Gastric Residual Volume
End of an Era

Todd W. Rice, MD, MSc

GASTRIC DYSMOTILITY IS COMMON IN CRITICALLY ILL patients. The pathophysiology is multifactorial including the severity and etiology of the underlying critical illness, use of narcotic analgesia and other sedatives, decreased blood flow from shock, and use of vasopressors. Gastric dysmotility results in delayed gastric emptying that may place patients at risk of developing complications such as vomiting, aspiration, and ventilator-associated pneumonia (VAP). To manage this risk, guidelines recommend monitoring gastric residual volumes (GRVs) on an intermittent schedule and holding enteral feedings when residual volumes exceed certain limits.

The practice of holding or interrupting enteral feedings for elevated GRV developed from a desire to detect intolerance to enteral feeding early and potentially prevent complications from vomiting or aspiration. Two decades ago, McClave et al[1] reported that 30% of critically ill patients experienced GRV greater than 200 mL compared with none of 20 normal control patients. These data convinced many that 200 mL was a reasonable GRV threshold for interrupting enteral feedings. A decade later, Pinilla et al[2] found similar rates of vomiting with a 250-mL compared with a 150-mL GRV threshold although the 150-mL threshold resulted in more than twice as many enteral feeding interruptions (53% vs 23% of patients). Numerous studies have demonstrated that elevated GRV represents the most common reason for interrupting enteral nutrition and not reaching goal enteral feeding rates.[3,4] Consequently, McClave et al[5] used calorimetric spheres and food coloring to demonstrate that rates of aspiration and regurgitation did not differ between patients randomized to 200 mL and 400 mL of GRV thresholds. Again, enteral feedings were interrupted significantly more with lower thresholds.

Mentejo et al[6] took the concept of higher GRV thresholds further by comparing clinical outcomes of patients randomized to 200- vs 500-mL thresholds. Patients managed with higher thresholds received a higher percentage of prescribed enteral nutrition over the first week and reached goal enteral feeding rates faster without experiencing increased rates of VAP. Other clinical outcomes, including duration of mechanical ventilation and ventilator-free days, intensive care unit (ICU) lengths of stay, and ICU and hospital mortality, were also similar. These data prompted many to increase their GRV threshold to between 300 mL and 500 mL or to require additional signs of gastrointestinal intolerance before interrupting enteral feedings.[7,8]

However, it still was not clear that GRVs alone were clinically important, that they were correlated with gastrointestinal intolerances, or that holding enteral feedings for some arbitrary volume provided any protection from feeding complications. Mentec et al[9] found that more than half of critically ill patients who vomited never had a GRV higher than 150 mL, whereas the patients who vomited did so before their GRV had increased to 150 mL (ie, elevated GRVs occurred after vomiting and could not be used to predict vomiting). However, GRVs higher than 500 mL correlated with vomiting but not with increased VAP rates.

In addition, GRVs are dependent on caliber, position, and number of openings of the gastric tube and on patient positioning and, as such, lack reliable reproducibility[10] and do not correlate with either abdominal x-ray or with examination findings.[1] Physiologically, the stomach does not empty continuously. A certain volume of gastric content is necessary to stimulate contractions to facilitate emptying, and that volume varies from person to person. As such, an elevated GRV may simply be physiologic, as suggested by a study demonstrating that 80% of critically ill patients who experienced a GRV greater than 200 mL never had a second episode, despite continuing enteral feeding after the first episode.[11]

Given the data demonstrating safety of higher GRV thresholds and the uncertainty of their clinical utility, the next logical question was whether monitoring GRVs conferred any clinical benefit. In this issue of *JAMA*, the clinical trial by Reignier and colleagues[12] provides an answer to this question. The investigators randomized 449 adults receiving enteral nutrition via gastric tubes within 36 hours of initiation of mechanical ventilation, 222 of whom were randomized to a protocol in which GRV was checked every 6 hours, with adjustment of enteral feeding rates if the

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GRV exceeded 250 mL (the control group) and 227 patients whose GRVs were not checked and whose enteral feeding rates were adjusted only when patients experienced vomiting or regurgitation (the intervention group). Despite experiencing almost twice as much vomiting, patients in the intervention group still received a higher percentage of their goal calories because GRVs in excess of 250 mL limited enteral nutrition delivery in 36.5% of patients in the monitored group. More importantly, however, patients in the intervention group did not experience significantly more VAP and had similar outcomes to patients randomized to the monitoring protocol, such as ICU-acquired infection, duration of mechanical ventilation, ICU and hospital lengths of stay, and short- and long-term mortality.

The finding that the group without GRV monitoring had significantly higher incidence of vomiting that did not translate into higher rates of VAP supports the emerging concept that aspiration of oropharyngeal secretions plays a larger role in the development of VAP than gastric or gastrointestinal contents.[13] The rates of vomiting in both groups were higher than previously reported in other studies, even studies that used higher GRV thresholds[4,7-9] or calorimetric detection techniques.[5] This may be due to the aggressive feeding protocol the investigators used, whereby enteral feedings were started at goal rates and titrated down when feeding intolerances were experienced. In addition, a relatively high-risk population was studied with 15% having central nervous system failure and more than 50% having hypotension requiring vasoactive drug support at the time of enrollment, both risk factors for increased intolerance to enteral feedings. Both of these risk factors were slightly less prevalent in the intervention group, although not enough to bias the results significantly.

Despite this aggressive protocol, overall enteral caloric delivery did not seem to be better than a "ramp up" feeding protocol used in other studies.[4,7,8,11] However, starting enteral nutrition this aggressively should favor GRV monitoring if monitoring has clinical benefit. Although the control group received more enteral calories, clinical outcomes were similar, supporting previous studies that have failed to demonstrate improved outcomes with increased amounts of enteral calories.[7,8,14] Thus, the time and energy that health care practitioners expend on trying to rapidly achieve goal enteral feeding rates early in the course of critical illness may be better spent on other aspects of critical care.

The study had a number of strengths including its randomized design, relatively large size, and enrollment of a heterogeneous critically ill population from both academic tertiary care and nonacademic community ICUs. However, even though the nature of the study precluded blinding of the bedside nurses and primary care team, VAP episodes were determined by adjudicators blinded to randomization group. Although the a priori set noninferiority boundary of an absolute 10% difference in rates of VAP is wide, especially given an anticipated VAP rate in the control group of 19%, the results did not approach this boundary, suggesting that not monitoring GRVs was noninferior, or at least not inferior enough to be clinically relevant.

Despite emerging evidence to the contrary, many enteral feeding protocols continue to interrupt enteral feeding for relatively low GRVs, some with thresholds as low as 150 mL or twice the enteral feeding rate the patient is receiving at the time. The finding from the study by Reignier et al should instill confidence in clinicians to change practice and not routinely check GRVs in all patients mechanically ventilated receiving enteral nutrition.

Conflict of Interest Disclosures: The author has completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

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Effect of Not Monitoring Residual Gastric Volume on Risk of Ventilator-Associated Pneumonia in Adults Receiving Mechanical Ventilation and Early Enteral Feeding

A Randomized Controlled Trial

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Importance Monitoring of residual gastric volume is recommended to prevent ventilator-associated pneumonia (VAP) in patients receiving early enteral nutrition. However, studies have challenged the reliability and effectiveness of this measure.

Objective To test the hypothesis that the risk of VAP is not increased when residual gastric volume is not monitored compared with routine residual gastric volume monitoring in patients receiving invasive mechanical ventilation and early enteral nutrition.

Design, Setting, and Patients Randomized, noninferiority, open-label, multicenter trial conducted from May 2010 through March 2011 in adults requiring invasive mechanical ventilation for more than 2 days and given enteral nutrition within 36 hours after intubation at 9 French intensive care units (ICUs); 452 patients were randomized and 449 included in the intention-to-treat analysis (3 withdrew initial consent).

Intervention Absence of residual gastric volume monitoring. Intolerance to enteral nutrition was based only on regurgitation and vomiting in the intervention group and based on residual gastric volume greater than 250 mL at any of the 6 hourly measurements and regurgitation or vomiting in the control group.

Main Outcome Measures Proportion of patients with at least 1 VAP episode within 90 days after randomization, as assessed by an adjudication committee blinded to patient group. The prestated noninferiority margin was 10%.

Results In the intention-to-treat population, VAP occurred in 38 of 227 patients (16.7%) in the intervention group and in 35 of 222 patients (15.8%) in the control group (difference, 0.9%; 90% CI, −4.8% to 6.7%). There were no significant between-group differences in other ICU-acquired infections, mechanical ventilation duration, ICU stay length, or mortality rates. The proportion of patients receiving 100% of their calorie goal was higher in the intervention group (odds ratio, 1.77; 90% CI, 1.25-2.51; $P=.008$). Similar results were obtained in the per-protocol population.

Conclusion and Relevance Among adults requiring mechanical ventilation and receiving early enteral nutrition, the absence of gastric volume monitoring was not inferior to routine residual gastric volume monitoring in terms of development of VAP.

Trial Registration clinicaltrials.gov Identifier: NCT0113748

JAMA. 2013;309(3):249-256 www.jama.com

EARLY ENTERAL NUTRITION IS THE standard of care in critically ill patients receiving invasive mechanical ventilation.[1-3] However, numerous studies have shown that early enteral nutrition is frequently not used or associated with inadequate calorie delivery.[4-9] The main reason for nonuse is gastrointestinal intolerance to enteral nutrition,[6,8] which has been ascribed to gastroparesis with increased gastric volume, gastroesophageal reflux, and regurgitation or vomiting carrying a risk of aspiration and ventilator-associated pneumonia (VAP).[10-12] This theoretical sequence has prompted a recommendation[2,3] to monitor the residual gastric volume of mechanically ventilated patients receiving early enteral nutrition. When the residual gastric volume exceeds a predetermined cutoff, gastric prokinetic drugs are given and enteral nutrition is decreased or stopped to minimize the risk of aspiration and subsequent VAP.[13,14]

For editorial comment see p 283.

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However, no studies have established that residual gastric volume monitoring decreases the VAP risk, and the measurement technique has never been validated.[15] Moreover, the role for gastric content aspiration in VAP has been challenged.[16] No clear relationship has been demonstrated between increased gastric volume, regurgitation, gastric content aspiration, and VAP.[17-19] The results of a before-after study conducted in a single intensive care unit (ICU) in our study group suggested that absence of residual gastric volume monitoring might not be associated with an increased VAP rate compared with residual gastric volume monitoring.[20] Furthermore, several studies suggest that residual gastric volume monitoring may be associated with decreased calorie delivery and therefore, with underfeeding and increased morbidity.[8,21]

We designed a multicenter, randomized, noninferiority trial NUTRIREA1 to test the hypothesis that absence of residual gastric volume monitoring was not associated with an increased incidence of VAP compared with routine residual gastric volume monitoring in patients receiving invasive mechanical ventilation and early enteral nutrition. The secondary objectives of our trial included evaluations of whether absence of residual gastric volume monitoring affected enteral nutrition delivery and patient outcomes.

METHODS

Study Design and Setting

NUTRIREA1 was conducted in 9 intensive care units forming the Clinical Research in Intensive Care and Sepsis (CRICS) network (France). Of the 9 ICUs, 3 were medical and 6 were medical-surgical; 3 were in university hospitals and 6 in general university-affiliated hospitals. The study protocol was approved by the appropriate ethics committee (Comite de Protection des Personnes de Poitiers) on February 18, 2010. Because the strategies used in both study groups were considered standard care, there was no requirement for informed consent, although before study inclusion, all patients or next of kin were informed about the study and provided written confirmation.

Participants

Eligible patients were consecutive adults (aged ≥18 years) admitted to the study ICUs between May 2010 and March 2011, expected to require more than 48 hours of invasive mechanical ventilation, and started on enteral nutrition via a nasogastric tube within 36 hours after intubation.

Exclusion criteria were abdominal surgery within the past month; history of esophageal, duodenal, pancreatic, or gastric surgery; bleeding from the esophagus, stomach, or bowel; contraindications to prokinetic agents; enteral nutrition via a jejunostomy or gastrostomy; pregnancy; treatment-limitation decisions; and current inclusion in a trial of VAP prevention, enteral nutrition tolerance, or both. Patients admitted to the study ICUs were screened for eligibility by the physicians and clinical research nurses, regardless of the day or time of day.

Randomization, Allocation Concealment, and Follow-up

After written confirmation of information about the study was obtained, eligible patients were randomly allocated in a 1:1 ratio to the intervention group or control group. Randomization and concealment were achieved using a secure, computer-generated, interactive, web-response system managed by the biometrical unit of the Tours University Hospital, which had no role in recruitment. Randomization was stratified by center using permutation blocks of variable sizes. Day 1 was the day of randomization. Included patients were observed until day 90.

Intervention and Enteral Nutrition Delivery

The intervention consisted in not monitoring residual gastric volume. In the intervention group, intolerance to enteral nutrition was diagnosed when vomiting occurred.

In the control group, the diagnosis of intolerance to enteral nutrition relied on the presence of vomiting, of residual gastric volume greater than 250 mL, or both. Residual gastric volume was measured every 6 hours by aspiration through the nasogastric tube using a 50-mL syringe. Aspirates smaller than 250 mL were returned to the patient.

In both groups, vomiting was defined as gastric contents detected in the oropharynx or outside the mouth. This definition included spontaneous regurgitation of enteral nutrition solution but not regurgitation during procedures associated with the vomiting reflex (eg, oral cavity care).

Enteral nutrition was initiated within 36 hours after intubation and delivered according to the same protocol in both groups (eMethods and eFigure 1 available at http://www.jama.com). All nurses and physicians were experienced in the use of this enteral nutrition protocol and in residual gastric volume monitoring and vomiting detection. Patients were in a semirecumbent position (30° to 45°) and received oral care every 6 to 8 hours with chlorhexidine solution. Subglottic secretions were not aspirated.

Blinding of group assignment to the physicians and nurses was not feasible. However, the primary end point was adjudicated by a blinded committee.

Diagnosis of VAP

VAP was suspected in patients who had new and persistent or progressive infiltrates on the chest radiograph with at least 2 of the following criteria: peripheral leukocytosis (>10 000/μL), leukopenia (4000/μL), body temperature of at least 38.5°C or of 35.5°C or less, and purulent tracheal aspirates. In the study ICUs, the criterion for confirming VAP was positive quantitative bacteriologic cultures of distal respiratory specimens obtained by bronchoalveolar lavage (significant bacterial count threshold of $\geq 10^4$ colony-forming units [cfu]/mL), protected specimen brush (significant threshold of $\geq 10^3$ cfu/mL), or tracheobronchial aspirate (significant threshold of $\geq 10^5$ cfu/mL). VAP episodes were recorded until day 2 after extubation. For the trial, all VAP diagnoses were adjudicated by an independent blinded committee based on all available clinical, radiological, and bacteriological data.

Study Outcomes

The primary outcome was the proportion of patients with at least 1 VAP episode. Secondary outcomes were the cumulative VAP incidence and total number of VAP episodes; microorganisms causing VAP; proportions of patients with at least 1 vomiting episode, enteral nutrition intolerance, prokinetic treatment, and diarrhea; score variations in SOFA (Sepsis-related Organ Failure Assessment); variations in serum albumin and C-reactive protein (CRP) levels during the first week of enteral nutrition; proportions of patients with ICU-acquired infections (bloodstream, urinary tract, catheter-related, and other infections); proportion of patients given 100% of the calorie target; cumulative calorie deficit from day 0 to day 7; mechanical ventilation duration; ICU and hospital lengths of stay; and ICU, day-28, and day-90 mortality rates.

Sample Size

A 10% noninferiority margin was predetermined in accordance with previous guidelines and reviews.[22,23] Previous studies reported VAP in 9% to 27% of intubated patients.[24] Given this broad range and the potential beneficial effects of the absence of residual gastric volume monitoring (ie, improved enteral nutrition delivery), we considered that a 10% margin was clinically acceptable.

We assumed a 19% rate of VAP with residual gastric volume monitoring, as reported in a previous study in a single center of our group.[20] With a 10% noninferiority margin, we needed 191 patients in each group to establish noninferiority with 80% power and a 1-sided 5% type I error rate. To obtain this sample size in the per-protocol analysis, assuming that 10% of patients would finally receive invasive mechanical ventilation for fewer than 48 hours, at least of 420 patients were required.

Statistical Analysis

All analyses were conducted in both a modified intention-to-treat (ITT) population and a per-protocol population. The modified ITT population comprised all randomized patients except those who withdrew consent to study participation (as required by French legislation).[25] For the per-protocol analysis, we excluded patients who did not meet inclusion or exclusion criteria, received invasive mechanical ventilation for fewer than 48 hours, or had medical reasons for study withdrawal.

The between-group difference in proportions of patients with at least 1 VAP episode was estimated based on the 2-sided 90% CI. The upper boundary of the 90% CI (corresponding with a 1-sided 95% CI) was then compared with the prestated noninferiority margin of 10%. Because death was a competing event, a sensitivity analysis was performed using competing risk analysis.[26]

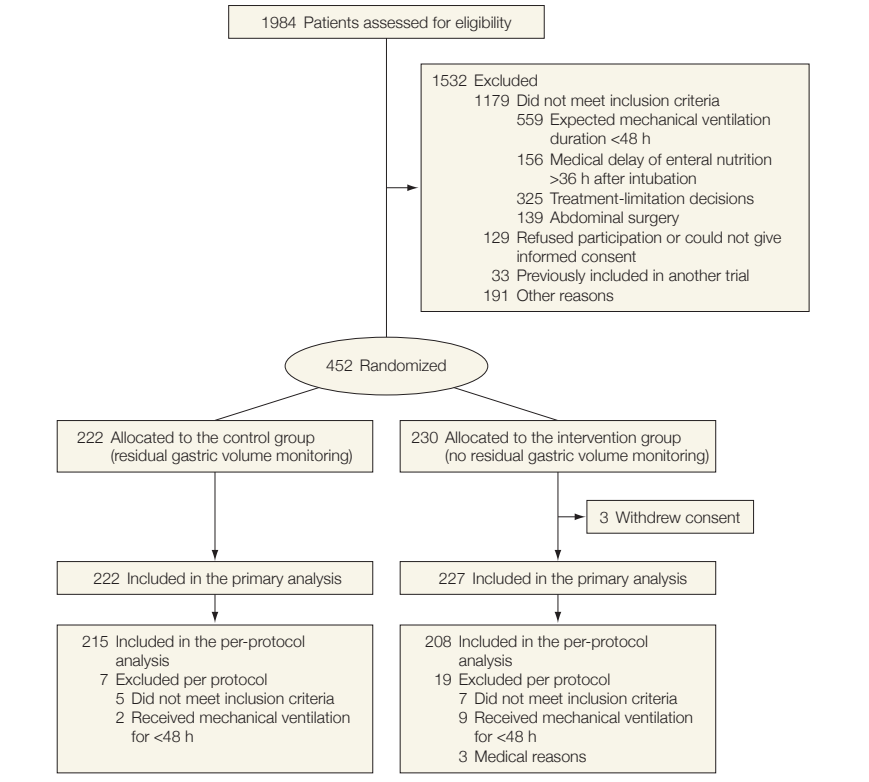
The number of VAP episodes per patient was evaluated using negative binomial regression. Microorganisms were described using numbers and percentages. For secondary outcomes, expressed as proportions of patients experiencing an event (vomiting, diarrhea, nosocomial infection, prokinetic treatment, or mortality), 2-sided 90% CIs of differences in proportions were estimated. The proportion of patients with enteral nutrition intolerance was not analyzed because the definition of enteral nutrition intolerance differed between the 2 groups. Linear mixed models were used to assess changes in SOFA, CRP, and albumin during the first week of enteral nutrition. Logistic random-effects models were used to compare proportions of patients given 100% of the calorie target during the first week of enteral nutrition in both groups. For the ICU mortality assessment, ICU discharge was considered a competing risk. For cumulative calorie deficit from day 0 to day 7, duration of mechanical ventilation, and ICU and hospital lengths of stay, 2-sided 90% CIs of median differences were estimated.

Statistical analyses were performed using SAS version 9.2 (SAS Institute Inc) and R 2.12.1 (http://www.r-project.org).

RESULTS

Of the 1984 mechanically ventilated patients assessed for eligibility, 452 were

Figure 1. Study Flow



allocated for randomization, 449 were included in the modified ITT (primary) analysis, and 423 were included in the per-protocol analysis (FIGURE 1). Baseline features were evenly balanced between the 2 study groups (TABLE 1).

Table 1. Baseline Characteristics of the Modified Intention-to-Treat Population[a]

	No. (%) of Patients	
	Intervention Group (n = 227)	Control Group (n = 222)
Age, mean (SD), y	61 (15)	62 (14)
Sex		
Men	159	156
Women	68	66
Weight, mean (SD), kg	77.2 (19.7)	79.0 (21.7)
BMI, mean (SD)[b]	27.3 (6.5)	27.8 (7.1)
SAPS II, mean (SD)[c]	49 (17)	51 (16)
SOFA at baseline, mean (SD)[d]	8 (4)	8 (3)
McCabe score[e]		
No fatal underlying disease (0)	132 (58.1)	150 (67.5)
Death expected within 5 y (score, 1)	82 (36.1)	66 (29.7)
Death expected within 1 y (score, 2)	13 (5.7)	6 (2.7)
Medical diagnosis at admission	205 (90.3)	212 (95.5)
Chronic disease at ICU admission	85 (37.4)	66 (29.7)
Respiratory	42 (18.5)	39 (17.6)
Cancer or immune deficiency	37 (16.3)	24 (10.8)
Liver	10 (4.5)	4 (1.8)
Heart	2 (0.9)	4 (1.8)
Renal, requiring dialysis	2 (0.9)	2 (0.9)
Diabetes mellitus	42 (18.5)	48 (21.6)
Acute organ/system failure at ICU admission		
Respiratory	116 (51.5)	101 (45.5)
Sepsis	33 (14.5)	22 (9.9)
Miscellaneous	30 (13.2)	27 (12.1)
Central nervous	27 (11.8)	40 (18.0)
Cardiac arrest	14 (6.1)	16 (7.2)
Heart	7 (3.0)	16 (7.2)
Treatment		
Sedative agents	188 (82.8)	192 (86.4)
Insulin	123 (54.1)	118 (53.2)
Proton pump inhibitor	122 (53.7)	118 (53.2)
Vasoactive drugs	115 (50.6)	124 (55.8)
Neuromuscular blocking agents	61 (26.8)	57 (27.5)
Dialysis	8 (3.5)	12 (5.4)
Laboratory test values, mean (SD)		
Serum albumin, g/dL	275 (73)	274 (60)
C-reactive protein, mg/L	12.71 (11.73)	12.73 (11.73)
Glucose, mg/dL	176.9 (100.4)	169.7 (105.2)
Lactate, mEq/L	2.5 (2.1)	2.5 (2.2)
Serum creatinine, mg/dL	1.3 (1.0)	1.5 (1.1)
Mechanical ventilator settings, mean (SD)		
FiO_2	56 (23)	56 (22)
PEP, cm H_2O	6 (3)	6 (3)

Abbreviations: BMI, body mass index; FiO_2, fraction of inspired oxygen; ICU, intensive care unit; PEP, positive end-expiratory pressure; SAPS II, Simplified Acute Physiologic Score; SOFA, Sequential Organ Failure Assessment.
SI conversion factors: to convert serum albumin to g/L, multiply by 10; C-reactive protein values to nmol/L, multiply by 9.524; creatinine values to μmol/L, multiply by 88.4; glucose values to mmol/L, multiply by 0.0555.
[a] Demographic characteristics were recorded at time of study inclusion.
[b] BMI is calculated as weight in kilograms divided by height in meters squared.
[c] SAPS II[59] scores range from 0 (lowest level of critical illness) to 163 (most severe level of critical illness with 100% predicted mortality). A score of 50 predicts a 46.1% risk of death. SAPS II was calculated 24 hours after ICU admission.
[d] SOFA[60] scores range from 0 (no organ failure) to 24 (most severe level of multiple-organ failure).
[e] Data adapted from McCabe and Jackson.[61]

Primary Outcome: Ventilator-Associated Pneumonia

In the modified ITT population, 38 of 227 patients (16.7%) in the intervention group and 35 of 222 patients (15.8%) in the control group had at least 1 VAP episode (difference, 0.9%; 90% CI, −4.8% to 6.7%). In the per-protocol population, 37 of 208 patients (17.8%) in the intervention group and 35 of 215 patients (16.3%) in the control group had at least 1 VAP episode (difference, 1.5%; 90% CI, −4.5% to 7.5%). In both populations, the upper limit of the 90% CI was within the prestated 10% noninferiority margin.

Secondary Outcomes

The hazard ratio of the cumulative VAP incidence in the intervention group vs the control group was 1.06 (90% CI, 0.72-1.55; $P = .80$) in the modified ITT population and 1.09 (90% CI, 0.74-1.60; $P = .80$) in the per-protocol population (FIGURE 2). For the total number of VAP episodes, the odds ratio in the intervention group was 0.98 (90% CI, 0.66-1.43) in the modified ITT analysis and 1.01 (90% CI, 0.68-1.49) in the per-protocol analysis (eTable 1). In each modified ITT group, 58 microorganisms causing 43 VAP episodes were identified. The proportions of *Staphylococcus aureus*, *Streptococcus* spp, Enterobacteriaceae, Pseudomonadaceae, and other gram-negative bacteria did not differ between the 2 groups (eTable 2).

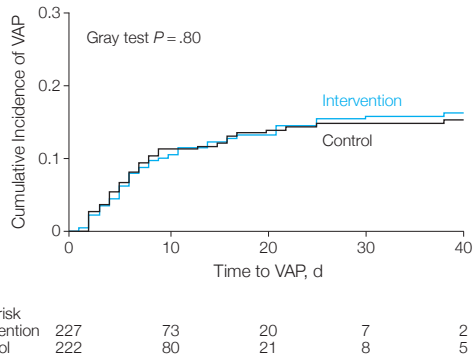
TABLE 2 reports the results for the other secondary outcomes. Proportions of patients who vomited were significantly higher in the intervention group than in the control group, and more vomiting episodes were reported in the intervention group than in the control group (eTable 3; modified ITT: odds ratio [OR], 1.86; 90% CI, 1.32-2.61; $P = .003$; per-protocol OR, 1.93; 90% CI, 1.36-2.75; $P = .002$). However, the proportion of patients meeting the group-specific definition of enteral nutrition intolerance was higher in the control group, which also had a higher proportion of patients given the prokinetic agent erythromycin. The calorie target was achieved in a higher proportion of pa-

tients in the intervention group than in those in the control group (FIGURE 3; modified ITT OR, 4.13; 90% CI, 2.20-7.69; $P<.001$; per-protocol OR, 4.95; 90% CI, 2.59-9.12; $P<.001$). Consequently, patients in the intervention group had a lower cumulative calorie deficit from day 0 to day 7 compared with patients in the control group (Table 2). The rates of diarrhea and ICU-acquired infections did not differ between groups (Table 2). Similar results were obtained in each infection subgroup (eTable 3). *Clostridium difficile* diarrhea was diagnosed in 2 patients in each group. Variations in SOFA score, albumin, and CRP during the first week showed no significant between-group differences (eFigure 2, eFigure 3, and eFigure 4). The hazard ratio of the cumulative incidence of ICU death in the intervention group compared with the per-protocol control group was 1.10 (90% CI, 0.81-1.48; $P=.62$) in the modified ITT population and 1.03 (90% CI, 0.75-1.42; $P=.87$) in the per-protocol population (eFigure 5). The groups did not differ significantly for duration of invasive mechanical ventilation, ICU stay length, hospital stay length, day-28 mortality, or day-90 mortality (Table 2).

COMMENT

This multicenter, randomized, controlled, noninferiority trial shows that absence of residual gastric volume monitoring in patients receiving invasive mechanical ventilation and early enteral nutrition is not inferior to residual gastric volume monitoring in terms of VAP prevention. Despite a higher vomiting rate without residual gastric volume monitoring, prokinetic drug use was lower and the proportion of patients achieving calorie targets higher in this group. Absence of residual gastric volume monitoring was not inferior to residual gastric volume monitoring regarding new infections, ICU and hospital stay lengths, organ failure scores, or mortality rates.

Figure 2. Development of Ventilator-Associated Pneumonia in the Groups With (Control) and Without (Intervention) Residual Gastric Volume Measurement



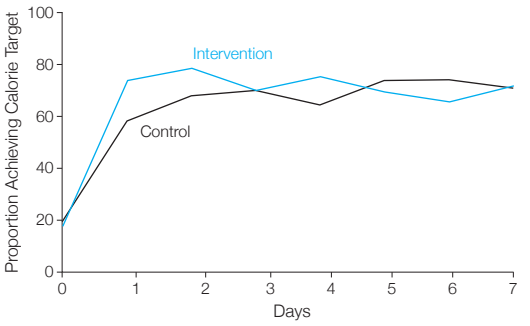
Cumulative incidence of ventilator-associated pneumonia (VAP) in both groups in the modified intention-to-treat analysis. For the analysis of time from randomization to VAP, death was handled as a competing risk. Results were similar in the per-protocol analysis.

Table 2. Secondary Outcomes

	Analysis of Gastric Volume Monitoring by Study Group					
	Modified ITT			Per Protocol		
	Intervention (n = 227)	Control (n = 222)	% or Median Difference (90% CI)	Intervention (n = 208)	Control (n = 215)	% or Median Difference (90% CI)
Vomiting, No. (%)	90 (39.6)	60 (27.0)	12.6 (5.4-19.9)[a]	87 (41.8)	57 (26.5)	15.3 (7.8-22.8)[a]
Intolerance to enteral nutrition, No. (%)[b]	90 (39.6)	141 (63.5)		87 (41.8)	138 (64.2)	
Erythromycin as prokinetic treatment, No. (%)	89 (39.2)	139 (62.6)	−23.4 (−31.0 to −15.9)[a]	85 (40.9)	137 (63.7)	−22.9 (−30.6 to −15.1)[a]
Other prokinetic treatment, No. (%)	5 (2.2)	6 (2.7)	−0.5 (−2.9 to 1.9)[a]	4 (1.9)	6 (2.8)	−0.9 (−3.3 to 1.6)[a]
Cumulative calorie deficit from day 0 to day 7, median (IQR), kcal[c]	319 (93-1012)	509 (185-1252)	−111 (−198 to −36)[d]	314 (89-996)	518 (177-1257)	−119 (−210 to −42)[d]
Diarrhea, No. (%)	51 (22.5)	51 (23.0)	−0.5 (−7.0 to 6.0)[a]	49 (23.6)	50 (23.3)	0.3 (−6.5 to 7.1)[a]
ICU-acquired infection, No. (%)[e]	60 (26.4)	60 (27.0)	−0.6 (−7.5 to 6.3)[a]	58 (27.9)	58 (27.0)	0.9 (−6.2 to 8.0)[a]
Duration of mechanical ventilation, median (IQR), d	7 (4-13)	7 (5-13)	0 (−1 to 0)[d]	7 (4-14)	7 (5-13)	0 (−1 to 0)[d]
ICU length of stay, median (IQR), d	10 (6-17)	10 (7-17)	−1 (−2 to 0)[d]	10 (6-17)	10 (7-17)	0 (−1 to 1)[d]
Hospital length of stay, median (IQR), d	17 (9-31)	19 (10-32)	−1 (−3 to 1)[d]	18 (10-31)	19 (10-33)	−1 (−3 to 2)[d]
Mortality						
Day 28, No. (%)	63 (27.8)	61 (27.5)	0.3 (−6.7 to 7.2)[a]	53 (25.5)	58 (27.0)	−1.5 (−8.5 to 5.5)[a]
Day 90, No. (%)	82 (36.3)	76 (34.2)	2.1 (−5.4 to 9.5)[a]	53 (25.5)	72 (33.5)	1.3 (−6.3 to 8.9)[a]

Abbreviations: ICU, intensive care unit; IQR, interquartile range; ITT, intention-to-treat.
[a] Data are reported as percentage difference (90% CI).
[b] In the intervention group, intolerance to enteral nutrition was defined as vomiting (no monitoring of residual gastric volume) and in the control group (group with monitoring of residual gastric volume) as vomiting and/or a residual gastric volume greater than 250 mL.
[c] Cumulative calorie deficit from day 0 to day 7 was the sum of the differences between calories required and the calories received by the patient each day from day 0 to day 7.
[d] Data are reported as Median difference (90% CI).
[e] ICU-acquired infections included ventilator-associated pneumonia, bacteremia, urinary tract infections, catheter-related infections, and other infections.

Figure 3. Proportions of Patients Who Achieved Their Calorie Target During the First Week in the Groups With (Control) and Without (Intervention) Residual Gastric Volume Monitoring



No. of patients								
Intervention	227	222	206	184	153	141	119	103
Control	222	220	212	193	166	142	132	113

The data are those in the modified intention-to-treat analysis. The per-protocol analysis produced similar results.

Several reasons may explain these results, which are consistent with findings from a single-center study conducted previously by our group.[20] First, residual gastric volume measurement is not standardized or validated. Although residual gastric volume monitoring was more accurate than physical examination and radiography for detecting gastrointestinal intolerance to enteral nutrition,[13] the accuracy of gastric aspiration for residual gastric volume measurement may vary according to tube position and diameter, number of tube openings, level of aspiration in the stomach, and experience of the evaluator.[15,27,28] Measurement by refractometry or gastric content labeling is not feasible in everyday practice.[29-32]

Second, no residual gastric volume cutoff value associated with significantly increased risks of vomiting or VAP has been identified. We used a 250-mL cutoff to define enteral nutrition intolerance in the control group, in keeping with current guidelines.[3] However, in previous studies, residual gastric volume values lower than 250 mL were not associated with decreased complication rates[33,34] and values as high as 500 mL were not associated with increased VAP rates.[35] Moreover, residual gastric volume values failed to correlate with regurgitation or aspiration rates.[17]

Third, the role for the gastropulmonary route in VAP development has been challenged by many studies.[18,19,36-38] VAP is chiefly ascribable to leakage around the endotracheal tube cuff of subglottic secretions containing pathogenic microorganisms. The role for the stomach as a reservoir of VAP-causing microorganisms is controversial.[16,18] In theory, gastric overdistension due to gastroparesis may lead to regurgitation and aspiration. However, there is no evidence of a sequence leading over time from gastric colonization to VAP.[39] Data suggesting that the 45° semirecumbent position may decrease the risk of regurgitation and VAP have been challenged by recent studies.[40-42] Studies involving bacterial DNA analysis strongly suggested that VAP was caused by oropharyngeal bacteria.[43] Oral antiseptic use was effective in preventing VAP,[44] whereas sucralfate therapy to modulate the gastric flora by lowering the intragastric pH failed to influence VAP rates.[45,46] Continuous enteral nutrition may modify the gastric bacterial flora by raising the intragastric pH, but intermittent enteral nutrition delivery in an attempt to restore intragastric acidity failed to affect gastric or oropharyngeal colonization rates or VAP rates.[47,48] Interestingly, our group without residual gastric volume monitoring had a higher vomiting rate but no change in the VAP rate compared with the group with residual gastric volume monitoring. This finding constitutes an additional argument against a major role for the gastropulmonary route in the pathogenesis of VAP.

The main limitation of this study is that blinding of group assignment to clinicians and patients was not feasible. Therefore, we cannot completely exclude a change in nurse behavior related to knowledge of group assignment. Nurses may have responded to absence of residual gastric volume monitoring by overreporting vomiting and subsequently reducing enteral nutrition delivery. A strong argument against this hypothesis is the larger volume of enteral nutrition solution delivered in the group without residual gastric volume monitoring. This result suggests that the unblinded design had little or no effect on reported vomiting rates. Moreover, our use of end point adjudication by an independent blinded committee working with all available clinical, radiological, and bacteriological data probably substantially limited any influence of the unblinded design on VAP rates. Another limitation may be the predefined 10% noninferiority margin. Although determined according to previous guidelines and reviews, this margin may be considered large.[22,23] However, the absolute between-group difference was less than 1% with an upper confidence bound of only 7%.

Strengths of our study include the multicenter randomized controlled design, large sample size, and reporting of results in accordance with CONSORT guidelines for noninferiority trials.[23,49] This study was conducted in medical and surgical mechanically ventilated patients admitted to university and nonuniversity hospitals. Our study patients had SAPS II (Simplified Acute Physiology Score) and SOFA scores indicating severe acute illness. The beneficial effect of early enteral nutrition on survival may be most marked in the most severely ill patients.[50] Rates of vomiting during early enteral nutrition were consistent with

previous studies of enteral nutrition intolerance[4,6,8,20,51,52] and the 16.3% VAP rate was very similar to rates in previous studies of VAP.[44,53,54] Moreover, the results for all our end points are coherent. Thus, absence of residual gastric volume monitoring was not inferior to residual gastric volume monitoring in terms of SOFA score changes, ICU-acquired infections, mechanical ventilation duration, stay length, or mortality. All these findings support the generalizability of our results to all patients treated with mechanical ventilation and early enteral nutrition.

Eliminating residual gastric volume monitoring from standard care may have beneficial effects. First, in the present study, absence of residual gastric volume monitoring was associated with improved enteral nutrition delivery. High residual gastric volume values often lead to enteral nutrition discontinuation, which in turn causes underfeeding with increases in morbidity and mortality rates.[21,55] We found no difference in mortality rates. However, our enteral nutrition protocol was more aggressive than previously reported protocols[2,3]: enteral nutrition was started at the rate required to meet the calorie target and was stopped gradually in the event of intolerance.[56] Moreover, enteral nutrition solution lost by vomiting, being discarded, or both was not measured, thus resulting in potential overestimation of delivered calories. These factors may have attenuated any mortality difference related to differences in delivered enteral nutrition volume. Additionally, recent data challenge the influence on mortality of lower calorie delivery during initial trophic enteral nutrition instead of full-energy enteral nutrition in mechanically ventilated patients with acute respiratory failure.[57] Second, VAP pathogenesis involves several mechanisms, and preventive care bundles have been designed.[36,58] Compliance and efficacy are best when all interventions in the care bundle have documented beneficial effects, ie, when none of the interventions results in an unjustified increase in the nurse workload.[58] Residual gastric volume monitoring requires repeated gastric content aspiration and measurement and therefore adds to the nurse workload. Removing residual gastric volume monitoring from care bundles would allow an increased focus on interventions proven to decrease the VAP risk.[36]

In conclusion, the current study supports the hypothesis that a protocol of enteral nutrition management without residual gastric volume monitoring is not inferior to a similar protocol including residual gastric volume monitoring in terms of protection against VAP. Residual gastric volume monitoring leads to unnecessary interruptions of enteral nutrition delivery with subsequent inadequate feeding and should be removed from the standard care of critically ill patients receiving invasive mechanical ventilation and early enteral nutrition.

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Obtained funding: Reignier.
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Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflict of Interest and none were reported.
Funding/Support: The Centre Hospitalier Departemental de la Vendee was the study sponsor.
Role of the Sponsor: The study sponsor took full administrative responsibility but had no role in the recruitment of patients; in the management, analysis, or interpretation of the data; or in the preparation, review, or approval of the manuscript.
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Online-Only Material: eMethods, eTables 1 through 5, and eFigures 1 through 5, and eReferences are available at http://www.jama.com.
Additional Contributions: We thank A. Wolfe, MD, for assistance in preparing and reviewing the manuscript. We thank B. Giraudeau, PhD, INSERM CIC 0202, Tours, France; and J. Dimet, PharmD, Clinical Research Unit, and J. C. Lacherade, MD, Medical-Intensive Care Unit, District Hospital Center, La Roche-sur-Yon, France, for their helpful comments during the preparation of the study and the writing of the manuscript. We are grateful to all medical staff, staff nurses, and research nurses in the 9 sites, who strongly contributed to the success of the study. A. Wolfe was compensated in association with work completed for this article. The other individuals mentioned in this acknowledgement were not compensated. An institutional affiliation is not applicable for A. Wolfe.

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