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Full Force Enteral Nutrition: A New Hope, or the Dark Side? A Critical Look at Enhanced Enteral Feeding Protocols



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Enteral nutrition (EN) is the preferred method of providing nutrition support to critically ill patients, but EN is often interrupted and, as a result, many patients receive less than full nutrition. Multifaceted strategies for increasing the delivery of EN have been developed, including compensatory increased feeding rates after interruptions (volume-based feeding). Enhanced EN protocols, including volume-based feeding (VBF), have been highly promoted, but evidence suggests that some “enhanced” EN protocols may be harmful to some critically ill adult patients and should be avoided. Although observational studies have reported an association between delayed provision of goal nutrition and compromised patient outcomes, interventional studies have reported more compromised outcomes than benefits from early goal nutrition and VBF in critically ill adult patients. There is a need for additional research before enhanced enteral feeding protocols and VBF are routinely adopted in clinical practice.

Background

A number of observational studies of adult critically ill patients have reported an association between decreased EN provision and compromised patient outcomes.¹⁻³ The association between decreased EN provision and compromised ICU outcomes is not a recent finding, since this relationship has been described since the early 1980's.⁴ Furthermore, observational studies have suggested that the initial days of critical illness are particularly important for providing adequate nutrition. A failure to provide a threshold level of

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nutrition within the early portion of an adult ICU stay was reported to be associated with increased infectious complications.¹

Clinical nutrition and other medical professionals are trained that associations noted in observational studies should never be used to infer causality, nor should the results of observational studies alone be used to suggest practice changes.^{5,6} However, nutrition support professionals also have an intimate understanding regarding the hypermetabolism and accelerated catabolism that occurs during critical illness or injury, as well as the negative consequences of malnutrition. Witnessing the negative clinical sequela caused by severe malnutrition in hospitalized patients

often leaves an indelible impression on clinicians. Undoubtedly, for many clinicians, the observational studies documenting associations between nutrition provision and patient outcomes appeared to confirm what their training and experience had suggested about nutritional adequacy in the ICU.

Enteral Nutrition Comes of Age

Studies have consistently documented that many critically ill patients receive only a portion of the amount of EN that is ordered.⁷⁻⁹ EN is frequently and often repeatedly interrupted for essential diagnostic and therapeutic interventions, real and perceived feeding intolerance, routine bedside care, enteral access device occlusion or displacement, and a myriad of other feeding disruptions in the ICU.⁷⁻⁹ Over the past three decades, increased experience and research with EN has gradually contributed to more effective nutrition provision at many facilities. We have learned that initial feedings do not need to be diluted or initiated at low rates, then gradually advanced over several days, and that physiologic volumes of feeding and secretions in the stomach (gastric residuals) may not be a reason to stop EN.¹⁰ However, studies continue to document that EN is often incompletely delivered.^{9,11}

Although some professionals have recommended early supplemental parenteral nutrition (PN) to avoid nutrition deficits, concerns regarding the increased cost and infectious complications related to PN have spurred the development of methods to improve EN delivery.¹²⁻¹⁴

Full Force Enteral Nutrition

In order to avoid delayed delivery of full nutrition goals, a number of enhanced EN protocols have been developed to permit more timely and complete nutrition.^{11,15-24} One strategy that has been proposed to allow increased EN delivery is volume based feeding (VBF). The strategy of VBF is centered on using a compensatory increase in feeding rate upon restarting a feeding after any EN interruption, so that the daily goal volume is more consistently delivered. VBF has often been studied as part of a multi-faceted enhanced EN protocol and each study has included some, but not all of the following components: education programs for physicians and/or nursing, daily monitoring of amounts of

nutrition delivery, early initiation of EN, starting EN at goal flow rate, reducing time without nutrition prior to operative procedures, starting EN with an increased calorie goal, routine use of prokinetics, supplemental protein, use of calorie-dense formulas and/or the use of a semi-elemental feeding formula (See Table 1).^{11,15-24} Different studies have utilized various components of these enhanced feeding protocols in addition to different VBF procedures and maximum allowed feeding rates.^{11,15-24} The 2016 ASPEN/SCCM guidelines for adult critically ill patients endorses the use of volume-based, multi-strategy enhanced enteral feeding protocols.²⁵

It's a Trap

Research has documented that enhanced EN protocols can often increase nutrition delivery and reduce the delay for reaching nutrition goals in the ICU.^{11,15-24} However, the real concern is whether increasing the delivery of EN in the ICU actually confers beneficial effects on patient outcomes. In contrast to the associations identified in observation studies, the weight of evidence from randomized studies in the past 8 years is that modest calorie deficits within the first week of critical illness have no negative effects on clinical outcomes.²⁶⁻²⁹ It is perhaps not surprising then, to find out that most studies of enhanced feeding protocols reported no improvement in patient outcome, despite significantly improving the timeliness and completeness of EN delivery.^{11, 15-22} Even more concerning is that several investigations of “enhanced” enteral feeding protocols have reported a dark side, in the form of negative outcomes, including increased mortality in some studies in the group receiving increased EN delivery.¹⁵⁻¹⁸ A closer look at the methods and limitations of the key studies should be helpful for clinicians deciding on EN feeding protocols for their facility.

Intensive EN and Patient Harm?

One study that has increased attention to the potential harm from enhanced EN protocols was a single-center, randomized study of 78 patients from medical or surgical ICUs with acute lung injury.¹⁵ The intensive nutrition group received feeding tubes and started EN sooner, used continuous

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feeding (no bolus or cyclic feeds), EN infusions were monitored daily, rates were increased after feeding interruptions occurred (VBF), and the amount of nutrition received was recorded. Following extubation, the intensive nutrition group had oral intake initiated as soon as safe swallowing function returned.¹⁵

The intensive EN group received significantly greater kcal/kg/d compared to the standard EN group (mean 25.4 kcal/kg vs. 16.6 kcal/kg, respectively).¹⁵ However, the data safety monitoring board stopped the study early when it was revealed that significantly more deaths occurred in the intensive EN group compared with the standard group (40% intensive EN vs. 16% standard EN).¹³ There were no significant differences between the groups in other outcomes (hospital or ICU stay, duration of mechanical ventilation, number of infections).¹⁵

Due to the fact that this study was terminated early (with less than the full number of participants enrolled), it is possible that this statistically significant difference in mortality occurred from chance alone.¹⁵ However, several other studies of enhanced EN have reported negative outcomes, most without any significant improvement in patient outcomes.¹⁶⁻²⁴

Another study that has reported only a negative outcome with enhanced EN was a before-after cohort study of 49 medical ICU patients.¹⁶ The intensive EN group received a calorie-dense feeding, and feeding rates were increased to 150% of goal to compensate for EN interruptions.¹⁶ The intensive EN group received significantly increased mean calorie provision compared to the standard group (1198 vs. 474 kcals, respectively). Although baseline characteristics were similar (including APACHE II score) between the 2 groups, the intensive EN group had a significantly increased ICU length of stay, compared to the standard group (13.5 vs. 8.0 days).¹⁶

One before-after cohort study in 110 surgical-trauma ICU patients reported a trend towards negative outcomes, without improvement in outcomes.¹⁷ The intensive EN protocol utilized VBF, a 350mL threshold for gastric residuals, plus an educational program for ICU caregivers.¹⁷ This study was notable for delaying the start of

the VBF portion of the protocol until patients had established tolerance to the initial goal rate of EN. The intensive EN group received a significantly increased percentage of goal calories, compared to the standard group (89% vs. 63%, respectively). Not only was no outcome improved from the increased calories, there was actually a trend towards a longer ICU length of stay compared to the standard group (15.0 days vs. 12.2 days, respectively).¹⁷ When the patients who died were excluded, the strength of this trend was decreased, but still persisted ($P = 0.09$). The incidence of diarrhea was significantly increased in the intensive EN group, compared to the standard group.¹⁷

Intensive EN: No Benefit, No Harm

Two studies have reported neither harm, nor outcome benefits from an intensive EN protocol.¹⁹⁻²⁰ One was a before-after cohort study of 77 mixed ICU patients.¹⁹ Patients in the intensive EN group received a significantly greater percentage of prescribed calories than those in the standard group (74% vs. 57%, respectively). On the initial analysis, patients in the intensive EN group had a significantly longer length of ICU stay (14 vs. 9 days), as well as days on the ventilator (9 vs. 7). However, patients in the intensive EN group had a greater APACHE II score, and after controlling for the admission APACHE II score, the differences in clinical outcomes were not statistically significant.¹⁹

The second study with neither harm nor benefits was a larger multi-center cohort study where the different facilities were randomized to implement either the intensive EN protocol, or continue with standard care ("cluster randomized").²⁰ This study was one of the larger studies to date with over 1059 patients initially enrolled, but only 252 received the enhanced EN protocol.²⁰ This larger study utilized VBF (PEP uP protocol), initiated EN at goal flow rate, used a peptide-based EN formula for initial feedings, used a prokinetic agent, increased the gastric residual threshold (300mL) and encouraged trophic feeding for patients initially deemed unsuitable for full feeding. Perhaps reflecting the difficulties in implementing a new protocol in diverse hospitals, compliance was not 100%, and as a result only 1/3 of the intervention group had EN started at goal rate, with ultimately only a 12% increase in calorie delivery in the PEP uP protocol

Table 1. Enhanced EN Study Protocols

Author/Year	Standard Formula	Study Formula	Kcal Goal	Protein Goal	Compensatory Feed Rate	Prokinetics	Protein Supplements	Other Enhanced Protocol	Other
Lee 2017	Varied	Varied	25-30/kg actual wt (ideal if obese)	1.5-2.0 gm/kg actual wt (ideal if obese)	150mL/hr max	As needed (gastric residual > 500mL)	No	Shorter pre-procedure npo, surgical tubes	Education program, VBF held if glucose > 200 mg/dl
Sheean 2012	Per RD Assessment	2 kcal/mL	30 kcal/kg actual wt (adjusted if obese)	1.2g/kg actual wt (ideal if obese)	No	Not reported	No	Feed rate to provide 150% of goal	Feed volume ↓ if > 100% goal received
Taylor 1999	Not reported	Not reported	Schofield equation X 1.4	1.5 gm/kg	No	No	No	Goal rate feeding, increased gastric residual threshold	34% NJ tubes
Taylor 2014	Varied	Varied	BMI based: 35-40/kg for BMI < 15, 30-35/kg for BMI 15-19, 20-25/kg for BMI 20-29 and 15-20/kg for BMI > 30	1.0-1.5 gm/kg ideal wt, (1.7-2.0/kg IBW if obese)	120mL/hr max	No	No	Education program, 350mL gastric residual	VBF implemented after goal feeding reached
Haskins 2017	Per RD assessment	Per RD assessment	ASPEN/SCCM 2009 guidelines	ASPEN/SCCM 2009 guidelines	Yes (150mL/hr max)	No	No	MD and RN Education	n/a
Braunschweig 2015	Per RD assessment	Per RD assessment (unchanged)	30 kcal/kg actual wt (adjusted if obese)	1.5g/kg ideal wt (adjusted if obese)	Yes (rate not reported)	Not reported	No	EN within 6 hrs	Feed volume monitored daily
Heyland 2013	Various	Varied Peptide based 1.5 kcal/mL (67.5%)	Not stated (per usual protocol)	Not stated (per usual protocol)	Yes (max rate not stated)	Yes (48.5%)	Yes (31.7%)	250-300mL residual threshold, trophic option	Staff Training
McClave 2015	Not reported	Not reported	Not reported	Not reported	280mL/hr max gastric 150mL/hr max jejunal	No	No	n/a	VBF implemented after goal feeding reached
Declercq 2016	Various	Varied Peptide Based (28%)	Not reported	Not reported	Yes (max rate not stated)	Yes (38%)	Yes (64%)	n/a	n/a
Yeh 2017	Polymeric 1 kcal/mL	Polymeric 1.0 kcal/mL	25 kcal/kg	2 gm/kg	150mL/hr max	No	Yes	Increased protein goal	n/a

group (from 32% of goal at baseline to 44% of goal on the PEP uP protocol).²⁰

Two additional studies of VBF did not report any patient outcomes, only that more EN was received.²¹⁻²² One cohort study of the PEP uP protocol in 57 surgical patients demonstrated no increase in nutrition delivery when compared to surgical patients at sites that did not implement the PEP uP protocol.²¹

A second study of VBF randomized patients to either VBF or standard protocol after they had reached goal EN rate following a slow feeding rate progression over 24 hours.²² In the 57 patients who completed the study, VBF received 92.9% of calorie goals, while the standard group received 80.9%

of calorie goals. Although the authors suggest this study provides evidence that VBF is “safe”, no information regarding patient outcomes were reported, and far too few patients were enrolled to provide reliable safety data.²²

Intensive EN: Reported Benefits (but with fine print)

One study that reported potential benefits of an intensive EN protocol was a before-after cohort study of 239 adult trauma ICU patients.¹⁸ Data was collected only for those patients who required ≥ 7 days of mechanical ventilation and who did not receive parenteral nutrition. The enhanced EN protocol consisted of early start of EN, a physician

education program, intraoperative small bowel tube placement, EN ordering “bundle”, continued EN prior to procedures until patients were called to the OR and a VBF protocol with “catch-up” feeding rate if feedings were held.¹⁸

The intervention group received significantly increased calories during the first 3 days compared to baseline and received 100% of calorie goals after day 3.¹⁸ The cumulative calorie deficit was -1907 kcals in the intervention group and -7240 kcals in the baseline group. The intervention group had significantly decreased incidence of pneumonia (42%) compared to the baseline group (56%). Although pneumonia incidence was decreased, the intervention group had a greater requirement

for mechanical ventilation, with significantly more days on the ventilator at day 28 compared to the baseline group.¹⁸ Although reading the abstract of this study may make it seem in favor of the intensive EN protocol, the exclusion of any data from patients who died before day 7, the high (56%) incidence of baseline pneumonia in the standard group, and the increased need for mechanical ventilation (in the setting of decreased pneumonia) raise concerns that this is not necessarily data in favor of the intensive EN protocol.¹⁸

Another study reporting positive outcomes was a before-after cohort study of 213 adult surgical ICU patients.²³ The intensive EN group

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focused primarily on increasing protein delivery by increasing the standard initial protein goal from a baseline of 1.5 gm/kg to 2 gm/kg to be achieved with protein supplements. Calorie goals were unchanged from baseline, and although VBF was encouraged, it was not strictly implemented in the intervention group.

The intervention group received significantly more calories/kg (18.6 kcal/kg/d vs. 16.5 kcal/kg/d) and protein/kg (1.2 g/kg/d vs. 0.8 g/kg/d) compared to the standard group.²³ The ICU length of stay (LOS) and hospital LOS were both significantly shorter in the intervention group (10 vs. 15 days, and 20 vs. 29 days, respectively). In the intervention group, there was a trend toward fewer late infections (mean 0.7 vs. 0.9, respectively).²¹ A regression analysis that adjusted for age, sex, BMI, APACHE II score, and GI surgery demonstrated that the aggressive EN protocol was associated with a significantly lower risk of late infection.²³ Of note, thirty-day mortality was significantly

increased in the intervention group compared to the control group (13.6% intervention vs. 7.4% control, respectively), but hospital mortality was not significantly different between the groups.²³ This was primarily a study of increased protein delivery, with a clinically trivial difference in calorie provision between groups, and even the intensive EN group received hypocaloric feeding due to incomplete compliance with the VBF protocol.²³

One of the studies used as evidence for positive outcomes from enhanced enteral feeding protocols was an unblinded, randomized investigation of 82 patients with severe head injury who required mechanical ventilation.²⁴ This study was one of the 2 studies cited in the ASPEN/SCCM guideline endorsing volume-based, multi-strategy enhanced enteral feeding protocols.²⁴ The control patients' EN was started at a very slow rate of 15mL/hr, with a very conservative feeding advancement schedule.²⁴ The rate of control feedings could be doubled every 8 hours, but the rate was only

increased if gastric residual measurement was < 50mL X 2 consecutive measurements, and the feeding rate was reduced by 50% if a single gastric residual volume was ≥ 150mL. The intervention group received nasointestinal feeding when the tube could be successfully advanced (34% of group), or an NG tube when it could not.²⁴ The intervention group had EN started at the goal flow rate; the feeding rate for the NG-fed portion of the intervention group was not decreased unless gastric residuals exceeded 200mL. Considering the very conservative feeding regimen used in the control group, it is not surprising that median calorie and protein delivery were less than 50% of goal even by day 7 of the study.²⁴ The intervention group received significantly greater calories and protein throughout the first week of the study, compared to the control group. Mean energy delivery in the control group was 36.8% of goal, compared to 59.2% of goal in the intervention group.²⁴ The intervention group had significantly less infections compared to the standard group (61% vs. 85%,

respectively) and significantly less total other complications (37% vs. 61%, respectively).²⁴ There was also a trend for improved neurologic complications at 3 months in the intervention group, but no difference at 6 months. However, when the results were analyzed by disease severity, there were no statistically significant improvements in patient outcome, but there was still a trend towards improved neurologic outcome at 3 months. When the methods of this study are compared to other enhanced enteral protocols it is important to note that the intervention group did not actually receive VBF, but rather hypocaloric nutrition that was gradually increased over several days to a maximum of just over 70% of goal calories by day 5-6.²⁴

Discussion and Clinical Implications

There are inadequate randomized data to provide strong evidence for how much nutrition should be provided in the early stage of critical illness for optimized patient outcome. The randomized

Table 2. Enhanced EN Study Details and Outcomes

Author	Study Design	Number Analyzed	Population	Volume Based	Avg BMI	Calorie Difference (% goal, enhanced vs std)	Protein Provided	Positive Outcomes	Negative Outcomes
Lee 2017	Before-after cohort	239	Trauma	Yes	26.5	94% vs 75%	104% vs 74%	Decreased Pneumonia	Decreased 28-day ventilator free days
Sheean 2012	Before-after cohorts	49	MICU	No	29.2	60% vs 25%	65% goal vs 39% goal	None	ICU LOS increased
Taylor 1999	Randomized	82	Head Injury	No	N/R	59.2% vs 36.8%	Not Reported	Trend towards improved 3 month neurologic outcome	None reported
Taylor 2014	Before-after cohorts	110	Surgical/Trauma ICU	Yes	29.7	89% vs 63%	1.26 gm/kg vs 1.13 gm/kg	None	Increased diarrhea, trend for increased LOS
Haskins 2017	Before-after cohorts	77	MICU/SICU	Yes	27	74% vs 57%	Not Reported	None	None (after adjustment for APACHEII)
Braunschweig 2015	Randomized	78	Acute Lung Injury	Yes	29.9	84.7% vs 55.4%	76.1% vs 54.4%	None	Mortality increased
Heyland 2013	Cluster randomized	519 (for outcomes)	Mixed Adult ICU	Yes	29	44% vs 32%	47% vs 34%	None	None
McClave 2015	Randomized	57	Medical ICU	Yes	30	92.9 % vs 80.9%	Not reported	Not Reported	Not Reported
Declercq 2016	Cohort	57 Enhanced EN; 1413 Standard	Surgical ICU	Yes	N/R	Not significantly different	Not significantly different	Not reported	Not reported
Yeh 2017	Before-after cohorts	110	Surgery-Trauma	Yes (not enforced)	27.4	77% vs 68%	92% vs 64%	Decreased ICU & hospital LOS	Increased 30-day mortality

studies that are available suggest that the data from observational studies is misleading.²⁶⁻²⁹ The topic of early nutrition adequacy in the medical ICU has been highlighted as one of the notable occasions where data from observational data has led to clinical recommendations demonstrated to be incorrect by randomized data.³⁰ It would seem reasonable that we should first know the proper timing and amount of nutrition to provide to critically ill patients for best outcome, before expending time and energy implementing protocols aimed at maximizing early nutrition delivery.

One of the problems faced when attempting to evaluate the studies of enhanced enteral feeding in critically ill patients is that all of the investigations enrolled a relatively small number of patients.^{11,15-24} These studies all lack statistical power to have confidence that any significant outcome difference between groups did not occur by chance alone.^{11,15-24} The varied populations as well as different methods used to enhance enteral delivery in the various studies do not lend this data to allow a scientifically valid meta-analysis; even if all of the studies were combined, it is likely that there are too few patients studied to allow adequate analysis of outcomes such as mortality in a mixed medical, surgical, and trauma ICU population.

However, what is striking is that those studies that were successful in increasing early calorie delivery, not only reported no improvement in patient outcome, but some may have actually caused net harm.^{15,16} Considering that the intensive EN groups also had other interventions such as nurse or MD education programs and daily monitoring of nutrition delivery, it would be reasonable to expect improved outcomes from staff education and close monitoring alone. The single study that actually provided full calories (Intensive EN group received 25.4 kcals/kg) had to be stopped for patient safety due to increased mortality.¹⁵ The studies that reported no harm, or some improved outcomes, generally were slower to meet calorie goals, had less compliance with VBF (or no VBF), and generally provided hypocaloric feeding to most patients, even in the “intensive EN” group.^{23,24} While it is quite possible that meeting full calorie expenditure in the earliest stages of critical illness itself may have detrimental effects, it is also possible that the negative effects reported in VBF

studies are related to the method for increasing calorie delivery.

One topic that has not received adequate attention is the potential effect of VBF on glucose variability. Increased variability of serum glucose is associated with compromised outcomes in the ICU, and has been reported to potentially be more important to good ICU outcomes than the absolute glucose values.³¹ We know that providing full calories increases insulin requirements in critically ill patients, compared to hypocaloric feeding.²⁷ No study has provided data about glucose variability during VBF, but accelerating feeding rates immediately after feeding is held, especially while providing full calories may be a risk for increased glucose variability.³² Glucose variability with VBF is potentially more likely, now that many facilities have abandoned insulin infusion protocols with hourly serum glucose checks in favor of basal-bolus protocols with less frequent glucose monitoring.

It is possible that full calories, or even VBF, may be helpful for some patients, but detrimental to others. The average BMI for the studies of intensive EN (see Table 2) demonstrates that, on average, the patients in these studies were overweight, and a number were likely obese. Obese patients appear to benefit from hypocaloric, full protein feedings, even while critically ill.³³ Obese patients in the intensive EN groups of some studies would have exceeded the recommended calorie goals for obese critically ill patients.²⁵

It is also possible that very malnourished patients who receive early full calories may experience detrimental effects. One study has demonstrated that failure to decrease calorie provision in patients who are experiencing refeeding hypophosphatemia may increase mortality.³⁴ However, after refeeding syndrome has resolved, it is possible that patients with more severe malnutrition may benefit from efforts to improve nutrition delivery. Those patients with decreased BMI and minimal fat stores, patients who require extended ICU stays, or those who require repeated surgical interventions may benefit from efforts to minimize accumulated nutritional deficits. The initial days of critical illness, with unavoidable catabolism and increased insulin resistance may also be the wrong time to enforce

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full calorie provision. It is possible that enhanced EN protocols may have benefits once the initial phase of critical illness has subsided, and patients are capable of recovering from catabolism and regaining lean muscle mass.

More recently, additional associations from observational studies have been used to suggest that nutritional adequacy is critical only for those more severely ill patients (increased NUTRIC score).³⁵ It is important to remember that the NUTRIC score is based on data only from observational studies. Analysis of data from patients randomized to receive reduced-calorie feeding has demonstrated that the NUTRIC score is not a valid indicator of patients who benefit from full calorie nutrition support.³⁶

CONCLUSIONS

There is insufficient evidence to support intensive EN protocols in the early portion of critical illness in adult patients. Furthermore, VBF that meets full calorie expenditure within the first several days of critical illness may have negative effects and may even increase mortality in some populations. The best available data from randomized studies of hypocaloric feeding have demonstrated that the associations described from observational studies are not cause and effect: a modest calorie deficit in the early portion of critical illness does not compromise patient outcome, even in those patients with an increased NUTRIC score. Early VBF that meets calorie goals may be detrimental for some critically ill adult patients, and in the absence of data showing clear benefit, intensive, early VBF EN protocols should be avoided in routine use, especially in patients above their ideal weight. Additional research is required to see if a more gradual increase in calories with a focus on nutrition adequacy after the most critical stress has passed, or a focus on protein adequacy may have outcome benefits. There is a need for studies that focus efforts to increase nutrition provision in patients that are underweight, malnourished and have extended ICU admissions. ■

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POSITION AVAILABLE

Johns Hopkins University School of Medicine, Division of Gastroenterology is looking for a gastroenterology hospitalist with experience in ERCP, EUS, and enteroscopy. Applicants should have at least five years of post fellowship experience in gastroenterology and have completed a two year advanced interventional endoscopy fellowship. Experience in motility and fluency in Spanish helpful.

For further information please contact:

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