Immediate or Postponed Intervention for Infected Necrotizing Pancreatitis

TO THE EDITOR: Boxhoorn et al. (Oct. 7 issue)[1] report that in the POINTER (Postponed or Immediate Drainage of Infected Necrotizing Pancreatitis) trial, immediate drainage was not superior to postponed drainage with respect to complications in patients with infected necrotizing pancreatitis necrosis and led to more frequent invasive interventions. However, there are certain caveats to this interpretation.

First, only 20% of the patients in their trial had organ failure, a percentage lower than in previous studies,[2,3] and only 20% had greater than 50% necrosis. This corresponds to a cohort with predominantly "milder" infected necrotizing pancreatitis and thus to lower mortality. Whether immediate drainage can benefit patients with extensive necrosis with greater infective loads (i.e., those with "severe" infected necrotizing pancreatitis) remains to be determined. We have reported, in our interim analysis, the benefit of immediate drainage in a cohort with predominantly severe infected necrotizing pancreatitis.[4]

Second, the median intervention time in the immediate-drainage group was 24 days. The conventional practice is to intervene beyond 4 weeks. Thus, whether this intervention is early enough to lead to a beneficial difference between immediate and postponed drainage (median time, 29 days) is not clear. Third, the authors used both endoscopic drainage and percutaneous drainage, which have been established to have different outcomes[5]; thus, this introduces substantial heterogeneity that may complicate a generalized interpretation of the results.

Jayanta Samanta, D.M.
Jahnvi Dhar, D.M.
Rakesh Kochhar, D.M.

Postgraduate Institute of Medical Education and Research
Chandigarh, India
dj_samanta@yahoo.co.in

No potential conflict of interest relevant to this letter was reported.

1. Boxhoorn L, van Dijk SM, van Grinsven J, et al. Immediate versus postponed intervention for infected necrotizing pancreatitis. N Engl J Med 2021;385:1372-81.
2. Jain S, Mahapatra SJ, Gupta S, Shalimar, Garg PK. Infected pancreatic necrosis due to multidrug-resistant organisms and persistent organ failure predict mortality in acute pancreatitis. Clin Transl Gastroenterol 2018;9:190.
3. Schepers NJ, Bakker OJ, Besselink MG, et al. Impact of characteristics of organ failure and infected necrosis on mortality in necrotising pancreatitis. Gut 2019;68:1044-51.
4. Dhar J, Samanta J, Singh AK, et al. Sa1351 comparison between proactive versus standard percutaneous drainage in patients with acute necrotizing pancreatitis — interim analysis of a randomized controlled trial. Gastroenterology 2020;158:S-326-S-327. abstract.
5. Bakker OJ, van Santvoort HC, van Brunschot S, et al. Endoscopic transgastric vs surgical necrosectomy for infected necrotizing pancreatitis: a randomized trial. JAMA 2012;307:1053-61.

DOI: 10.1056/NEJMc2117813

TO THE EDITOR: The trial by Boxhoorn et al. showed that catheter drainage performed immediately did not lead to better clinical outcomes than postponed drainage in patients with acute infected necrotizing pancreatitis. However, we think several details need to be clarified further.

First, the locations of the necrosis were unclear. We know that specific treatment strategies for pancreatic necrosis differ among different sites.[1,2] It is relatively easy to perform a puncture for necrosis of the pancreatic body and tail, whereas drainage for necrosis of the pancreatic head or neck is difficult. In addition, the puncture methods in the trial were unknown. The numbers of patients who underwent ultrasound-guided puncture or computed tomography (CT)–guided puncture in the trial were unclear. The authors need to clarify the selection criteria for the puncture methods.

Finally, a less invasive method called the "step-up approach" has been adopted to treat pancreatic necrosis and its complications.[3] In this trial, the number of patients who received catheter drainage and subsequently received treatment with interventional radiology techniques, minimally invasive surgery, and advanced life support was a concern.

Jianguo Qiu, M.D.

First Affiliated Hospital of Chongqing Medical University
Chongqing, China
qiujianguo456@163.com

Tang Wei, M.D.

Xiangya Hospital of Central South University
Changsha, China

No potential conflict of interest relevant to this letter was reported.

1. Kokosis G, Perez A, Pappas TN. Surgical management of necrotizing pancreatitis: an overview. World J Gastroenterol 2014; 20:16106-12.
2. Dani L, Carbonaro G, Natta F, et al. Treatment of acute necrotising pancreatitis and its complications: the surgeon's perspective. Case Rep Gastroenterol 2021;15:759-64.
3. Arvanitakis M, Dumonceau J-M, Albert J, et al. Endoscopic management of acute necrotizing pancreatitis: European Society of Gastrointestinal Endoscopy (ESGE) evidence-based multidisciplinary guidelines. Endoscopy 2018;50:524-46.

DOI: 10.1056/NEJMc2117813

TO THE EDITOR: The trial by Boxhoorn et al. showed no benefit of early drainage in patients with infected pancreatic necrosis: the percentages of patients with complications was similar in the immediate-drainage and postponed-drainage groups, as was mortality (13% and 10%, respectively), and more interventions were performed in the early-drainage group.

This trial clearly highlights that the arbitrarily defined period of 4 weeks to diagnose walled-off necrosis in patients with acute necrotizing pancreatitis is not valid. In this trial, pancreatic and peripancreatic necrosis was largely or fully encapsulated in 33 patients (60%) in the immediate-drainage group and in 21 patients (70%) in the postponed-drainage group at a mean of 24 days and 34 days, respectively. This indicates that in some patients necrosis becomes walled off before 4 weeks, whereas in other patients it may not become walled off even after 4 weeks. For drainage-related decisions, we should be guided by each patient's clinical condition, response to antibiotic treatment, and radiologic findings rather than by the period of 4 weeks. The subgroup analysis involving patients with a disease duration of less than 20 days may show some interesting results.

Ujjwal Sonika, M.D., D.M.
Siddharth Srivastva, M.D., D.M.
Ashok Dalal, M.D., D.M.
Govind Ballabh Pant Hospital
New Delhi, India
drashokdalal83@gmail.com

No potential conflict of interest relevant to this letter was reported.

DOI: 10.1056/NEJMc2117813

THE AUTHORS REPLY: Samanta and colleagues suggest that patients with infected necrotizing pancreatitis who underwent randomization in our trial had "milder" disease than those in previous studies. We hypothesized that early intervention might prevent clinical deterioration and could improve outcomes. Therefore, we designed a highly proactive approach for the diagnosis of infected necrosis as compared with previous trials.[1,2] Thus, in some patients infected necrotizing pancreatitis was diagnosed before the development of organ failure.

To avoid intervention in sterile necrotic collections, the diagnostic process must be performed accurately, which may have caused a small delay in randomization. However, as shown in the Supplementary Appendix of our article (available at NEJM.org), patients in the immediate-drainage group received drainage at a mean of 3 days after diagnosis of infected necrotizing pancreatitis. We think that the cohort of patients and the time of drainage accurately reflect clinical practice.

The suggestion that patients with extensive necrosis might benefit from immediate drainage unfortunately cannot be answered with the current data. However, in the subgroup analysis involving the most severely ill patients with organ failure at the time of randomization, we found no difference in the primary outcome between immediate drainage and postponed drainage.

Both endoscopic and percutaneous drainage techniques were allowed in our trial in order to maximize the probability of successful catheter drainage. Our previous randomized trial (Transluminal Endoscopic Step-up Approach versus Minimally Invasive Surgical Step-up Approach in Patients with Infected Pancreatic Necrosis [TENSION]) did not show differences in major complications or death between the two techniques.[2] Therefore, we think that the use of both techniques did not cause relevant heterogeneity in outcomes. It is noteworthy that not all collections in patients with pancreatic or peripancreatic necrosis can be reached endoscopically. Furthermore, the use of both techniques reflects daily practice in most pancreatic centers and allowed us to intervene in nearly all necrotic collections, regardless of the location of the necrosis, as was pointed out by Qiu and Wei. Since we consider both techniques as equal, the location of necrosis consequently is irrelevant for the outcome. In the patients receiving percutaneous

drainage, we did not distinguish between ultrasound-guided drainage and CT-guided drainage. The choice was made at the discretion of the treating interventional radiologist.

We agree with Sonika and colleagues that the development of walled-off necrosis differs between individual patients, as we ourselves previously reported.[3] This underlines that the treatment of infected necrotizing pancreatitis requires a tailor-made and multidisciplinary approach. Regardless of the extent of encapsulation, however, antibiotic treatment can be the first step in treatment.[1,2] This approach may allow for the avoidance of invasive interventions and may reduce the total number of interventions.

Sven M. van Dijk, M.D., Ph.D.

Amsterdam UMC
Amsterdam, the Netherlands

Hjalmar C. van Santvoort, M.D., Ph.D.

St. Antonius Hospital
Nieuwegein, the Netherlands

Marc G. Besselink, M.D., Ph.D.

Amsterdam UMC
Amsterdam, the Netherlands
m.g.besselink@amsterdamumc.nl

Since publication of their article, the authors report no further potential conflict of interest.

1. van Santvoort HC, Besselink MG, Bakker OJ, et al. A step-up approach or open necrosectomy for necrotizing pancreatitis. N Engl J Med 2010;362:1491-502.
2. van Brunschot S, van Grinsven J, van Santvoort HC, et al. Endoscopic or surgical step-up approach for infected necrotising pancreatitis: a multicentre randomised trial. Lancet 2018;391:51-8.
3. van Grinsven J, van Brunschot S, van Baal MC, et al. Natural history of gas configurations and encapsulation in necrotic collections during necrotizing pancreatitis. J Gastrointest Surg 2018;22:1557-64.

DOI: 10.1056/NEJMc2117813

INSTRUCTIONS FOR LETTERS TO THE EDITOR

Letters to the Editor are considered for publication, subject to editing and abridgment, provided they do not contain material that has been submitted or published elsewhere.

Letters accepted for publication will appear in print, on our website at NEJM.org, or both.

Please note the following:

- Letters in reference to a *Journal* article must not exceed 175 words (excluding references) and must be received within 3 weeks after publication of the article.
- Letters not related to a *Journal* article must not exceed 400 words.
- A letter can have no more than five references and one figure or table.
- A letter can be signed by no more than three authors.
- Financial associations or other possible conflicts of interest must be disclosed. Disclosures will be published with the letters. (For authors of *Journal* articles who are responding to letters, we will only publish new relevant relationships that have developed since publication of the article.)
- Include your full mailing address, telephone number, fax number, and email address with your letter.
- All letters must be submitted through our online submission system at NEJM.org.

Letters that do not adhere to these instructions will not be considered. We will notify you when we have made a decision about possible publication. Letters regarding a recent *Journal* article may be shared with the authors of that article. We are unable to provide prepublication proofs. Submission of a letter constitutes permission for the Massachusetts Medical Society, its licensees, and its assignees to use it in the *Journal*'s various print and electronic publications and in collections, revisions, and any other form or medium.

THE *JOURNAL*'S WEB AND EMAIL ADDRESSES

To submit a letter to the Editor: authors.NEJM.org
For information about the status of a submitted manuscript: authors.NEJM.org
To submit a meeting notice: meetingnotices@NEJM.org
The *Journal*'s web pages: NEJM.org