

# NUTRIREA-2 trial finds that early enteral nutrition and early parenteral nutrition do not differ with regards to major clinical outcomes

Feng Tian<sup>1,2</sup>, Gordon S. Doig<sup>1</sup>

<sup>1</sup>Intensive Care Research Unit, Northern Clinical School, Royal North Shore Hospital, University of Sydney, Australia; <sup>2</sup>Research Institute of General Surgery, Jinling Hospital, Medical School of Nanjing University, Nanjing 210093, China

*Correspondence to:* Gordon S. Doig, Intensive Care Research Unit, Northern Clinical School, Royal North Shore Hospital, University of Sydney, Pacific Hwy, St. Leonards, Sydney, NSW 2065, Australia. Email: gdoig@med.usyd.edu.au.

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Clinicians and researchers believe that the route, timing and amount of nutrition support can affect outcome from critical illness. Major international guidelines for nutrition support in critical illness recommend enteral nutrition (EN) in preference to parenteral nutrition (PN) because EN is accepted to significantly reduce infections (1,2). However, the most recent large scale multicenter clinical trial conducted in the UK, the CALORIES trial, randomized 2,400 critically ill patients to receive early EN or early PN and found no difference in infectious complications (3). Interestingly, although the CALORIES trial did not start EN or PN while patients were in active shock (systolic blood pressure <90 mmHg and not yet responding to treatment), 84% of enrolled patients did receive a vasoactive agent at some time during the study period.

Despite the fact that the CALORIES trial provides evidence that EN and PN are safe in patients who are not in active shock but who are still receiving a vasoactive agent, many clinicians remain concerned about using EN or PN in this specific group of patients. The primary purpose of the NUTRIREA-2 trial was to study this specific group of patients more closely.

NUTRIREA-2 randomized 2,410 ventilated adult patients who were receiving a vasoactive agent to commence EN or PN within 24 hours of the onset of critical illness. The onset of critical illness was defined as the time of

endotracheal intubation (4).

## Study design

The major design features of NUTRIREA-2 are robust. Allocation concealment was maintained by the use of a web-based system that stratified randomization within each of the 44 study sites. The primary outcome, mortality at study day 28, was available in 100% of the 2,410 enrolled patients. A blinded adjudication committee was used to diagnose ventilator associated pneumonia and the primary analysis was implemented by intention to treat, with all patients analyzed in the groups to which they were originally assigned. Although patient recruitment was discontinued after the second planned interim analysis, it was discontinued because the independent data monitoring committee determined that continued recruitment to the original target of 2,854 patients could not mathematically alter current results. Early discontinuation is therefore not a concern.

## Patient population

Patients were randomized within 24 hours of intubation for invasive mechanical ventilation or within 24 hours after ICU admission if mechanical ventilation was started before

ICU admission. Patients were only eligible if they were receiving a vasoactive agent at time of enrolment.

Either EN or PN was started at 20–25 kcal/kg/day and protein goals were set according to local practice. PN was continued for at least 72 h. After 72 h, if the patient had their vasoactive agent stopped, PN patients could be switched to EN.

In addition to the primary outcome of 28-day mortality, 90-day mortality, blood glucose concentration and gastrointestinal complications were also reported. Quality of life, physical function and costs were not assessed in this primary publication.

## Findings

There were no differences in deaths on study day 28 (443/1,202 EN *vs.* 422/1,208 PN,  $P=0.33$ ), deaths at 90-day follow-up (530/1,185 EN *vs.* 507/1,192 PN,  $P=0.28$ ) or ICU-acquired infections between the two groups (173/1,202 EN *vs.* 194/1,208 PN,  $P=0.25$ ). Compared with the EN group, patients in the PN group received more calories over the entire study period (17.8 kcal/kg/d EN *vs.* 19.6 kcal/kg/d PN,  $P<0.0001$ ) and more protein (0.7 g/kg/d EN *vs.* 0.8 g/kg/d PN,  $P<0.0001$ ). PN patients also had fewer gastrointestinal complications such as vomiting (406/1,202 EN *vs.* 246/1,208 PN,  $P<0.0001$ ), diarrhea (432/1,202 EN *vs.* 393/1,208 PN,  $P=0.009$ ), bowel ischemia (19/1,202 EN *vs.* 5/1,208 PN,  $P=0.007$ ), and acute colonic pseudo-obstruction (11/1,202 EN *vs.* 3/1,208 PN,  $P=0.04$ ). More than twice as many hypoglycaemic events were reported in the EN group (29/1,202 EN *vs.* 13/1,208 PN,  $P=0.006$ ). There were no differences between the two groups in any other secondary outcomes.

## Commentary

The NUTRIREA-2 trial is a well-designed, pragmatic, large scale, multicentred clinical trial. It is the first nutrition trial to focus specifically on patients who require vasoactive agents to support their circulation. The results show that early EN and early PN do not differ with regard to the major clinical outcomes of mortality and infections, however PN resulted in fewer gut-related complications and hypoglycaemic events.

NUTRIREA-2 is the first nutrition trial that we are aware of to report rates of bowel ischemia and acute colonic pseudo-obstruction as outcomes. Although objective criteria

were used to define each of these complications, they were not diagnosed by blinded adjudication committees.

## Implications for practice

The NUTRIREA-2 trial revealed that early PN resulted in improvements to some tertiary outcomes (vomiting, diarrhea, bowel obstruction, acute colonic pseudo-obstruction, and hypoglycaemia), however, these differences did not translate to improvements in clinically important outcomes such as pneumonia, duration of mechanical ventilation, ICU stay or mortality. Furthermore, some of these tertiary outcomes were relatively rare. For example, 85 patients would require treatment with early PN to prevent one case of bowel ischemia. In 2012, the total cost of delivering one day of EN to an ICU patient was estimated to be \$US52.50 (5) whereas the total costs of delivering one day of PN to an ICU patient was estimated to be \$US229.66 (6).

### *Should I use early PN instead of early EN?*

Major clinical trials and systematic reviews have suggested that initial permissive hypocaloric EN is associated with a lower risk of gastrointestinal intolerance (7,8). NUTRIREA-2 started EN at a full-target dose rate of 20 to 25 kcal/kg/day. We are not aware of any major clinical guidelines that recommend commencing early EN at full-target dose rates. Therefore, we question whether early hypocaloric EN is more appropriate in critically ill patients who require continued vasoactive support after resuscitation from active shock. Given the economic considerations, we do not believe NUTRIREA-2 provides enough evidence to recommend early PN instead of early EN.

### *If I can't use early EN, should I consider early PN?*

In patients who have an absolute contraindication to early EN, NUTRIREA-2 provides additional convincing evidence that early PN is a viable clinical option. Early PN does not increase infections or lead to any harmful effects and compared to withholding nutrition support, early PN may actually reduce costs (6).

## Summary

NUTRIREA-2 is a well conducted clinical trial that provides convincing evidence that early PN does not worsen

clinically important outcomes when used in mechanically ventilated patients who require vasoactive agents for hemodynamic support.

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