Monitoring for Intolerance to Gastric Tube Feedings: A National Survey

By Norma A. Metheny, RN, PhD, Andrew C. Mills, RN, PhD, and Barbara J. Stewart, PhD

Background Confusion about how to assess for intolerance to feedings often results in unnecessary feeding interruptions. Objectives To report findings from a national survey of methods used by critical care nurses to assess tolerance to gastric tube feedings and to discuss the findings in light of current enteral nutrition guidelines. Methods A paper-and-pencil survey was mailed to 1909 members of the American Association of Critical-Care Nurses. In addition, the same survey was posted online in a newsletter circulated to association members. Results from both surveys were pooled for data analysis. Results A total of 2298 responses were obtained; most respondents reported using a combination of methods to assess tolerance to gastric tube feedings (listening for bowel sounds, measuring gastric residual volumes, observing for abdominal distention/discomfort and for nausea and vomiting). More than 97% of the nurses reported measuring gastric residual volumes; the most frequently cited threshold levels for interrupting feedings were 200 mL and 250 mL. About 25% of the nurses reported interrupting feedings for gastric residual volumes of 150 mL or less; only 12.6% of the respondents reported allowing gastric residual volumes of up to 500 mL before interrupting feedings. Conclusions Practice among the 2298 critical care nurses varied widely. Many of the survey respondents are practicing in ways that can unnecessarily diminish the delivery of calories to patients. Protocols based on current enteral nutrition guidelines must be developed and implemented in practice settings. (American Journal of Critical Care. 2012;21:e33-e40)
Most critically ill patients receive their nutrients via tube feeding (either into the stomach or small bowel). Gastric feedings are often tried first because they are easier to administer; however, they may be associated with increased risk for aspiration in some patients. Therefore, monitoring for intolerance to feedings is a major nursing function. In this article, we report findings from a national survey of methods used by critical care nurses to assess tolerance to gastric tube feedings and discuss the findings in light of current enteral nutrition guidelines.

**Background**

Signs of intolerance to gastric feedings are difficult to quantify and can be easily confused with gastrointestinal symptoms associated with a patient’s medications or underlying illness. Thus, it is understandable that clinicians are unsure about how to determine when intolerance to feedings is present.

**Listening for Bowel Sounds**

Bowel sounds are an unreliable marker of normal bowel function. According to guidelines developed jointly in 2009 by the Society for Critical Care Medicine and the American Society for Parenteral and Enteral Nutrition (SCCM/ASPEN), “neither the presence or absence of bowel sounds nor evidence of passage of flatus and stool is required for the initiation of enteral feeding in intensive care patients.” Several recent protocols for monitoring for gastrointestinal intolerance to tube feedings omit the assessment of bowel sounds.

**Measuring Gastric Residual Volumes**

Studies of the impact of gastric residual volume (GRV) on critically ill patients have been significantly underpowered to guide practice definitively. As indicated in the following review, it is difficult to compare findings from GRV studies, primarily because of differing sample sizes, methods, and outcome measures.

An often-cited study by Mentec et al included a sample of 153 critically ill patients, all with 14F nasogastric tubes. The investigators reported on 2 outcomes: pneumonia and “upper digestive intolerance” (the latter was defined as 1 or more GRVs greater than 500 mL, or 2 consecutive GRVs between 150 mL and 500 mL, or vomiting). GRVs exceeding 500 mL were found in 13% of the patients and another 19% had 2 or more consecutive volumes between 150 and 500 mL. The study associated upper digestive intolerance with a higher incidence of pneumonia (43%) than when upper digestive intolerance was absent (24%). The investigators assumed that pneumonia was a consequence of aspiration; however, aspiration was not measured and other causes of pneumonia were not ruled out. The most positive feature of this study was use of the same type of feeding tube in all of the patients; further, the tube’s large diameter made it likely that high GRVs were identified.

In 2005, McClave et al studied a much smaller group (40 critically ill patients) with 8F or 12F nasogastric tubes or gastrostomy tubes. The patients were followed up for 3 days during which GRVs were measured every 4 hours and 587 samples of tracheal secretions were collected to assess for aspiration. An attempt was made to compare aspiration and 2 levels of GRVs (>200 mL and >400 mL). A positive feature of the study was the use of a laboratory assay to detect aspiration. However, because only 1.4% of the GRVs exceeded 400 mL, it was not possible to make a meaningful comparison between the 2 GRV groups. It is difficult to compare findings from this study with results of other studies because the investigators reported the total number of aspirations above a specific volume (not the number of patients with 1 or more high GRVs).

More recently, Montejo et al followed up 219 patients in 28 intensive care units (ICUs) who were receiving nasogastric feedings. The investigators attempted to compare aspiration and pneumonia in groups randomized to allowable GRV threshold values of 200 mL or 500 mL. The types of tubes used in the study varied from less than 8F to greater than 12F. Although the inclusion of 28 different ICUs could be viewed as a positive feature, it was also a
weakness in that differing methods were used to measure GRVs. That is, some ICUs used gravity drainage and others used the syringe aspiration method. The most troubling aspect of the study was the investigators’ definition of aspiration (visualization of formula in tracheal secretions). This method (even when blue dye has been added to the formula) is unreliable for detecting aspiration. The incidence of pneumonia was similar in the 2 groups, causing the investigators to conclude that a GRV of 500 mL can be recommended as a normal limit for GRV. However, the study was not sufficiently controlled or statistically powered to justify this recommendation.

In a study of 206 critically ill patients followed up for 3 consecutive days, investigators measured GRVs with 60-mL syringes every 4 hours. Most of the patients had nasogastric feeding tubes ranging in size from 10F to 18F. About 39% of the patients had 1 or more GRVs of at least 150 mL, 27% had 1 or more of at least 200 mL, and 17% had 1 or more of at least 250 mL; large-diameter tubes identified most of the high GRVs. Aspiration was assessed by a laboratory assay. No consistent relationship was found between GRVs and aspiration. However, patients identified as frequent aspirators had a significantly greater frequency of 2 or more GRVs of at least 200 mL and 1 or more GRVs of at least 250 mL. Positive features of this study were the laboratory assay for aspiration and the consistent technique used to measure GRVs. Negative features included the study’s descriptive nature and the wide variance in feeding tube characteristics.

In 2010, Poulard et al reported no difference in the rate of ventilator-associated pneumonia in critically ill patients when GRVs were measured than when they were not measured. The authors acknowledged that a greater number of patients would be required to provide adequate power to conclude that GRV monitoring is not important. And, as in previous studies that used pneumonia as the sole outcome, it is difficult to determine if the pneumonia was due to aspiration or other causes.

In summary, a large controlled and adequately powered study will be necessary to settle the controversy about significant GRV threshold levels in critically ill patients. It is unlikely that a specific volume can be identified that will “fit all,” given wide variations in patients’ characteristics and clinical factors.

**Bowel sounds are an unreliable marker of normal bowel function.**

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**It is unlikely a specific residual volume can be identified that will “fit all.”**

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**Recommendations in Published Guidelines.** There is consensus among guidelines that GRV should be monitored to assess tolerance to enteral nutrition. However, the recommended threshold volumes vary. For example, SCCM/ASCP* jointly issued the following recommendation in 2009: “Gastric residual volumes in the range of 200-500 mL should raise concern and lead to the implementation of measures to reduce risk of aspiration, but automatic cessation of feeding should not occur for GRVs < 500 mL in the absence of other signs of intolerance.” The Canadian clinical practice guidelines for nutrition support in critically ill adult patients receiving mechanical ventilation include the following information: “a protocol that incorporates prokinetics at initiation and tolerates a gastric residual volume of 250 mL should be considered as a strategy to optimize delivery of enteral nutrition in critically ill adult patients.” The European Society for Parenteral and Enteral Nutrition offers the following information for intensive care patients: “consider the intravenous administration of metoclopramide or erythromycin in patients with intolerance to enteral feeding (eg, with high gastric residuals).” A definition of “high” GRV was not provided.

**Observing for Abdominal Distention and/or Discomfort**

Guidelines developed jointly by SCCM/ASCP in 2009 recommend that patients be monitored for tolerance to enteral nutrition by noting abdominal distention and complaints of abdominal pain, as well as observing for the passage of flatus and stool. Monitoring for abdominal distension or discomfort is also advocated in the ASPEN enteral nutrition practice recommendations published in 2009. Abdominal distention is a common but late sign of nonocclusive bowel necrosis associated with early enteral nutrition.

**Observing for Nausea and/or Vomiting**

Nausea is difficult to detect in patients who are unable to communicate their distress; in contrast, vomiting is a readily observable event. Vomiting was one of the signs of upper digestive intolerance identified by Mente et al as being associated with pneumonia in critically ill gastric-fed patients. Further, vomiting was identified as a significant risk factor for aspiration in a study of 360 critically ill tube-fed patients.

**Objectives**

As indicated earlier, the purpose of this article is to report findings from a national survey of methods...
used by critical care nurses to assess tolerance to gastric tube feedings and to discuss the findings in light of current enteral nutrition guidelines. The following 3 questions were included on the survey:

1. Which of the following measures are advocated in your ICU to monitor for gastrointestinal intolerance to gastric tube feedings? (Please mark all that apply):
   a. Listening for bowel sounds
   b. Measuring gastric residual volumes
   c. Observing for abdominal distention
   d. Observing for abdominal discomfort
   e. Observing for nausea
   f. Observing for vomiting

2. If your ICU advocates measurement of GRVs during gastric tube feedings, how often are the measurements recommended?
   a. Every 4 hours
   b. Every 6 hours
   c. Every 8 hours
   d. Depends on patient acuity level
   e. Not applicable because GRVs are not measured in my facility

3. If your ICU advocates measurement of gastric residual volumes during gastric tube feedings, which of the following is most likely to cause nurses to stop the feeding and notify the physician?
   a. 100 mL
   b. 150 mL
   c. 200 mL
   d. 250 mL
   e. 500 mL
   f. Not applicable because GRVs are not measured in my facility

Methods

The study was approved by the appropriate institutional review board and carried out with the ethical standards set forth in the Helsinki Declaration of 1975. Permission was obtained from the American Association of Critical-Care Nurses (AACN) to purchase a list of members who were certified as critical care nurses (CCRNs) and who worked in an adult intensive care unit in a university-based medical center. Only the names of the nurses who had indicated on their membership forms that they were willing to be contacted by researchers were provided. A paper-and-pencil, researcher-developed survey was mailed to all of the nurses on the list with an enclosed self-addressed stamped envelope. No participant identifiers were included on the survey or the envelope. After the mailed survey had been completed, permission was also obtained from the AACN to advertise for participants in the AACN Critical Care Newsline (an electronic newsletter distributed to all AACN members each week). Readers were invited to participate in the online project if they were registered nurses who worked in an adult intensive care setting and had not already completed the mailed survey. A link to introductory material was provided in the newsletter; for those who consented to participate, the survey was accessible via the same link. Participants were assured that their responses would be anonymous; the Internet provider addresses were blocked.

Mailed Survey

The paper-and-pencil survey was mailed to 1909 nurses who were CCRNs and worked in an adult ICU in a university-based medical center. The survey consisted of 20 multiple-choice questions; however, only items that pertained to monitoring for gastrointestinal intolerance to tube feedings (and nurse characteristics such as certification status and type of work setting) are addressed in this report. Although a specific space was not provided on the survey for written responses, the participants occasionally wrote comments in the margins. Responses to the mailed survey were received between August 9, 2010, and December 20, 2010.

Online Survey

Questions on the online survey were identical to those on the mailed survey with the exception of 2 additional questions: (1) CCRN status, and (2) university medical center status. These 2 questions were needed on the online survey to identify which nurse respondents were comparable to nurses who had responded to the mailed survey (in terms of CCRN status and university medical-center status). An expandable space was provided at the end of each question for respondents to provide comments if they wished. Responses to the online survey were received between October 28, 2010, and January 3, 2011.

Participants

The number of nurses who responded to the mailed survey was relatively low (450/1909, 23.6%); a higher number (n = 1848) responded to the online survey. More than half (58.1%) of the total respondents (N = 2298) were certified by the AACN as
CCRN. Earned by completing an examination, the CCRN for registered nurses certifies they possess competencies beyond basic licensure to care for patients who are acutely and critically ill in hospitals. The AACN-sponsored credential signals to patients and their families (and to employers) a level of knowledge, safety, and professional practice in critical care nursing based on well-defined standards of excellence.

About one-fourth (22.3%) of the nurses reported working in critical care units that possess Beacon Award for Excellence status, a designation afforded by the AACN to formally recognize high standards of achievement. The Beacon Award is given to those patient environments that exemplify a systems level of quality; the standards of practice and leadership embedded in these units support nurses to deliver superior care. Forty-two percent of the nurses reported working in a university-based medical center. A university-based medical center is typically a hospital that is owned by a university or one that has a formal partnership with a medical school as a place to teach medical students and other health professionals. It differs from a community-based medical center in that its mission not only includes hospital services but also provides an academic setting for medical education and research.

**Data Analysis**

Generally, comparisons of Web and mail versions of surveys result in similar response distributions; for example, Kerwin and colleagues reported that Web and mail versions of their survey resulted in very similar responses on the items of interest. Only 5 of 54 items had response distributions that differed by Web versus mail survey when a large P level of .10 was used. In the study reported here, data from both surveys were pooled for data analysis. To evaluate whether such pooling was justified, $\chi^2$ tests were performed to compare the question-level responses on the mailed and online surveys, using only nurse respondents who were CCRNs and worked in a university-based medical center. As indicated by Julnes and Mohr, many large P values would suggest that responses to the mailed and online surveys were similar. Of the 50 individual $\chi^2$ tests, the P values were less than .01 (6%), from .02 to .05 (4%), from .06 to .09 (10%), from .10 to .49 (44%), and from .50 to 1.00 (36%). Because 90% of the P values were larger than the conventional .05 level, it was judged that the responses to most questions did not differ by survey type.

Descriptive statistics were used to determine the percentage of nurses who used specific methods to assess for intolerance to gastric tube feedings. $\chi^2$ tests were used to analyze whether CCRN status, Beacon status, and university medical center status were associated with differences in how nurses assessed for intolerance to gastric feeding (three 2 cross-tabulations) and decided to stop tube feedings (three 2 x 5 cross-tabulations). Because the 3 status variables were not highly related (CCRN with Beacon, $r = 0.01$; CCRN with university, $r = 0.23$; Beacon with university, $r = 0.16$), we have analyzed each status variable separately.

**Results**

A total of 2298 usable responses were obtained from the mailed and online surveys. As shown in Figure 1, the most frequently cited method for monitoring for gastrointestinal intolerance was measurement of GRVs (97.1%). Most nurses also reported assessing for abdominal distention (88.5%), vomiting (86%), bowel sounds (79.7%), nausea (79.6%), and abdominal discomfort (79.3%) as signs of intolerance to gastric feedings. Almost 64% (n = 1455) reported using all 6 assessments whereas less than 5% (n = 110) reported using only 1 method (108 only measured GRVs, 1 only listened to bowel sounds, and 1 only observed for abdominal distention). Assessment of bowel sounds was less frequent among CCRNs than non-CCRN (77% vs 84%, respectively, P < .001). Similarly, the practice was less frequent among nurses who work in a university-based medical center as opposed to those who work in a center that is not university based (75% vs 83%, respectively, P < .001). A slightly higher percentage of CCRNs (as opposed to non-CCRN) reported measuring GRVs (98% vs 96%, respectively).
As depicted in Figure 2, 80% of the respondents reported measuring GRVs every 4 hours; only 2% (n = 45) reported that they do not measure GRVs. CCRNs were more likely to measure GRVs every 4 hours than were nurses without this certification (P = .007).

As depicted in Figure 3, the most frequently cited GRV threshold values for interrupting feedings were 200 mL (36.5%) and 250 mL (24.1%); about one-fourth (24.9%) of the respondents reported interrupting feedings for GRVs of 150 mL or less. Only about 12.6% reported interrupting feedings at a GRV level of 500 mL.

As shown in Table 1, nurses who work in ICUs with Beacon Award status were less likely to interrupt feedings at GRV levels of 150 mL or less than were nurses who worked in ICUs without Beacon Award status (20.1% vs 27.3%, respectively) and more likely to interrupt feedings at levels of 250 mL or greater (43.3% vs 34.8%, respectively). Similarly, nurses who work in university-based medical centers were less likely to interrupt feedings at GRV levels of 150 mL or less than were those who work in facilities not associated with a university medical center (21.8% vs 28.2%, respectively) and more likely to interrupt feedings at GRV levels of 250 mL or more (42.3% vs 33.6%, respectively). Most (n = 2035) of the 2298 nurses selected one of the multiple-choice options in question 3. Of the 263 nurses who did not, 146 wrote brief comments outlining decision rules they use to determine when to interrupt or otherwise deal with gastric feedings; these responses are summarized in Table 2.

Table 1
Gastric residual volumes that would cause nurses to interrupt feedings, reported according to certification status and type of work setting

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>100</th>
<th>150</th>
<th>200</th>
<th>250</th>
<th>500</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCRN</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (n = 1188)</td>
<td>8.5</td>
<td>14.7</td>
<td>37.8</td>
<td>25.3</td>
<td>13.6</td>
<td></td>
</tr>
<tr>
<td>No  (n = 786)</td>
<td>12.1</td>
<td>16.3</td>
<td>36.4</td>
<td>23.7</td>
<td>11.5</td>
<td></td>
</tr>
<tr>
<td>Intensive care unit has Beacon Award</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes  (n = 448)</td>
<td>7.4</td>
<td>12.7</td>
<td>36.6</td>
<td>28.1</td>
<td>15.2</td>
<td>.004</td>
</tr>
<tr>
<td>No   (n = 1259)</td>
<td>10.7</td>
<td>16.6</td>
<td>37.8</td>
<td>24.5</td>
<td>10.3</td>
<td></td>
</tr>
<tr>
<td>University-based medical center</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes  (n = 857)</td>
<td>7.7</td>
<td>14.1</td>
<td>35.9</td>
<td>27.7</td>
<td>14.6</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No   (n = 1128)</td>
<td>12.0</td>
<td>16.2</td>
<td>38.2</td>
<td>22.1</td>
<td>11.5</td>
<td></td>
</tr>
</tbody>
</table>

*Except for P values, numbers in table are percentages of respondents. Because of missing data in response to the question about gastric residual volumes used to interrupt feedings, the numbers of nurses indicated in this table do not match the numbers included in the description of subjects. The P values are from 2 x 5 χ² tests.
Table 2
Summary of “write-in” decision rules regarding gastric residual volumes (GRVs; n = 146)

<table>
<thead>
<tr>
<th>Response</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>If GRV &gt; 30 mL, stop feeding</td>
<td>1</td>
</tr>
<tr>
<td>If GRV &gt; 50 mL, reduce rate or stop feeding</td>
<td>1</td>
</tr>
<tr>
<td>If GRV &gt; 160 mL on 2 consecutive checks, stop feeding</td>
<td>1</td>
</tr>
<tr>
<td>Variations on 200 mL</td>
<td>9</td>
</tr>
<tr>
<td>• If &gt; 200 mL, reduce rate to 10-20 mL/h</td>
<td>(3)</td>
</tr>
<tr>
<td>• Stop feeding if &gt; 200 mL on 2 consecutive checks</td>
<td>(3)</td>
</tr>
<tr>
<td>• If &gt; 200 mL, reduce rate by half</td>
<td>(1)</td>
</tr>
<tr>
<td>• Stop feeding if &gt; 200 mL more than once</td>
<td>(1)</td>
</tr>
<tr>
<td>• Stop feeding if &gt; 200 mL and give a prokinetic</td>
<td>(1)</td>
</tr>
<tr>
<td>Variations on 250 mL</td>
<td>6</td>
</tr>
<tr>
<td>• Stop feedings if &gt; 250 mL on 2 consecutive checks</td>
<td>(4)</td>
</tr>
<tr>
<td>• Stop feedings if &gt; 250 mL more than once</td>
<td>(1)</td>
</tr>
<tr>
<td>• If &gt; 250 mL, give back 200 mL, then decrease rate</td>
<td>(1)</td>
</tr>
<tr>
<td>If GRV &gt; 300 mL, stop feeding</td>
<td>32</td>
</tr>
<tr>
<td>If GRV &gt; 350 mL, stop feeding</td>
<td>6</td>
</tr>
<tr>
<td>Variations on 400 mL</td>
<td>22</td>
</tr>
<tr>
<td>• Stop feeding if GRV &gt; 400 mL</td>
<td>(19)</td>
</tr>
<tr>
<td>• Stop feeding if GRV &gt; 400 mL on 2 consecutive checks</td>
<td>(2)</td>
</tr>
<tr>
<td>• Stop feeding if GRV &gt; 400 mL and intolerance evident</td>
<td>(1)</td>
</tr>
<tr>
<td>If GRV &gt; 450 mL on 2 consecutive checks, stop feeding</td>
<td>1</td>
</tr>
<tr>
<td>If GRV &gt; 1000 mL, stop feeding</td>
<td>1</td>
</tr>
</tbody>
</table>

Stop feeding if gastric residual volume greater than
- Hourly flow rate | 10 |
- 1.5 times the hourly flow rate | 40 |
- 2 times the hourly flow rate | 5 |
- 2.5 times the hourly flow rate | 5 |
- 3 times the hourly flow rate | 1 |
- 4 times the hourly flow rate | 5 |

Discussion

Responses from the majority of nurses that are congruent with current critical care guidelines include assessing for GRVs, abdominal distention, and abdominal discomfort. Another positive finding was that most nurses check GRVs every 4 hours (a practice that is congruent with the 2009 ASPEN enteral nutrition practice recommendations).7

Most of the respondents reported monitoring bowel sounds as an indication of tolerance to feedings, although this practice is not included in several current protocols. A disturbing finding was that one-fourth of the survey’s participants are inclined to interrupt feedings for GRV levels of 150 mL or less (a practice that contributes to inadequate caloric delivery to patients). Critical care enteral nutrition guidelines do not allude to GRV volumes < 200 mL as being of concern. Implementation of measures to reduce aspiration risk (such as the use of prokinetics to increase gastric emptying) is advocated in the presence of high GRVs. The respondents’ infrequent reports of allowing GRVs of up to 500 mL before interrupting feedings (despite recommendation of this level in the 2009 SCCM/ASPEN guidelines) could indicate a lack of awareness of the recommendation or perhaps uncertainty about its level of supportive evidence. As indicated earlier, information presented in the Canadian clinical practice guidelines suggests a lower GRV value (250 mL) may be significant.20,21 Despite uncertainty about specific GRV threshold values, it is important for nurses to consider GRVs in relation to the presence or absence of other signs of gastrointestinal intolerance to feedings.7

Because of the survey’s large sample size (n = 2298), its statistically significant findings may have only marginal clinical significance. As indicated earlier, CCRNs reported greater use of every-4-hour GRV measurements; further, they were less likely to assess bowel sounds. Interruption of feedings for GRVs at levels of 150 mL or less was reported less often by nurses who worked in ICUs with Beacon Award status and by nurses who work in university-based medical centers. Despite relatively minor differences between groups, it is possible that certification status and work setting are associated with greater awareness of current guidelines.

Limitations

The survey did not include options for the number of times a GRV occurs before nurses would opt to interrupt feedings (such as 2 or more GRVs > 200 mL). Also, the survey did not provide options for values other than 100 mL, 150 mL, 200 mL, 250 mL, and 500 mL. As noted in Table 2, these omissions caused a number of nurses to write notations regarding decision rules they use to determine if feeding intolerance is present. A question regarding observing for the passage of gas and stool was not included on the survey; this was an important omission in that 40 respondents added this assessment in the comments section. Finally, there was no mechanism to ensure that the same person did not complete both forms of the survey; however, it is unlikely that this occurred.

Conclusions

Despite several positive findings, this survey indicates that many of the respondents are practicing in ways that can unnecessarily diminish the delivery of calories to their patients (such as stopping feedings for low GRVs). The gap between evidence and practice identified in this survey is consistent with findings from health services research overall. Several sets of enteral nutrition guidelines for critically ill patients are available and should be reviewed.

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Finally, researchers need to design and conduct adequately powered studies to identify the most effective protocols for delivering enteral feedings to critically ill patients.\textsuperscript{20}

**FINANCIAL DISCLOSURES**

None reported.

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**REFERENCES**


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