CORRESPONDENCE

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Severity of Acute Pancreatitis: Impact of Local and Systemic Complications

Dear Sir:

We read with interest a recent report by van Santvoort et al[1] on a large cohort of patients with acute pancreatitis who were considered for enrollment in 2 interventional studies. The cohort represents a mix of patients who received conventional management or an experimental intervention, which had a significant impact on the mortality and morbidity of at least a quarter of the patients in the combined cohort.[2,3] The paper makes an important contribution to the evidence in support of a more conservative and less invasive approach to the treatment of necrotizing pancreatitis. Beyond that, the authors have attempted to answer several important questions related to the impact of local and systemic factors on the severity of acute pancreatitis. It is this latter aspect that requires further discussion if future studies will take us forward.

With regard to local complications of acute pancreatitis, the authors have reported a significantly higher mortality for patients with pancreatic necrosis compared with patients with peripancreatic necrosis alone. However, it is difficult to see how this is possible in the cohort where patients with "pancreatic necrosis" included those with and those without coexisting peripancreatic necrosis. The important question that needs to be answered in further noninterventional studies is whether the outcomes of patients with peripancreatic necrosis alone are comparable with those of pancreatic necrosis alone.

Another noticeable finding is that half of patients in the cohort had peripancreatic necrosis alone. Although the existence of this entity is unquestionable, the reported incidence of 49% (315/639) is surprisingly high. One of the reasons for that might be that peripancreatic necrosis alone was defined by a single person only as a computed tomography severity index of 3 or 4. One might argue that computed tomography severity index of 4 could be representative of <30% pancreatic necrosis and peripancreatic fat stranding, not necessarily peripancreatic changes exceeding fat stranding.[4] The authors also indicated that in all patients with peripancreatic fat necrosis alone, in whom necrosectomy was performed, it was confirmed during surgery. However, fewer than one quarter of patients with supposed peripancreatic fat necrosis alone did undergo surgery.

The generalizability of this study is made more difficult because of the reported incidence and impact of systemic complications. The 30% (8/27) mortality in patients with transient organ failure is considerably higher than that found in the contemporary literature.[5,6] Also considerably higher in this cohort is that 89% (213/240) of patients had persistent rather than transient organ failure.[5,6]

Another finding that requires further discussion is the greater mortality associated with organ failure during the first week compared with organ failure that developed later. To suggest that early organ failure represents "a different clinical entity" is speculative for 3 reasons. First, it is necessary to time the onset of the disease from the onset of symptoms and not from the time of hospital admission.[7] Second, there is no evidence that 1 week is the optimal cutoff to make this distinction.[7] Third, no attempt has been made to adjust for possible confounders and the differential effects of different treatments in this cohort. Somewhat awkwardly, the authors have made an adjustment for some confounders when arguing the case for the timing of intervention.

It is also noteworthy that the authors have chosen to discuss the pattern of mortality with the main emphasis on the impact of organ failure. And yet 44% (41/93) of patients who died had infected pancreatic necrosis. As a result, the impact of infected pancreatic necrosis on mortality is probably underestimated and more so because only patients with primary pancreatic infection were included, and not those who developed secondary pancreatic infection (ie, after catheter drainage or emergency laparotomy).

In conclusion, the relative and respective role of local and systemic complications in determining the severity of acute pancreatitis is beginning to be understood.[7,8] The data from this report highlight the need for purportedly designed noninterventional prospective studies if we are to find true answers on topical questions related to the natural history of acute pancreatitis and the impact of local and systemic complications.

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1. van Santvoort HC, et al. Gastroenterology 2011;141:1254–1263.
2. Besselink MG, et al. Lancet 2008;371:651–659.
3. van Santvoort HC, et al. N Engl J Med 2010;362:1491–1502.
4. Balthazar EJ, et al. Radiology 1990;174:331–336.
5. Johnson CD, et al. Gut 2004;53:1340–1344.
6. Lytras D, et al. Pancreas 2008;36:249–254.

7. Petrov MS, et al. Am J Gastroenterol 2010;105:74–76.
8. Petrov MS, et al. Gastroenterology 2010;139:813–820.

Conflicts of interest
The authors disclose no conflicts.

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Reply. We thank Dr Petrov and colleagues for their interest in our paper and welcome further discussion on the impact of local and systemic factors on the severity of acute pancreatitis.

It is questioned whether conclusions can be drawn on the difference in outcomes between patients with peripancreatic necrosis alone and patients with pancreatic necrosis because the patients with pancreatic necrosis also had peripancreatic necrosis. Our aim was to evaluate the outcome of patients with peripancreatic necrosis alone as a separate clinical entity. We showed that these patients have a lower rate of organ failure, infected necrosis, and mortality.

The authors suggest that future studies should compare patients with peripancreatic necrosis alone to patients with pancreatic necrosis alone. The latter is very rare, so this comparison is probably not relevant. In our consecutive cohort, only 4 out of 639 patients (0.6%) had pancreatic necrosis without any signs of peripancreatic necrosis.

The limitation of diagnosing peripancreatic necrosis on computed tomography (CT) with a CTSI score of 3 or 4 was already discussed in our paper[1] and needs no further emphasis here. Peripancreatic necrosis was not defined by a single person only: Radiologists in the 19 centers judged CTs and 1 experienced radiologist subsequently reviewed the CTs. It is correct that a CTSI of 4 can also be reached if a patient has <30% necrosis (2 points) and only fat stranding (2 points). However, this was the case in only 4 out of 639 patients (0.6%) and we correctly included these patients in the group with pancreatic necrosis.

We disagree that generalizability of our study is made difficult because of the higher incidence of persistent organ failure and higher mortality of transient organ failure, as compared with earlier studies.[2,3] The most important question when judging the external validity of a study is whether the study population is comparable with the patients encountered in day-to-day clinical practice; that is, did selection of a certain subgroup of patients occur that limits extrapolation of the results?[4] This was not the case for our study: We prospectively included an unselected, consecutive cohort of patients with necrotizing pancreatitis. The fact that the incidence and outcome of organ failure differed from other studies may be explained by several factors, such as differences in case mix and definitions of outcomes. The studies[2,3] referred to by Petrov included patients with "predicted severe acute pancreatitis," clearly a less severe subgroup of patients than our inclusion criteria of "necrotizing pancreatitis." These studies also used other, less stringent definitions for organ failure such as a low platelet or fibrinogen count and hypocalcaemia.

Petrov et al question our suggestion of early organ failure as a separate entity with 3 arguments. First, we reported time from admission to organ failure, rather than time from onset of symptoms. In our cohort, the median time between onset of symptoms (abdominal pain) and admission was 0 days (interquartile range, 0–1). Second, because we used a cutoff point of 1 week. This may indeed not be the optimal cutoff, but was in line with important previous studies on this topic.[2,5] Third, we did not adjust for baseline confounders such as differences in severity parameters on admission. These parameters are probably not confounders, but more likely a reflection of early organ failure. For this letter, however, we performed a multivariable analysis of early versus late organ failure, adjusting for age, gender, ASA-class, CTSI, APACHE-II score, and intervention. Early organ failure was still associated with an increased risk of mortality: Adjusted odds ratio 1.9; 95% confidence interval, 1.6–3.7.

In our analysis on timing of intervention versus mortality, we adjusted for baseline factors (eg, APACHE-II score 24 hours before intervention). We disagree that this is "awkward," because an analysis on timing of intervention is prone to selection bias; were patients undergoing earlier intervention more critically ill, and is earlier intervention therefore associated with poorer outcomes?

The outcome in several disease subgroups was analyzed and no emphasis was put on organ failure over infected necrosis. We reported on primary infected necrosis only, because inclusion of secondary infected necrosis after interventions such as open abdomen strategy for abdominal compartment syndrome would have skewed our evaluation of the natural course of necrotizing pancreatitis.

We conclude that the results of our study are valid and have been put in the correct perspective. Of course, we agree that further research in acute pancreatitis is very much needed. We invite Dr Petrov and others to conduct similar, noninterventional, prospective studies.

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