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JPEN Journal Club 17. Composite End Points

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In the article to be discussed in this installment of the *JPEN* Journal Club, Bakker and a number of Dutch colleagues[1] postulated that early enteral nutrition (EN) would be beneficial in adult patients with their first episode of acute pancreatitis that was predicted on admission (based on prognostic formulae [Acute Physiology, Age, and Chronic Health Evaluation II (APACHE II) or Glasgow scores] or C-reactive protein levels >150 mg/L) to pursue a severe course. They designed a prospective trial in which eligible patients who had presented to the emergency room within 24 hours were randomized into 1 of 2 groups. The patients in the experimental arm had a nasojejunal feeding tube placed as soon as possible (and within 24 hours of randomization) and were begun on EN. These nutrient infusions were stopped when the patient was able to take oral feedings. The control patients did not receive any nutrition intervention for the first 72 hours and then were begun on oral feedings. Those who could not tolerate those oral feedings in the following 24 hours were subsequently given EN through a nasojejunal tube. (Those control patients who requested and tolerated oral feedings within the first 72 hours were so treated at that time.) This group will henceforth be referred to as the "on-demand" group.

The primary end point was a composite one consisting of either death or a major infection. A major infection was considered to have occurred if the patient developed infected pancreatic necrosis, bacteremia, or pneumonia. Predefined secondary end points included necrotizing pancreatitis, the development of organ failure, APACHE II scores, C-reactive protein levels, and the development of the systemic inflammatory response syndrome (SIRS).

Both the generation of the randomization sequence and concealment of allocation were adequately performed. While the investigators and patients could not be blinded, the assessment of the primary outcome was made by a committee consisting of 4 surgeons and a gastroenterologist; these individuals evaluated each randomized patient for the occurrence of the primary outcome without any knowledge of what nutrition intervention had been provided.

This Dutch group has an interest in pancreatitis and, a few years ago, published a randomized trial addressing the use of a probiotic preparation in such patients.[2] They used the data from the placebo group in that trial, as well as an expectation that the early EN would result in a reduction in the incidence of the primary outcome from 40% to 22%, to calculate that 208 patients would need to be studied, assuming that there would be a 1% loss.

In total, 102 and 106 patients were randomized to the early EN and on-demand groups, respectively. However, one early EN patient and 2 on-demand patients were excluded because the diagnosis of acute pancreatitis was incorrect, leaving 101 and 104 patients in each group. Twenty-one baseline features (12 presented in Table 1 of the article and the remaining 9 provided in the online appendix) of the 2 groups were largely comparable; the early EN group was slightly more overweight (body mass index [BMI] 29 vs 27 kg/m^2, $P = .01$). As we have discussed before,[3,4] when a number of analyses are performed, type I errors are more likely to occur. In this case, the likelihood of there being at least one apparent difference associated with a P value = .01, when 21 analyses are done, is 19%, so the randomization process can be viewed as having worked. The trial is at low risk of bias.

The patients assigned to the early EN received significantly more calories during the course of the study. (This information is available in the online appendix.) The primary end point occurred in 30% (30/101) of the early EN group and 27% (28/104) of the on-demand group. Mortality rates in the early

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This column was written prior to "*JPEN* Journal Club 18. Duplicate Publication," which was moved earlier in publication because the February 2016 issue contained a notice of redundant publication. The column numbering remains in the order of the columns' submission dates. The content in number 17 is intended to precede the content in number 18.

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EN/on-demand groups were 11%/7%, and major infections occurred in 25%/26%. Necrotizing pancreatitis occurred in 63% of the early EN patients and 62% of the on-demand patients. Of these 2 groups, 18% and 19% required admission to the intensive care unit (ICU). No differences were seen in the markers of inflammation, APACHE II scores, or incidences of SIRS. Similarly, no differences between the groups were seen with regard to duration of stay in the hospital (or ICU for those transferred there), pain scores, or adverse events. In fact, the only other difference that was seen was an increase in the numbers of nasojejunal tube placements in the early EN group.

The investigators concluded that the early EN did not provide any benefit to patients with predicted severe acute pancreatitis. They also challenged the concept of the gut mucosa–preserving effect of early EN.

The investigators spent a large part of the Discussion in this article trying to square their observation with what is currently advocated in the nutrition literature regarding the value of early EN. They noted that a number of observational studies have indicated that patients who had feeding established within the first 48 hours had better outcomes than did those whose feeding was more delayed but raised the concern often discussed in this Journal Club series—namely, the difference between association and causation. An equally tenable interpretation of these observational studies is that less severely ill patients can be fed earlier.

They cited systematic reviews of randomized trials that have shown that, in patients with pancreatitis, recipients of EN appear to have better outcomes than do comparison groups of patients receiving parenteral nutrition (PN). They noted that such observations could be due to an adverse effect (more infections) of the PN rather that a protective effect of luminal nutrients on the gastrointestinal mucosa. We have discussed the issue of relative efficacy before.[5] When 2 interventions are compared and the absolute value of neither is known, only a relative effect can be assessed; such trials cannot establish that either intervention is better (or worse) than doing nothing. When my colleagues and I reviewed a large number of randomized trials comparing PN with no nutrition support, we observed that the recipients of the PN did have more infectious complications.[6]

They also addressed the alleged benefits of early EN (compared with no or delayed EN) in the critically ill by noting that the method of those trials has been challenged, citing the article that Tim Lipman and I published.[7] The investigators concluded that, "for critically ill patients in general and for those with acute pancreatitis specifically, large, high-quality, randomized controlled trials that show an improved outcome with early enteral feeding are lacking."[1(p1989)]

The trial was set up such that, if a patient in the on-demand group was not eating by the fifth day, EN was begun. The rationale for doing so, as noted in the Discussion, was that waiting longer would put patients "at risk for malnutrition." According to the investigators, 32 of the 104 on-demand patients "required" a nasojejunal feeding tube; the verb *required*, when applied to the use of EN at day 5, actually appears several times in the article. However, no evidence was cited to justify this assertion; in our systematic review of PN, waiting for periods of up to 2 weeks did not appear to be harmful.[6] Thus, the "requirement" was more a matter of following the protocol than the result of any definitive evidence that waiting more than 5 days before supplying some type of nutrition support was harmful.

Only about one-fifth of the patients in this trial required admission to the ICU, so this trial is not applicable to that population. This fact actually also points out the limitations of various prognostic signs, not only the ones employed in this trial but also others (such as initial computed tomography scans, Ranson's criteria, and the Bedside Index for Severity in Acute Pancreatitis [BISAP]) in actually identifying those who will go on to develop complicated pancreatic disease; the positive predictive values of such tests are usually <50%.[8,9]

My reason for selecting this article for discussion was the use of a composite end point—namely, a combination of 2 or more different outcomes added together. This phenomenon is often encountered in randomized trials, especially in the field of cardiology.[10] Typically, as we saw with the current article, such an end point is the primary outcome in the trial.[10] Interestingly, at least for the cardiology trials, significant differences ($P < .05$) were reported more often than not.[10]

The usually cited reason for using such end points is that, by increasing the numbers of events, sample sizes can be smaller and trials easier to undertake and complete.[11] For example, if one expects the adverse outcome rate to be 10% and one wants to conduct a trial to demonstrate superiority defined as a reduction in that rate by 50% with a P value of .05 and an 80% likelihood (power) that such a difference will not be missed, one would require 432 patients in each group.[12] On the other hand, if the adverse outcome rate is 20%, keeping the other parameters the same would require only 197 patients in each group.[12] In addition, the use of composite end points permits investigators to avoid having to choose between several important outcomes.[11]

However, such end points have substantial limitations. The end points may be of widely different importance to patients, such as a combination of death and rehospitalization. Typically, the number of events in the outcome of greater importance is small, so the alleged effect of the intervention depends on less important outcomes.[11] For example, death as an individual outcome usually made only a minimal contribution in the cardiology trials.[10] Readers must not assume that the effect on the composite outcome applies to each individual outcome.

It also appears that the various components can be combined inappropriately, not defined well, or even not consistently reported.[13] It is often of interest to decision makers to know how much of a difference that a particular intervention would create would be the lower limit of clinical meaningfulness to practitioners. The use of composite outcomes makes such insights more difficult.[13] In this same vein, sample size calculations and the numbers needed to treat can be obfuscated.[14] Finally, if the outcomes are moved in different directions, beneficial or harmful effects may be masked.[14]

One may think that these considerations are not particularly relevant in the current trial because there were no significant

differences in either component of the composite outcome. However, the trial was actually underpowered to be sure that there was not any difference in either outcome. The overall expected rate of the composite outcome was 40%, and the investigators assumed that the intervention would reduce that rate to 22% (a relative risk reduction of 45%). If 10% were expected to die and 30% to become infected, and if we use an α error of 5%, a power of 80%, and a 45% reduction in the adverse outcomes (eg, a mortality of 5.5% and an infection rate of 16.5%), the numbers required for each of these 2 outcomes would be 346 or 150 per group.[12] (These calculations assume that there are no losses to follow-up; the numbers required would be even higher if this factor is also considered.) Of course, it should be remembered that such a type II error could have been in either direction (ie, missing a benefit or missing a harm).

You may have other thoughts about this article. If so, I would encourage you to engage in discussion on ASPENConnect's Journal Club discussion board. I would also again remind you that the American Society for Parenteral and Enteral Nutrition has created an information kit with guidelines for how chapters, hospitals, and universities can develop their own journal clubs (www.nutritioncare.org/journalclub).

For the next installment, please read the following articles:

1. Zhu X, Wu Y, Qiu Y, Jiang C, Ding Y. Effects of ω-3 fish oil lipid emulsion combined with parenteral nutrition on patients undergoing liver transplantation. *JPEN J Parenter Enteral Nutr*. 2013;37:68-74.
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3. Koretz RL. *JPEN* Journal Club 9. Prognostic indicators. *JPEN J Parenter Enteral Nutr*. 2015;39(1):129-130.
4. Koretz RL. *JPEN* Journal Club 11. Early stopping. *JPEN J Parenter Enteral Nutr*. 2015;39(3):369-371.
5. Koretz RL. *JPEN* Journal Club 14. Relative vs absolute efficacy. *JPEN J Parenter Enteral Nutr*. 2015;39(6):743-745.
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14. Ross S. Composite outcomes in randomized clinical trials: arguments for and against. *Am J Obstet Gynecol*. 2007;196(2):119.e1-6.