Sedation for awake fiberoptic intubation in the adult critical care unit

To the Editor:

We recently read the excellent review of the difficult airway in the adult critical care unit by Lavery and McCloskey (1). Awake fiberoptic intubation, as the authors of this review article describe, is an important technique to be considered early in the management of a potentially difficult airway. One of the most serious limitations of this technique, however, is the necessity to provide adequate sedation and anxiolysis to facilitate the procedure, while minimizing the deleterious effects that sedative agents may have on the sensorium, the respiratory system, the protective airway reflexes, and the hemodynamic status of the patient. To this end, we believe that dexmedetomidine (Hospira, Lake Forest, IL) should be considered for sedation in this setting as it may provide appropriate levels of sedation and hemodynamic stability during awake fiberoptic intubation in the critical care unit.[1]

The use of dexmedetomidine for sedation during awake fiberoptic intubation has recently been reported in several case series in an operating room environment that can, perhaps, serve as a template for its application to the critical care unit (2–10). Dexmedetomidine, a short-acting, highly selective α_2-agonist already approved for short-term sedation of intubated patients in the intensive care unit, has both sedative and analgesic effects. Patients sedated with dexmedetomidine maintain a normal respiratory pattern without significant ventilatory depression and a relatively normal respiratory response to blood carbon dioxide tension (11, 12). In addition, in patients with unstable cervical spine injuries, those sedated with dexmedetomidine may be capable of undergoing serial neurologic examination immediately after placement of the endotracheal tube (8). The typical administration of dexmedetomidine in these reports was an initial bolus of 0.7–1.0 μg/kg given for more than 10 minutes followed by a continuous infusion of 0.5–1.0 $\mu g \cdot kg^{-1} \cdot hr^{-1}$, titrated to an appropriate level of sedation. Most patients also required topical anesthesia of the oropharyngeal or nasopharyngeal mucosa during this technique, although there are reports of awake fiberoptic intubation with dexmedetomidine alone (3, 4). Of note, dexmedetomidine should be administered with caution in patients with high-degree heart block, significant intravascular volume depletion, or vasoconstriction because dexmedetomidine can cause bradycardia and hypotension.

Awake fiberoptic intubation is, indeed, a very useful tool in the management of the difficult airway in the critical care unit if patients are given appropriate sedation such that they remain cooperative. The use of dexmedetomidine for sedation in this scenario may provide acceptable intubating conditions with few negative consequences.

Supported, in part, by Department of Anesthesiology, University of Kentucky College of Medicine, Lexington, KY.

The authors have not disclosed any potential conflicts of interest.

Matthew J. Swan, MD, Kevin W. Hatton, MD, Department of Anesthesiology, University of Kentucky College of Medicine, Lexington, KY

REFERENCES

1. Lavery GG, McCloskey BV: The difficult airway in adult critical care. *Crit Care Med* 2008; 36:2163–2173
2. Stamenkovic DM, Hassid M: Innovative uses of dexmedetomidine. *J Clin Anesth* 2007; 19: 644–645
3. Abdelmalak B, Makary L, Hoban J, et al: Dexmedetomidine as sole sedative for awake intubation in management of the critical airway. *J Clin Anesth* 2007; 19:370–373
4. Bergese SD, Khabiri B, Roberts WD, et al: Dexmedetomidine for conscious sedation in difficult awake fiberoptic intubation cases. *J Clin Anesth* 2007; 19:141–144
5. Stamenkovic DM, Hassid M: Dexmedetomidine for fiberoptic intubation of a patient with severe mental retardation and atlantoaxial instability. *Acta Anaesthesiol Scand* 2006; 50:1314–1315
6. Jooste EH, Ohkawa S, Sun LS: Fiberoptic intubation with dexmedetomidine in two children with spinal cord impingements. *Anesth Analg* 2005; 101:1248
7. Maroof M, Khan RM, Jain D, et al: Dexmedetomidine is a useful adjunct for awake intubation. *Can J Anaesth* 2005; 52: 776–777
8. Avitsian R, Lin J, Lotto M, et al: Dexmedetomidine and awake fiberoptic intubation for possible cervical spine myelopathy: A clinical series. *J Neurosurg Anesthesiol* 2005; 17: 97–99
9. Grant SA, Breslin DS, MacLeod DB, et al: Dexmedetomidine infusion for sedation during fiberoptic intubation: A report of three cases. *J Clin Anesth* 2004; 16: 124–126
10. Scher CS, Gitlin MC: Dexmedetomidine and low-dose ketamine provide adequate sedation for awake fiberoptic intubation. *Can J Anaesth* 2003; 50:607–610
11. Ramsay MAE, Luterman DL: Dexmedetomidine as a total intravenous anesthetic agent. *Anesthesiology* 2004; 101:787–790
12. Venn RM, Hell J, Grounds RM: Respiratory effects of dexmedetomidine in the surgical patient requiring intensive care. *Crit Care* 2000; 4: 302–308

DOI: 10.1097/CCM.0b013e3181986e69

The critical airway: The difficult airway in the adult critical care

To the Editor:

We agree with Lavery and McCloskey that "all patients in critical care should initially be viewed as having a potentially difficult airway" (1). The American Society of Anesthesiologists Practice Guidelines for management of the difficult airway (2) is centered on the ability to predict the difficult airway in elective cases. The outside of the operating room (OR) airway, in general, and the critical care airway, in particular, is nonelective. Prediction of "difficulty" is impractical and of dubious value.

Although technical difficulty is the most feared and studied aspect of airway management, it is not the only aspect impacting the progression of events. The outcome of the critical care airway management is the result of many variables not included in difficult airway management algorithms, which can define the urgency of oxygenation.

The outside of the OR airway is inherently difficult and nonelective. Urgency is defined by its indications (shock or hypoxemia), poor physiologic reserve of the patient, and the small margin of safety in the event of the unanticipated difficult airway. In this context, we consider the outside of the OR airway, including the

critical care airway, distinct from the OR airway: the "Critical Airway" (CA) (3).

The CA is a dynamic clinical paradigm defined by the immediate need to oxygenate the critically ill patient. It is an umbrella concept that considers all the variables with potential to impact on oxygenation: the patient (airway "difficulty" and health status), the intubator (skill), the environment (devices and pharmacologic agents available and help), and the time available to oxygenate. To optimally manage the CA, the provider should be skilled in a variety of airway devices and should be able to quickly assess the patient's condition and the surrounding environment (airway devices, suction, help).

The CA is a theoretical and a practical concept. This new paradigm assumes specific training to not only address technical aspects but also increase awareness of the complexities in managing the outside of the OR airway. The current technical approach of "bag valve mask-direct laryngoscopy-laryngeal mask airway" should be broadened to "bag valve mask-supraglottic-glottic-infraglottic" techniques. Any one of these airway management techniques may be used first in an attempt to immediately oxygenate the critically ill. Very promising in the intensive care unit setting are the new indirect laryngoscopes, e.g., the reusable GlideScope (Verathon Inc., Bothell, WA) and the disposable Air traq (King Systems, Noblesville, IN). The argument can be made for their use with the first intubation attempt as these devices are easier to use in difficult intubations than the direct laryngoscopes (4, 5).

Airway management in the intensive care unit is not a single provider technical event. The CA concept can be used to address organizational needs for airway management in the intensive care unit. CA management starts with the design of the patient's bed, the workplace (intensive care unit room), and the airway device such that it will allow an ergonomic approach to the patient's airway in minimal time. It also assumes training of the "helping" staff and continuous effort from the airway provider to improve clinical and technical skills.

Drs. Matioc and Ardnt have received royalties from Cook Inc. Dr. Jofee has not disclosed any potential conflicts of interest.

Adrian A. Matioc, MD, Department of Anesthesiology, University of Wisconsin School of Medicine and Public Health, William S. Middleton Memorial Veterans Hospital, Madison, WI; George Arndt, MD, Department of Anesthesiology, University of Wisconsin School of Medicine and Public Health, Madison, WI; Aaron Jofee, MD, Department of Medicine, University of Wisconsin School of Medicine and Public Health, Madison, WI

REFERENCES

1. Lavery GG, McCloskey BV: The difficult airway in adult critical acre. *Crit Care Med* 2008; 36:2163–2173
2. The American Society of Anesthesiologists Task Force: Practice guidelines for management of the difficult airway. *Anesthesiology* 2003; 98:1267–1277
3. Matioc A, Arndt G: The critical airway [letter]. *Can J Anesth* 2005; 52:993
4. Kim HJ, Chung SP, Park IC, et al: Comparison of the GlideScope video laryngoscope in simulated tracheal intubation scenarios. *Emerg Med J* 2008; 25:279–282
5. Maharaj CH, Costello JF, Harte BH, et al: Evaluation of the Airtraq and the Macintosh laryngoscopes in patients at increased risk for difficult tracheal intubation. *Anaesthesia* 2008; 63:182–188

DOI: 10.1097/CCM.0b013e3181986ec0

Parenteral nutrition in intensive care patients with sepsis: Is it dangerous when indications are complied?

To the Editor:

I read with great interest in the recent issues of *Critical Care Medicine* the articles by the German Competence Network Sepsis (SepNet) describing the current therapy habits and practice in nutritional support in patients with sepsis (1, 2). These surveys follow the recent update of international guidelines published at the beginning of 2008 (3). Insights into the current clinical practice of German intensive care units reveal poor routines among doctors (1) and poor knowledge of the specific indications for the best route to provide nutritional support in this setting (2). But, with particular regard to the former, this is not a unique case as it appears a widespread attitude (4). Along with this, it is probably shocking to observe that in the recent guidelines there was no mention of nutritional screening and support in such patients. Nutritional treatment is now considered an important part of medical therapy, and, at least, in those undernourished, this should be started early (within 12–24 hours). Nevertheless, also those screened at-risk at admission might benefit of this support in view of inadequate intake and stress-induced hypercatabolism (5, 6). Indeed, most of the International Societies (German, European, American, and Canadian) concerned with the nutritional care strongly enforce nutritional screening procedures and agree that enteral nutrition should always be the first choice (6, 7). However, in patients who cannot meet their nutritional requirements via this route, parenteral nutrition may be considered effective in achieving nutrient requirements, and in Europe, the new guidelines by the European Society for Parenteral and Enteral Nutrition are expected for the next year (2009). In regard to this, during the last congress (Florence, Italy; September 2008), the development of global guidelines has been reported "a true partnership" and all the societies are invited to associate with the European Society for Parenteral and Enteral Nutrition as block members. Unfortunately, parenteral nutrition is often looked as a danger to the patient, and the results presented by Elke et al (2) seem to confirm this belief. But, what would be the outcome when only patients with a clear indication to have administered their nutritional therapy by the chosen route were included? Is it possible for the authors to retrieve such data and perform further analyses or at least to provide the agreement between indications? I think that providing these results to the scientific community would help not only to improve current practices and the ongoing guidelines, but also to better understand the real advantages of one route over another in different subgroups of patients, such as those septic, as well as the potential safety and benefits of parenteral nutrition when stringent criteria are considered to guide clinicians choice.

The author has not disclosed any potential conflicts of interest.

Emanuele Cereda, MD, International Center for the Assessment of Nutritional Status, University of Milano, Milano, Italy

REFERENCES

1. Brunkhorst FM, Engel C, Ragaller M, et al; German Sepsis Competence Network (SepNet): Practice and perception—A nationwide survey of therapy habits in sepsis. *Crit Care Med* 2008; 36:2719−2725
2. Elke G, Schädler D, Engel C, et al; German Competence Network Sepsis (SepNet): Current practice in nutritional support and its

association with mortality in septic patients—Results from a national, prospective, multicenter study. *Crit Care Med* 2008; 36:1762–1767
3. Dellinger RP, Levy MM, Carlet JM, et al; International Surviving Sepsis Campaign Guidelines Committee; American Association of Critical-Care Nurses; American College of Chest Physicians; American College of Emergency Physicians; Canadian Critical Care Society; European Society of Clinical Microbiology and Infectious Diseases; European Society of Intensive Care Medicine; European Respiratory Society; International Sepsis Forum; Japanese Association for Acute Medicine; Japanese Society of Intensive Care Medicine; Society of Critical Care Medicine; Society of Hospital Medicine; Surgical Infection Society; World Federation of Societies of Intensive and Critical Care Medicine: Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med* 2008; 36:296–327
4. Bavelaar JW, Otter CD, van Bodegraven AA, et al: Diagnosis and treatment of (disease-related) in-hospital malnutrition: The performance of medical and nursing staff. *Clin Nutr* 2008; 27:431–438
5. Kreymann KG, Berger MM, Deutz NE, et al; DGEM (German Society for Nutritional Medicine); ESPEN (European Society for Parenteral and Enteral Nutrition): ESPEN Guidelines on Enteral Nutrition: Intensive care. *Clin Nutr* 2006; 25:210–223
6. Scurlock C, Mechanick JI: Early nutrition support in the intensive care unit: A US perspective. *Curr Opin Clin Nutr Metab Care* 2008; 11:152–155
7. Kochevar M, Guenter P, Holcombe B, et al; ASPEN Board of Directors and Task Force on Parenteral Nutrition Standardization: ASPEN statement on parenteral nutrition standardization. *JPEN J Parenter Enteral Nutr* 2007; 31:441–448

DOI: 10.1097/CCM.0b013e3181986f32

The authors reply:

We acknowledge Dr. Cereda's combining remarks on the results of our recent studies (1, 2) from the German SepNet in the context of the observed gap of clinical practice and current or upcoming guidelines in nutrition therapy in critically ill and septic patients, respectively (3, 4).

The author raises the interesting question whether parenteral nutrition remains "dangerous" in septic patients when the prescribed route of nutrition therapy would have complied with the patients' indication. In other words, would we have observed different results with regard to the association of parenteral nutrition and increased mortality when patients only with clear contraindications to the initiation of enteral nutrition had received total parenteral nutrition?

From the true methodologic point of view, we are unable to retrieve the requested information and provide possible agreement between indications and prescription as stipulated by Dr. Cereda because clear indications to parenteral or respective absolute contraindications to enteral nutrition were not documented in this observational, 1-day point prevalence study. However, irrespective of this methodologic limitation, we think that an answer to this question is already given by our article.

To recapitulate our results, we attempted to bypass the limitation of our study design by identifying clinical diagnoses suspected to influence the route of nutritional therapy: 1) gastrointestinal or intra-abdominal infection, 2) acute pancreatitis, or 3) neoplasm of the upper or lower gastrointestinal tract. These diagnoses—together with septic shock and mechanical ventilation—obviously influenced the ICU physician to preferentially choose the parenteral route even though these conditions *per se* do not reflect true contraindications to enteral nutrition. In our opinion, the lower likelihood of prescribing enteral nutrition in these conditions allows two explanations. 1) The prescription rate of enteral nutrition in these patients was influenced by the level of critical care required and not by the fact of true intolerance to enteral feeding. This reflects a confounded indication for parenteral nutrition, which denotes that indication and chosen route did not comply. 2) Septic shock led to multifactorial intolerance to enteral feeding or at least one of the identified clinical diagnoses was potentially accompanied by true intestinal failure (e.g., bowel fistula) on the study visit day. In this situation, the chosen route of nutrition—namely parenteral—did indeed comply with the indication. Although speculative, either situation resulted in a greater likelihood of using parenteral nutrition—given alone or in combination with enteral nutrition—and, in total, the parenteral route was independently associated with increased mortality. This association was neither affected by the elevated mean serum glucose concentration (which was similar among all groups) nor the administered amount of insulin (patients with mixed nutrition required higher doses to maintain equal serum glucose levels). To what extent a tighter glycemic control or the prevention of a likely overfeeding in these patients groups may have influenced our results remains inconclusive not the least because of the lack of information on caloric intake.

According to the current guidelines (4, 5), we certainly agree that parenteral nutrition has its role in patients with clear contraindications to enteral nutrition or in these situations where nutritional requirements are not met by the enteral route and where all strategies to maximize enteral nutrition (use of small bowel feeding tubes, motility agents) have been attempted.

In correspondence to our reply to Dr. Ortiz-Leyba, the results of our observational study once more point out the importance of enteral nutrition as the preferred route. The definitive causality of these hypothesis-generating results will contingently be confirmed by ongoing randomized controlled trials, which also address the issue of consistency between indication and nutrition route (e.g., refer to clinical trials.gov, NCT00512122).

The authors have not disclosed any potential conflicts of interest.

Frank M. Brunkhorst, MD, Department of Anaesthesiology and Intensive Care Medicine, Friedrich-Schiller-University Jena, Jena, Germany, for the German Competence Network Sepsis (SepNet); Gunnar Elke, MD, Department of Anesthesiology and Intensive Care Medicine, University Medical Center Schleswig-Holstein, Campus Kiel, Kiel, Germany

REFERENCES

1. Elke G, Schädler D, Engel C, et al: Current practice in nutritional support and its association with mortality in septic patients—Results from a national, prospective, multicenter study. *Crit Care Med* 2008; 36:1762–1767
2. Brunkhorst FM, Engel C, Ragaller M, et al: Practice and perception—A nationwide survey of therapy habits in sepsis. *Crit Care Med* 2008; 36:2719–2725
3. Dellinger RP, Levy MM, Carlet JM, et al: Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med* 2008; 36: 296–327
4. Kreymann KG, Berger MM, Deutz NE, et al: ESPEN guidelines on enteral nutrition: Intensive care. *Clin Nutr* 2006; 25:210–223
5. Reinhart K, Brunkhorst FM, Bone HG, et al: Diagnosis and therapy of sepsis: Guidelines of the German Sepsis Society Inc. and the German Interdisciplinary Society for Intensive and Emergency Medicine. *Internist* 2006; 47:356–373

DOI: 10.1097/CCM.0b013e31819bb742

Can pulse pressure variations really better predict fluid responsiveness than static indices of preload in patients with acute respiratory distress syndrome?

To the Editor:

The recent publication from Huang et al (1) motivates comments on both physiology and statistics. If fluid challenge is a common therapy for unstable patients, the study reported fluid challenge response on stable patients (Methods section). What was the goal for fluid challenge in (at least) seven of the patients who did not receive vasoactive agents? Indeed, if hypovolemia may aggravate organ perfusion, fluid overload may worsen pulmonary edema and Q_s/Q_t (2).

Looking at the data presented, some results comparing responders vs. nonresponders are surprising: cardiac index and pulmonary artery occluded pressure (PAOP) differed significantly at baseline between responders and nonresponders to fluid loading. This suggests that these variables may be of value to identify responders to fluids in this specific population. The only response to this question would be to perform receiver operating characteristic curve analysis for baseline cardiac index, as recently done by Perner and Faber (3). The authors already performed receiver operating characteristic curve analysis for PAOP, providing a 0.187 value for the area under the curve. However, we can seriously doubt these results. The significant difference in PAOP between responders and nonresponders suggest that there was minimal overlap between groups, and a value higher than 0.5 in the receiver operating characteristic curve is thus expected. The 0.187 value is surprisingly low and contrasts to another study in patients with acute respiratory distress syndrome (4). This result even suggests that PAOP performed less efficiently compared with chance. All together, this allows suspecting some errors in the calculation.

Of note, we were surprised by the values of global end-diastolic volume index and intrathoracic blood volume index also reported for nonresponders. As for PAOP, the low area under the curve for these variables also suggests some error in receiver operating characteristic curve calculation.

Finally, the discrepancy between nonsignificant stroke volume variations and significant pulse pressure variation (PPV) was unclear. Because systolic pressure variations results mainly from stroke volume variations, the nonsignificant difference in stroke volume variations may only result from an increased arterial elastance induced by hypovolemia, as suggested by the authors, or an error in measurements. As mean arterial pressure was identical, an increased elastance would be accompanied by an increased diastolic pressure, but this value was not given. If this occurs, we also expect PPV to be greater than stroke volume variations (5). It would also be interesting to calculate pulse pressure to stroke volume ratio, which reflects vascular tone and aortic elastance.

In our opinion, these pathophysiological and statistical issues must be clarified before one can conclude from these data that PPV is better than the other markers to predict fluid responsiveness in patients with acute respiratory distress syndrome. In addition, the term *accurately* for the shown value of area under the curve seems to be rather optimistic.

The authors have not disclosed any potential conflicts of interest.

Didier Payen, MD, PhD, Fabrice Vallée, MD, Département d'Anesthésie–Réanimation-SMUR, Hôpital Lariboisière, AP-HP & Université Paris 7 Denis Diderot Equipe d'Accueil EA 322, Paris, France; Arnaud Mari, MD, Pôle Anesthésie et Réanimation, Unité de Réanimation Polyvalente de Purpan, GRCB 48, Université Paul Sabatier, Toulouse, France; Jean Christophe M. Richard, MD, PhD, Service de Réanimation Médicale, Hôpital Charles Nicolle, UPRES EA 38 30, CHU de Rouen, France; Daniel De Backer, MD, PhD, Department of Intensive Care, Erasme University Hospital, Université Libre de Bruxelles, Brussels, Belgium

REFERENCES

1. Huang CC, Fu JY, Hu HC, et al: Prediction of fluid responsiveness in acute respiratory distress syndrome patients ventilated with low tidal volume and high positive end-expiratory pressure. *Crit Care Med* 2008; 36:2810–2816
2. Payen D, Carli P, Brun-Buisson C, et al: Lower body positive pressure versus dopamine during peep ventilation. *J Appl Physiol* 1985; 58: 77–82
3. Perner A, Faber T: Stroke volume variation does not predict fluid responsiveness in patients with septic shock on pressure support ventilation. *Acta Anaesthesiol Scand* 2006; 50: 1068–1073
4. De Backer D, Heenen S, Piagnerelli M, et al: Pulse pressure variations to predict fluid responsiveness: Influence of tidal volume. *Intensive Care Med* 2005; 31:517–523
5. Pinsky MR: Probing the limits of arterial pulse contour analysis to predict preload responsiveness. *Anesth Analg* 2003; 96:1245–1247

DOI: 10.1097/CCM.0b013e3181986f85

Physician practice variation in critical care: A stumbling block

To the Editor:

I read with interest the article by Adda et al (1). There have been several studies that confirm similar findings for predictors of noninvasive ventilation (NIV) failure and associated higher mortality in those who had delayed onset of invasive mechanical ventilation (IMV) (2). There is also evidence that early first-line IMV in cancer patients with acute respiratory failure is associated with reduced mortality, although this was higher than those who received first-line NIV that proved successful (3, 4). Hence, the weight is on predicting patients who will not succeed first-line NIV, so that endotracheal intubation and IMV can be provided earlier than later, because delayed IMV in patients with cancer is associated with poor survival, prolonged hospitalization, and increased resource utilization.

This study unfortunately looked at retrospective data spanning over a period of 10 years, and the authors did rightly mention this as the weakness of their study. It is most unlikely that the definitions for acute respiratory failure, indications for NIV, choice of interface, and techniques for NIV could have remained the same over that time period even in this single center trial. Also, during this period there were advances in the management of hematologic malignancies and ventilator management, in addition to advancement in NIV application and interface choice. Furthermore, in the past decade, there has emerged sufficient evidence toward early application of NIV in acute hypoxemic respiratory failure, along with advances in the management of critically ill patients with cancer (5).

Despite the presence of several well-designed evidence-based algorithms, such as weaning from mechanical ventilator, spontaneous breathing trials, and application and discontinuation of NPPV, the prevalence of physician practice variation seem to be a stumbling block for progress. There is sufficient evidence and

benefit related to predictors of NIV failure and early endotracheal intubation with IMV in patients with cancer, but physician practice variation and lack of adherence to evidence-based guidelines for common disorders could be an impediment to quality care and patient safety among critically ill patients.

The author has not disclosed any potential conflicts of interest.

S. Egbert Pravinkumar, MD, FRCP, EDIC, Department of Critical Care, The University of Texas - M.D. Anderson Cancer Center, Houston, TX

REFERENCES

1. Adda M, Coquet I, Darmon M, et al: Predictors of noninvasive ventilation failure in patients with hematologic malignancy and acute respiratory failure. *Crit Care Med* 2008; 36: 2766–2772
2. Antonelli M, Conti G, Moro ML, et al: Predictors of failure of non-invasive positive pressure ventilation in patients with acute hypoxemic respiratory failure: A multi-center study. *Intensive Care Med* 2001; 27:1718–1728
3. Depuydt PO, Benoit DD, Vandewoude KH, et al: Outcome in non-invasively and invasively ventilated hematologic patients with acute respiratory failure. *Chest* 2004; 126:1299–1306
4. Azoulay E, Alberti C, Bornstain C, et al: Improved survival in cancer patients requiring mechanical ventilatory support: Impact of noninvasive mechanical ventilatory support. *Crit Care Med* 2001; 29:519–525
5. Hilbert G, Gruson D, Vargas F, et al: Noninvasive ventilation in immunodepressed patients with pulmonary infiltrates. *N Engl J Med* 2001; 433:481–487

DOI: 10.1097/CCM.0b013e3181986fb4

Sepsis, mortality, and parenteral nutrition: The risk of dualism on nutritional support

To the Editor:

Nutritional support in sepsis is an issue that is still full of areas of disagreement. Although there is a common opinion about the need of nutrition in sepsis, neither the quality nor the requirements of substrates have been well defined yet. The most recent review of recommendations (1) on The Surviving Sepsis Campaign Guidelines shows no opinion on the subject.

Until now, there were only three studies reporting a sepsis-related mortality decrease with different nutritional strategies (2–4). We have now read with great attention the study by Elke et al (5) on 399 patients with sepsis in which the authors conclude that the use of parenteral nutrition was associated with an increased mortality. In our opinion, this conclusion seems too risky. There are important limitations in this study; some of them recognized by the authors, but some others, such as the appropriate empirical antibiotherapy or the resuscitation with fluids, remain hidden in the study. Hence, the adjustment for treatment factors is clearly incomplete.

Regarding the data expressed in Table 3, taking the group of no nutrition patients as the reference group, there are no differences in mortality among the different nutrition strategies. In other words, in a bivariate analysis, the mortality does not increase in any of the groups of intervention (enteral, parenteral, and mixed) vs. the group of no intervention. Furthermore, Table 4 shows an overlap of the results of enteral and parenteral nutrition groups (95% confidence interval), which means that enteral nutrition could also be associated with an increased mortality. Additionally, despite the adjustment declared by the authors, a higher rate of patients were submitted to the parenteral route, even in the medical group, and, according to Table 1, the parenteral group included more severe patients (higher Acute Physiology and Chronic Health Evaluation II, mechanical ventilation, renal replacement, Sequential Organ Failure Assessment score).

This type of conclusion, blaming parenteral nutrition for mortality in sepsis, increases the risk of dualism in the nutritional support of the patient with sepsis. This could add more bewilderment to a topic as complex as sepsis treatment, where each recommendation requires a firm body of evidence.

The authors have not disclosed any potential conflicts of interest.

Carlos Ortiz-Leyba, MD, PhD, José Garnacho-Montero, MD, PhD, Servicio de Cuidados Críticos y Urgencias, Hospital Universitario Virgen del Rocio, Avda Manuel Siurot s/n, Sevilla, Spain; and Aurelio Cayuela Dominguez, MD, PhD, Servicio de Documentación Clínica, Hospital Universitario Virgen del Rocio, Avda Manuel Siurot s/n, Sevilla, Spain

REFERENCES

1. Dellinger RP, Levy MM, Carlet JM, et al: Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008. *Intensive Care Med* 2008; 34:17–60
2. Garcia de Lorenzo A, Ortiz leyba C, Planas M, et al: Parenteral administration of different amounts of branch-chain amino acids in septic patients: Clinical and metabolic aspects. *Crit Care Med* 1997; 25:418–424
3. Galban C, Montejo JC, Mesejo A, et al: An immune-enhancing enteral diet reduces mortality rate and episodes of bacteremia in septic intensive care unit patients. *Crit Care Med* 2000; 28:643–648
4. Pontes-Arruda A, Aragao AM, Albuquerque JD, et al: Effects of enteral feeding with eicosapentaenoic acid, gamma-linolenic acid, and antioxidants in mechanically ventilated patients with severe sepsis and septic shock. *Crit Care Med* 2006; 34:2325–2333
5. Elke G, Schadler D, Engel C, et al: Current practice in nutritional support and its association with mortality in septic patients—Results from a national, prospective, multicenter study. *Crit Care Med* 2008; 36:1762–1767

DOI: 10.1097/CCM.0b013e3181986e1e

The author replies:

I would like to thank Dr. Ortiz-Leyba and colleagues for their interest in our study (1) and their insightful review. In their letter to the editor, the authors complement our previously highlighted study limitations and point out the importance of treatment factors in sepsis such as appropriate antibiotic therapy or fluid resuscitation, which were not covered in our analysis. We certainly agree that adjustment for these factors would have reinforced the results of multivariate analysis. Unfortunately, we were unable to control these factors because of the observational, 1-day point prevalence design of our study with its limitation to such time-dependent interventions missed by Dr. Ortiz-Leyba. Hence, it remains inconclusive from our study whether patients received an appropriate antibiotic therapy or fluid resuscitation in their early stage of disease and to what extent this might have influenced our results.

In the second part of their letter, the authors claim that there are no differences in mortality among the different nutrition strategies. This is not true. There are significant differences in the global group comparison ($p = 0.013$). If the group of no nutrition is compared with each of the three others (exclusively enteral, exclusively parenteral, mixed nutrition), no significant differences could indeed be detected. However, because the sample sizes are relatively low, these comparisons do not reach sufficient sta-

tistical power to conclude that differences do not really exist. Also, we cannot follow the conclusion that enteral nutrition could be associated with an increased mortality because the 95% confidence interval of the odds ratio overlaps with that of the parenteral nutrition. In contrast, it can be concluded from the estimated 95% confidence intervals that the probability that enteral nutrition confers a higher risk than parenteral nutrition is approximately 0.016, i.e., rather small.

Finally, we disagree that our conclusion seems to be too risky. It was clearly not our intention to imply causality between parenteral nutrition and mortality, which is beyond the scope of an observational study. We deliberately used the term "association," which in our opinion best reflects the hypothesis-generating, not hypothesis-corroborating result of our study. This, in fact, does not add more bewilderment to the complex topic of sepsis treatment but rather emphasizes once more the need for level I studies confirming the superiority of enteral nutrition in sepsis as demanded by Ortiz-Leyba and colleagues. The so-called "dualism in nutritional support" does not exist. The current recommendations suggest that nutrition should be given early and preferentially via the enteral route (2, 3). Two of the three studies cited by the authors support these recommendations (4, 5). Appropriately administered, glycemic-controlled parenteral nutrition should be viewed as a second choice for patients with clear contraindications to enteral feeding or in patients with accumulating energy deficit within their first week of intensive care unit stay indicating an insufficient enteral nutrition.

The author has not disclosed any potential conflicts of interest.

Gunnar Elke, MD, University Medical Center Schleswig-Holstein, Department of Anaesthesiology and Intensive Care Medicine, Kiel, Germany for The German Competence Network Sepsis (SepNet)

REFERENCES

1. Elke G, Schädler D, Engel C, et al: Current practice in nutritional support and its association with mortality in septic patients—Results from a national, prospective, multicenter study. *Crit Care Med* 2008; 36: 1762–1767
2. Kreymann KG, Berger MM, Deutz NE, et al: ESPEN guidelines on enteral nutrition: Intensive care. *Clin Nutr* 2006; 25:210–223
3. Reinhart K, Brunkhorst FM, Bone HG, et al: Diagnosis and therapy of sepsis: Guidelines of the German Sepsis Society Inc. and the German Interdisciplinary Society for Intensive and Emergency Medicine. *Internist* 2006; 47: 356–373
4. Pontes-Arruda A, Aragao AM, Albuquerque JD, et al: Effects of enteral feeding with eicosapentaenoic acid, gamma-linolenic acid, and antioxidants in mechanically ventilated patients with severe sepsis and septic shock. *Crit Care Med* 2006; 34:2325–2333
5. Galban C, Montejo JC, Mesejo A, et al: An immune-enhancing enteral diet reduces mortality rate and episodes of bacteremia in septic intensive care unit patients. *Crit Care Med* 2000; 28:643–6488

DOI: 10.1097/CCM.0b013e31819bb775

Fetal outcomes of critically ill pregnant women

To the Editor:

In a recent study Cartin-Ceba et al (1) reported on pregnant women admitted to the intensive care unit (ICU) during a 10-year period to mainly assess the fetal outcome of this group. We would like to focus on three main points in their report.

1. In the introduction it is stated that "to date published studies addressing pregnancy related admissions to the ICU have reported that the vast majority occur in postpartum period but do not address the effect of ICU care and ICU complication to the outcome of the fetus." We would like to address this statement first.

   We reported a cohort of women representing a large obstetrical unit of our tertiary center (approximately 11,000 births/yr) with an ICU admission rate of 0.8/1000 births. Twenty-nine percent were nonobstetrical admissions (medical and surgical complications and none of which were trauma and/or drug overdose). Maternal death occurred in the obstetrical group, similar to the two cases reported by the authors. However, 70% were antepartum cases and this reflects the nature of the center: obstetrical service along with ICU facility, i.e., all cases were admitted under the fetal–maternal medicine division and further required ICU admissions. All were viable pregnancies as early as 22 weeks gestation, and we reported no fetal/neonatal demise (2).

2. The authors reported 93 pregnant patients admitted to the ICU with critical nonobstetrical causes and describe adverse fetal outcomes being related to maternal shock, need for blood transfusion, and lower gestational age. However, it seems that 20 women (21.5%) were diagnosed with abortions, thus viable pregnancy was not considered and most pregnancies in this group were "incidental." Furthermore, 15 cases (17%) were related to trauma and 17 (18%) to drug overdose; altogether, these points pose the question of the diagnosis and severity of the primary injury together with a serious socioeconomic bias and lack of antenatal care, rather than an influence of the gestational age at diagnosis and the race bias stated by the authors. We are concerned that the authors' conclusions represent these selection biases rather than the true requirements of the antenatal management of this group of women.
3. The authors do not separately report the fetal outcome in the group of medical conditions complicating pregnancy that required ICU care and in which the fetus was of a real concern, rather than "an incidental finding." It is not stated what extent of obstetrical care was offered before and after admission, thus leaving as they state an influence of the gestational age at diagnosis, i.e., antenatal care, fetal well-being assessment, antenatal steroids for fetal lung maturation, and a "round-the-clock" specialist multidisciplinary approach deciding the time and mode of delivery. In our opinion, these considerations are critical for the decision making and the outcome of the mother–fetus dyad facing medical complications of pregnancy. The other determinants of the fetal outcome as identified by the authors are direct indicators of the maternal state and only secondarily of fetal/neonatal outcome. Thus, as shown by our group and many others, if the maternal state is carefully addressed, then the fetal/neonatal outcome is superior to the one reported in this study (3, 4).

The authors have not disclosed any potential conflicts of interest.

S. Grisaru-Granovsky, Department of Perinatology, Shaare Zedek Medical Center, Jerusalem, Israel; M. Hersch, Department of Intensive Care, Shaare Zedek Medical Center, Jerusalem, Israel; A. Ioscovich, Department of Anesthesiology, Shaare Zedek Medical Center, Jerusalem, Israel

REFERENCES

1. Cartin-Ceba R, Gajic O, Iyer VN, et al: Fetal outcomes of critically ill pregnant women admitted to the intensive care unit for nonobstetric causes. *Crit Care Med* 2008; 36: 2746–2751
2. Grisaru-Granovsky S, Shaya M, Hersch M, et al: Mortality risk assessment of maternal birth complications. *Int J Obstet Gynecol* 2004; 84: 166–168
3. Grisaru-Granovsky S, Ioscovich A, Hersch M, et al: Temporizing treatment for the respiratory-compromised gravida: An observational study of maternal and neonatal outcome. *Int J Obstet Anesth* 2007; 16:261–264
4. Ioscovich A, Briskin A, Fadeev A, et al: Emergency cesarean section in a patient with the Fontan circulation using an indwelling epidural catheter. *J Clin Anesth* 2006; 18:631–634

DOI: 10.1097/CCM.0b013e3181987023

The authors reply:

We thank Grisaru-Granovsky et al for their interest in our article (1) and for their insightful comments. Before addressing the specific comments that were raised, we want to emphasize that the main objective of our article was to describe the risk factors associated with poor fetal outcomes in maternal admissions to the intensive care unit (ICU) for primary nonobstetrical causes.

The study cited by Grisaru-Granovsky et al (2) does indeed describe antepartum ICU cases; however, outcome data were focused on prediction of maternal mortality and not on fetal complications. In addition, the authors did not include any patients admitted for primary nonobstetrical causes. In fact, they excluded 14 patients (29% of the sample) with preexisting medical/surgical conditions who presumably had preplanned ICU admissions without acute decompensation. The fetal mortality was not specifically stated in the published article, but we appreciate that this important finding has now been reported by them. This notwithstanding, the majority of publications related to obstetrical admissions to the ICU has focused on the postpartum period, and both ours and the cited article are some of the few that have reported the opposite.

Regarding the second comment, we would like to clarify our data. The reference to abortion refers to the fetal outcome in pregnant women with a viable fetus at ICU admission. Also, we have acknowledged the race disparity in the limitations of the study, and we do not believe either this or socioeconomic status can be inferred from the diagnosis of "trauma" and "drug overdose." We cannot address the socioeconomic bias of the study because this was not assessed in this retrospective study. Furthermore, although there were more fetal deaths in the incidental pregnancy group, there were no statistical differences in the fetal deaths between the two groups. In addition, the statistical difference between the two groups in the presence of antenatal care decreased after adjustment for severity of illness in a multivariable analysis.

Finally, we consider that incidental pregnancies in the ICU are a real concern and see no reason to exclude them from the study. In fact, they represent the same physiologic stress to the mother as a known pregnancy. Also, we do agree that information regarding preadmission obstetrical care is an important influence on fetal outcome in a critically ill mother. Furthermore, we clarify that all patients admitted were evaluated and comanaged by "around the clock" multidisciplinary specialists including obstetric and perinatal care and intensivists. However, we respectfully disagree that our identified indicators of maternal state only secondarily indicate fetal outcome. In contrast, we believe, as stated by Grisaru-Granovsky et al, that there is a strong interdependent "mother–fetus dyad," in which the maternal state has profound direct effects on fetal well-being. This is one of the important messages that our article intends for the reader to appreciate.

Grisaru-Granovsky et al (3) state that compared to the findings of our study superior fetal outcome has been previously reported. However, the aim of this cited study to support their claims was focused specifically to "describe the effect of prolonged antepartum mechanical ventilatory support on the mother and neonate" and reported on only three patients. As such, these data cannot be generalized to a larger population as we have reported.

The authors have not disclosed any potential conflicts of interest.

Rodrigo Cartin-Ceba, MD; Ognjen Gajic, MD, Msc; Vivek N. Iyer, MBBS; Nicholas E. Vlahakis, MD, Department of Internal Medicine, Division of Pulmonary and Critical Care Medicine, Mayo Epidemiology and Translational Research in Intensive Care (M.E.T.R.I.C.), Mayo Clinic College of Medicine, Rochester, MN

REFERENCES

1. Cartin-Ceba R, Gajic O, Iyer VN, et al: Fetal outcomes of critically ill pregnant women admitted to the intensive care unit for nonobstetric causes. *Crit Care Med* 2008; 36:2746–2751
2. Grisaru-Granovsky S, Shaya M, Hersch M, et al: Mortality risk assessment of maternal birth complications. *Int J Gynaecol Obstet* 2004; 84: 166–168
3. Grisaru-Granovsky S, Ioscovich A, Hersch M, et al: Temporizing treatment for the respiratory-compromised gravida: An observational study of maternal and neonatal outcome. *Int J Obstet Anesth* 2007; 16:261–264

DOI: 10.1097/CCM.0b013e31819bb7de

Evaluation of 30-day mortality of levosimendan versus enoximone

To the Editor:

In their article on levosimendan Fuhrmann et al (1) use the log-rank test to show a statistically significant difference in survival at 30 days for patients treated with levosimendan. The log-rank test they used also takes the time-to-death into account, which may be clinically relevant when deaths continue to occur for many months or years after the intervention (e.g., heart failure, cancer). However, I do not see the relevance here because Figure 2 shows that mortality stabilized at day 10. Another straightforward comparison of absolute numbers of death at day 30 with the chi-square or Fisher's exact test would have been fine or even preferable. However, the results would have been much less impressive with a p value of 0.2 when the survival of 11 of 16 versus 6 of 16 is compared. It is misleading that the authors state in the abstract that "Survival rate at 30 days was significantly higher in the levosimendan-treated group (69%, 11 of 16) compared with the enoximone group (37%, 6 of 16, $p = 0.023$)." Without mentioning the log-rank test, they suggest that mortality at 30 days was statistically different but p value at day 30 is actually 0.2 with chi-square. We can only speculate if this is just a matter of sample size or if there is no difference at all at the end? Should we conclude that patients on levosimendan died more slowly but at the end no significant difference in survival was observed?

The author has not disclosed any potential conflicts of interest.

Bart J. A. Rijnders, MD, PhD, Department of Internal Medicine, Section of Infectious Diseases, Erasmus MC, Rotterdam, The Netherlands

REFERENCE

1. Fuhrmann JT, Schmeisser A, Schulze MR, et al: Levosimendan is superior to enoximone in refractory cardiogenic shock complicating acute myocardial infarction. *Crit Care Med* 2008; 36:2257–2266

DOI: 10.1097/CCM.0b013e3181959b4e

Levosimendan or enoximone in refractory cardiogenic shock?

To the Editor:

In the August issue, Fuhrmann et al (1) published the results of an open-label, single-institution study of the mortality of patients with cardiogenic shock following myocardial infarction. From April 2003 to July 2005 the authors randomized 32 patients, who despite percutaneous coronary interventions, intra-aortic balloon counterpulsation, and inotropic amines, remained in cardiogenic shock to a continuous infusion of levosimendan or enoximone. The investigation was stopped early after an interim analysis had demonstrated an enormous survival benefit in the levosimendan arm of the study. Eleven of 16 patients (69%) survived in the levosimendan group. In contrast, only 6 of 16 (37%) treated with enoximone left the hospital alive.

After an *a priori* sample size calculation, the authors had planned to include 88 patients in their investigation. Furthermore, one interim analysis was stipulated.

I wonder what prompted the authors to do the first and only interim analysis after including only 32 of the planned 88 patients? How was it determined, before the investigation, that the first interim analysis should be done after including 36.4% of the expected number of patients needed to draw a firm conclusion?

Why was the study performed as an open-label investigation? With a single-institution, unblinded design it has been straightforward, for the investigators, to continuously evaluate a difference in mortality rates in the two groups. Can we feel confident that a premature interim analysis and early termination of the study was not influenced by this knowledge?

The fact that the decision to stop the trial was supported by the authors' institutional ethics committee is not reassuring. It was the very same committee that had accepted a methodologically imperfect study protocol in the first place.

Levosimendan was administered in a one dose that fits all manner whereas enoximone was titrated to achieve the "best hemodynamic response." Why this difference?

The circulation of the patients was supported with intra-aortic balloon counterpulsation. The authors "applied standard formulas for calculation of . . . systemic vascular resistance index . . .." What standard method was used to calculate the vascular resistance in a scenario where the arterial blood pressure was significantly different in the upper and lower part of the body? The 60-sec periods, where the support was turned off, are not long enough for the vigilance continuous cardiac output system to reliably re-estimate cardiac output.

The authors finish by acknowledging "Because of the open-label character of this study, a bias cannot be entirely excluded. Hence, we believe that interpretation of these results is limited." It would have been preferable had the methodologic limitations and concerns discouraged the authors from using a title that does not suggest the slightest doubt about the quality and results of the research (1). It would have been even better if the authors had refrained from submitting the article for publication and had awaited "A larger, multicenter clinical trial of double-blind, randomized design . . ." (1).

The author has not disclosed any potential conflicts of interest.

Preben G. Berthelsen, MD, Department of Anaesthesiology, Holstebro Hospital, Holstebro, Denmark

REFERENCE

1. Fuhrmann JT, Schmeisser A, Schulze MR, et al: Levosimendan is superior to enoximone in refractory cardiogenic shock complicating acute myocardial infarction. *Crit Care Med* 2008; 36:2257–2266

DOI: 10.1097/CCM.0b013e3181959be4

Experience with donation after cardiac death

To the Editor:

Naim et al. (1) briefly mentioned in the discussion of their study that narcotics and benzodiazepines were used when withdrawing life support for donation after cardiac death to treat pain and anxiety while recognizing the unintended side effects of possibly hastening death. They also remarked that the doctrine of double effect has been well supported in end-of-life care and by the Supreme Court (1).

Some of the patients who were described in the study by Naim et al. raised some questions. For example, patient 8, a 17-yr-old boy whose weight was only 34 kg, and suffered a hypoxic ischemic encephalopathy after a cardiac arrest, received 850 μg of fentanyl and 10 mg of midazolam from extubation to death. Death occurred 11 mins after extubation. Although the details regarding the history of this patient are not available, it is not difficult to assume that he was unresponsive and moribund. In consequence, the purpose of these medications, in such dosages as given to this patient is controversial. The same questions can be raised for patient 9.

I want to make clear that I fully support the practice of donation after cardiac death, and I commend the honesty of the authors of the study. However, in reference to patients 8 and 9, it is my impression that both narcotics and benzodiazepines were given to treat the pain and anxiety of the patient's family, nurses, and doctors.

The author has not disclosed any potential conflicts of interest.

Javier Daniel Finkielman, MD, Intensive Care Unit, Saint Alexius Medical Center, Bismarck, ND

REFERENCE

1. Naim MY, Hoehn KS, Hasz RD, et al: The Children's Hospital of Philadelphia's experience with donation after cardiac death. *Crit Care Med* 2008; 36:1729–1733

DOI: 10.1097/CCM.0b013e31818f300f