasion will culminate in death. Recently, two new classification systems [1, 2] have been published in an effort to improve the stratification of patients with acute pancreatitis in terms of severity. These comprehensive classification systems have helped clarify the terminology applied to complications of acute pancreatitis, particularly the differentiation of necrotic collections in or around the pancreas from pseudocysts. The new classification systems will also be very helpful in the design of clinical studies and in comparing reported series to assess the degree of severity in patient samples. Nevertheless, these systems are much less helpful in the care of an individual patient with acute pancreatitis, except for indicating which patients may be less likely to require a higher level of care (e.g., in an intensive care unit).

Related to this topic, the medical literature is replete with acute pancreatitis severity prediction methods that have employed individual laboratory test values or changes in such values including combinations of age, vital signs, laboratory tests, clinical assessment, and chest x-ray findings [e.g., Ranson's criteria, the Acute Physiologic and Chronic Health Evaluation (APACHE) II score, Systemic Inflammatory Response Syndrome (SIRS) score, Bedside Index of Severity (BISAP) score], and contrast-enhanced computed tomography (e.g., Balthazar score). The number and variety of such reports is a testimony to the ingenuity and dogged determination of the investigators involved in this pursuit for over 40 years. Still, it is clear from the number of approaches that have been proposed that none has been proven clearly superior [3], and like the new classification systems, all of these attempts to predict severity are much more useful in identifying those patients who are likely to have less severe disease and thus less likely to require higher levels of hospital care.

Despite all these efforts, in most circumstances clinicians caring for patients admitted to the hospital with acute pancreatitis do not have specific therapeutic interventions beyond general supportive care for the prevention of complications and adverse outcomes. To attempt to remedy, at least in part, this deficiency, Thandassery et al. [4] report in this issue of *Digestive Diseases and Sciences* the results of a study with more modest aims. Rather than trying to develop a universally applicable, global assessment of pancreatitis severity, they address a more limited question that nevertheless could significantly advance clinical care: Does organ failure in general or do specific types of organ failure promote the development of infected pancreatic necrosis? What they describe based on a relatively small number of patients (81) is that cardiovascular failure during the first week of hospitalization at their institution (defined as systolic blood pressure <90 mm of Hg for more than 48 h despite "adequate fluid resuscitation"), was strongly associated with the development of infected pancreatic necrosis, as determined by either

J. H. Grendell (✉)
Division of Gastroenterology, Hepatology and Nutrition, Winthrop University Hospital, 222 Station Plaza North, Suite 429, Mineola, NY 11501, USA
e-mail: JGrendel@Winthrop.org

J. H. Grendell
State University of New York at Stony Brook School of Medicine, Stony Brook, NY, USA

image-guided fine-needle aspiration of necrotic tissue or an operative necrosectomy specimen. This association was not observed for other types of organ failure. The odds ratio (OR) for development of infected necrosis for patients with persisting early hypotension was 2.5 (95 % CI 1.7–24.7, $p = 0.01$). Of the factors evaluated in this study, the only other one that was an independent predictor for the occurrence of infected necrosis using multivariate analysis was the APACHE II score, with an OR of 4.77 (95 % CI 3.14–7.24, $p < 0.001$). The authors hypothesize that persisting hypotension early in the course of acute pancreatitis increases intestinal permeability, facilitating bacterial translocation from the colonic lumen into lymphatics or into the systemic circulation. This hypothesis is consistent with the cultures obtained from areas of infected necrosis in this study as well as in previous reports. Furthermore, enteric bacteria were the predominant organisms cultured from blood, a finding significantly associated with the presence of prolonged hypotension during the first week of acute pancreatitis.

Although the aims and potential importance of this study are laudable, it has a number of very significant limitations which require its findings to be considered, at best, preliminary and tentative, necessitating confirmation by larger studies involving less selected patient samples with a more complete description of the early volume resuscitation administered to patients. The authors report that the current study included 81 consecutive patients who met their generally accepted diagnostic criteria for acute pancreatitis. Their patient sample consisted of relatively young (mean age 40) males (68 %) with alcohol as the predominant etiology (49 %). Because their institution is a referral center, the patients in this study were *much sicker* than would be expected in a typical, unselected series of patients [5]. For example, 74 % of patients were described as having organ failure, 79 % pancreatic necrosis, 16 % infected pancreatitis necrosis, and 35 % bacteremia. The number of patients requiring surgery and the overall mortality, both at $\sim$20 %, is considerably higher than that for community-based hospitals.

Yet of even greater concern is the ambiguity regarding the volume resuscitation and overall fluid management of these patients prior to and after admission to the investigators' medical center. In their discussion, the authors acknowledge this limitation, stating that "most of the patients were managed briefly (referral delay of 3.6 ± 2.1 days) at other hospitals" [4]. No information is provided about any treatment patients received prior to being transferred to the investigators' referral center. Moreover, the authors provide only limited, general information about the fluid management administered once the patients arrived at their institution. Given the likely critical importance of volume resuscitation during the initial 48–72 h of hospitalization for acute pancreatitis, particularly for the prevention and treatment of hypotension, the failure to provide more detailed quantitative data regarding this is a major omission and limitation of this work.

An additional question regarding the potential clinical application of the authors' findings is whether use of the presence of persisting hypotension during the first week of acute pancreatitis to identify a group of patients at increased risk for developing infected necrosis *is an improvement* over the APACHE II score when it is used for the same purpose. What would be needed to determine this relationship, but was not provided in the report, are data delineating the optimum APACHE II score for predicting the development of infected necrosis and how the predictive value of this score compared to that of the presence of persisting hypotension.

Despite these limitations, however, the authors of this report have provided an important service to those interested in the pathophysiology of acute pancreatitis and to those involved in the care of patients with this challenging disease. This report should provide an impetus for further work in both experimental models of acute pancreatitis and in the clinical setting, exploring the effects of hemodynamic alterations (including systemic hypotension and more localized changes in splanchnic blood flow) on intestinal mucosal permeability, bacterial translocation, and the subsequent development of infected pancreatic necrosis and bacteremia. If the findings of this report are confirmed in additional larger, well-designed clinical studies, potential clinical strategies could be implemented to try to prevent the development of infected pancreatic necrosis by focusing potential interventions on this specific high-risk group of patients with persisting hypotension during the first week of acute pancreatitis. Presumably, clinicians are already trying to prevent the development of persisting hypotension through aggressive volume resuscitation early in the course of the disease. What constitutes optimal volume resuscitation and fluid management for patients with acute pancreatitis, however, remains controversial and in need of further study [6].

When optimal volume resuscitation fails to prevent early persisting hypotension, alternative approaches could be employed in the care of these patients for the prevention of infected pancreatic necrosis or bacteremia such as by maintaining the integrity of the intestinal epithelium, thus preventing bacterial translocation; by reducing the abundance of gut flora capable of translocation; or by killing bacteria once translocation has occurred. Maintenance of epithelial integrity could be accomplished by something as simple as early enteral feeding or as elaborate as continuous veno-venous hemofiltration (CVVH) [7], reduction of gut flora by administration of non-absorbable antibiotics,

and killing of bacteria after translocation by a more selective use of prophylactic systemic antibiotics than has generally been heretofore used in clinical practice.

Although Thandassery et al. [4] have framed a relatively simple but very significant clinical question that their study does not fully answer, they lay the groundwork for future investigation that has the potential to change and greatly improve our care of patients with acute pancreatitis.

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