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agree that dose reduction is a reasonable option and one that may be associated with continued clinical benefit.

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

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TO THE EDITOR: Bakker et al. (Nov. 20 issue) found no benefit of early enteral nutrition in patients with predicted severe acute pancreatitis. Clinical trials involving patients with this condition are hampered by the low positive predictive value of current prognostic scoring systems, resulting in the inclusion of many patients who ultimately have mild acute pancreatitis and do not require early enteral nutrition. A composite end point allowed for sample-size reduction but ultimately resulted in an underpowered study, owing to the inequality between the individual end points. Death and infection have vastly different clinical significance, given that persistent organ failure, not infection, is the primary cause of death in patients with severe acute pancreatitis. The timing, type, and volume of fluid administered were not detailed in this study. Individual centers across this consortium may have different practices with regard to fluid resuscitation that potentially biased the results toward the null hypothesis. Enteral nutrition has consistently been shown to have a benefit in patients with severe acute pancreatitis, but we are still no closer to optimizing patient selection and the timing of enteral nutrition.

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TO THE EDITOR: The study by Bakker et al. requires careful interpretation. First, the actual delivery site of enteral nutrition is unclear. The authors did not disclose in the article that the original ethics committee approval was for tube feeding into the stomach, not the jejunum. Furthermore, feeding tubes were dislodged in 40% of the patients, which many would consider to be a rather high rate for leading research centers. Second, only one third of the study patients had actual, as opposed to predicted, severe or critical acute pancreatitis (i.e., persistent organ failure, infected pancreatic necrosis, or both). Hence, two thirds of the patients in the study were not posed to benefit from tube feeding. Third, the lack of superiority of feeding within 24 hours after presentation versus feeding at 72 hours (or later) after presentation does not mean that the latter should be deemed the preferred nutritional strategy. The weight of evidence indicates that the most effective time to start feeding in patients with acute pancreatitis is between 24 and 72 hours after presentation, and the exact timing of feeding in an individual patient is influenced by the adequacy of intravenous fluid resuscitation and opiate use.

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

In response to Petrov and Windsor: the first version of the protocol indeed included nasogastric instead of nasojugal feeding. After critical appraisal of the available evidence at the time, we decided to switch to nasojugal feeding to minimize the risk of aspiration. This decision was made before the start of patient recruitment and hence did not influence outcome (for details, see www.isrctn.com/ISRCTN18170985). The rate of tube dislocation is similar to rates found in the literature.\textsuperscript{3,4}

Our study did not show that starting an oral diet 72 hours after presentation is the most effective strategy for all patients with acute pancreatitis. However, our results show that routine early tube feeding in all patients at high risk for severe pancreatitis does not improve outcome and that the implementation of on-demand tube feeding will reduce patient discomfort and costs.

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**High-Cost Generic Drugs — Implications for Patients and Policymakers**

**To the Editor:** The Perspective article by Alpern et al. (Nov. 13 issue)\textsuperscript{1} states that manufacturers of new generic drugs can have delays before the Office of Generic Drugs of the Food and Drug Administration (FDA) approves their products.

Over the years, the increasing number of applications submitted to the FDA for the review of generic drugs resulted in a backlog that drove the establishment of the Generic Drug User Fee Amendments (GDUFA) of 2012.\textsuperscript{2} The GDUFA