Beyond the Blue: What Fellows Are Reading in Other Journals

Feeding, Simvastatin, and Linezolid

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Recommended Reading from the Johns Hopkins University Fellows; Henry E. Fessler, Program Director

Rice TW, et al.; National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Initial Trophic vs Full Enteral Feeding in Patients with Acute Lung Injury: The EDEN Randomized Trial. *JAMA* (1)

Reviewed by Biren B. Kamdar

Nutritional support is important but particularly challenging for patients receiving mechanical ventilation. Current guidelines for this population recommend early initiation of enteral feeding, supported by data associating enteral feeding with improved mortality and infection outcomes (2). Despite these recommendations, the optimal dose of enteral nutrition in intensive care unit patients remains unknown. Although some studies suggest that full enteric nutrition improves outcomes, others have demonstrated that trophic (minimal) feedings are sufficient and produce fewer gastrointestinal complications (2).

To resolve these conflicting data, Rice and colleagues present the results of an ARDS Clinical Trials Network randomized controlled trial comparing full versus trophic feeding in critically ill patients with acute lung injury (ALI) (1). Within 48 hours of ALI onset and 72 hours of initiation of mechanical ventilation, patients at 44 hospitals were randomized to receive 6 days of either a full-feeding protocol, starting at 25 ml/hour and up-titrated as tolerated toward a caloric goal, or a 10-ml/hour trophic-feeding protocol. After 6 days, patients still receiving mechanical ventilation were given the full-feeding protocol. During the study period, the 492 patients in the full-feeding group received approximately 1,300 kcal each day (80% of goal), whereas the 508 patients in the trophic-feeding group received approximately 400 kcal (25% of goal). Comparing the full- and trophic-feeding groups, there were no significant differences in ventilator-free days (15.0 vs. 14.9; $P = 0.89$), 60-day mortality (22.2 vs. 23.2%; $P = 0.77$), infection rates, organ failure-free days, or intensive care unit-free days. The trophic-feeding group had significantly lower gastric residual volumes and rates of regurgitation, emesis, and constipation, but actual rates of these complications were low in both groups.

The strengths of this study include its randomized, intention-to-treat design, large size, and use of standardized dosing protocols. Limitations include its open-label, nonequivalence design and the exclusion of critically ill patients without ALI.

Overall, this well-designed randomized controlled trial demonstrated no difference in ventilator-free days or mortality with initial full versus trophic feeding, and supports the relative safety of both strategies in ALI. It remains unknown whether other clinically important outcomes related to the timing or duration of feeding exist to favor one strategy over the other.

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2. McClave SA, Martindale RG, Vanek VW, McCarthy M, Roberts P, Taylor B, Ochoa JB, Napolitano L, Cresci G; A.S.P.E.N. Board of Directors, American College of Critical Care Medicine, Society of Critical Care Medicine. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). *JPEN J Parenter Enteral Nutr* 2009;33:277–316.

Ropponen JO, et al. Effect of Simvastatin on Development of Obliterative Airway Disease: An Experimental Study. *J Heart Lung Transplant* (3)

Reviewed by Jason A. Akulian

Although lung transplantation may be life-saving for patients with end-stage lung disease, 5-year posttransplantation mortality remains approximately 50%. Obliterative bronchiolitis is the leading cause of this late mortality. Previous studies have demonstrated that statins are associated with improved lung function (FEV₁ and FVC) and 6-year survival after lung transplantation; however, the mechanism remains unclear (4).

Ropponen and colleagues conducted a series of experiments in a rat tracheal allograft model, studying the role of statins in the immunologic pathways underlying the development of obliterative airway disease (OAD), an accepted histopathologic correlate to obliterative bronchiolitis using the rat trachea model (3). Major histocompatibility complex-mismatched rat tracheal allografts were heterotopically transplanted into the greater omentum of wild-type recipients. Control rats were transplanted with syngeneic tracheal grafts. Simvastatin (0.1, 0.5, 2, 5, and 20 mg/kg/d) was administered on the day of transplantation and continued throughout the study. Immunosuppressive medication was not administered. The development of OAD, cellular infiltration, proinflammatory cytokines, and the role of nitric oxide synthase (NOS) in mediating the effect of simvastatin (NOS was inhibited

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with *N*^ω-nitro-L-arginine methyl ester) in the tracheal allograft were then assessed on Days 3, 10, and 30 after transplantation.

After allotransplantation, there was an initial loss of respiratory epithelium regardless of simvastatin dose, but epithelial recovery was noted in statin-treated animals on Day 10 ($P < 0.05$). In addition, a dose-independent attenuation of tracheal OAD was noted at doses greater than 0.1 mg/kg/day when compared with controls ($P < 0.05$). Attenuation of infiltrative inflammatory cells and a wide array of proinflammatory cytokines were noted on Days 3 and 10 ($P < 0.05$). Last, the protective effect of simvastatin was partly abrogated by NOS inhibition.

There are several salient limitations of this model of lung transplantation. There are anatomic and potentially differing immune responses between the trachea and the bronchiole, and isolation of the transplanted trachea from the environment. The immune response to transplantation and effects of statins in the rat may differ from those seen in humans, and immunosuppression was withheld in this experimental model. Nevertheless, this study provides evidence suggesting the potential mechanism of the posttransplantation benefits of statins seen in observational studies.

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Wunderink RG, et al. Linezolid in Methicillin-Resistant *Staphylococcus aureus* Nosocomial Pneumonia: A Randomized, Controlled Study. *Clin Infect Dis* (5)

Reviewed by Andrew T. Braun

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a common cause of nosocomial pneumonia (6). Prior randomized controlled trials suggested superiority of linezolid compared with vancomycin in MRSA nosocomial pneumonia; however, these findings were limited as the vancomycin dose was not adjusted per usual clinical practice (7, 8).

Wunderink and colleagues conducted a prospective, randomized, double-blind, multicenter trial to assess the efficacy and safety of linezolid versus dose-optimized vancomycin for the treatment of MRSA nosocomial pneumonia in hospitalized adults (5). A total of 1,225 patients were randomized to intravenous linezolid (600 mg

every 12 h) or dose-optimized vancomycin (15 mg/kg every 12 h) for 7–14 days. Inclusion criteria included radiographically documented pneumonia, microbiologic presence of MRSA, and an expected survival of at least 72 hours. The primary outcome was clinical success, based on criteria prespecified by the clinical study, and determined by a blinded investigator at end of treatment (EOT) and end of study (EOS; 7–30 d after EOT). Because nosocomial pneumonia is generally treated empirically before obtaining microbiologic results, modified intention-to-treat (mITT) was required after randomization to analyze the population that cultured MRSA ($n = 448$). A per-protocol (PP) population of patients with complete outcome assessment was also analyzed for end points of clinical efficacy and safety ($n = 348$).

Randomization was generally balanced, although vancomycin-treated patients had higher rates of mechanical ventilation and MRSA bacteremia. In the PP population, 57.6% of linezolid-treated patients achieved clinical cure compared with 46.6% of vancomycin-treated patients at EOS (difference, 9.0% [95% confidence interval, 0.5–21.6%]; $P = 0.042$). Linezolid also achieved greater clinical success and microbiologic eradication at EOT and in the mITT patients. Furthermore, renal injury in patients with normal baseline renal function was increased with vancomycin, as compared with linezolid (61.2 vs. 48.1%). There was no difference in all-cause 60-day mortality between the linezolid and vancomycin treatment groups (15.7 vs. 17.0%).

This study is limited by heterogeneity between the treatment arms despite randomization, and nonoptimal data collection, as 100 mITT patients were excluded from the PP population. Nevertheless, this trial demonstrates improved clinical efficacy of linezolid over dose-adjusted vancomycin for MRSA pneumonia.

Author disclosures are available with the text of this article at www.atsjournals.org.

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