other than bowel ischaemia. Finally, it would be of interest to analyse if the occurrence of bowel ischaemia was related to the amount of enteral nutrition.

We declare no competing interests.

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In the NUTRIREA-2 trial,[1] patients who received mechanical ventilation and vasopressor support showed no statistically significant differences in mortality and infection rates when given either enteral nutrition or parenteral nutrition. Enteral nutrition was more frequently associated with adverse gastrointestinal events. Full doses of macronutrients corresponding to about 60–70% of daily requirements were provided throughout the intervention period.[1,2] Such a calorie target might attenuate the potential benefit of enteral nutrition and increase the risk of complications related to enteral nutrition. The current guidelines[3] show concerns about enteral nutrition for unstable patients who need high doses of vasopressor, because the gut is susceptible to ischaemia in such patients.

In a randomised controlled trial,[4] which enrolled 200 patients on mechanical ventilation, no differences were observed in mortality between individuals assigned to full-energy enteral nutrition (average delivery of 74·8% of calorie requirements) and individuals assigned to trophic enteral nutrition (average delivery of 15·8% of calorie requirements) for 6 days. Trophic enteral nutrition had a trend towards less adverse gastrointestinal events.[4] Also, in a larger randomised controlled trial,[5] which recruited mechanically ventilated patients, initial trophic enteral nutrition (400 kcal per day) resulted in a significant reduction in gastrointestinal intolerance with similar mortality and infection rates compared with full-energy enteral nutrition (1300 kcal per day). A non-significant risk difference in mortality at day 28 (2·0%, 95% CI −1·9 to 5·8) in favour of parenteral nutrition appears to have occurred at the end of the intervention on day 7.[1] These findings would suggest the need for refinements in calorie targets for early enteral nutrition in severe, critical illness with a potentially ischaemic gut.

I declare no competing interests.

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In the NUTRIREA-2 trial,[1] enteral nutrition was compared with parenteral early nutrition in ventilated adults with shock. In particular, the authors aimed at ascertaining whether early first-line enteral nutrition showed positive clinical effects compared with parenteral nutrition. Both arms of the study targeted normocaloric supplementation in patients needing invasive mechanical ventilation and vasopressor support for shock.[1] The results show that early isocaloric enteral and parenteral nutrition did not differ in mortality or risk of secondary infections. However, enteral nutrition was associated with a greater risk of gastrointestinal complications.[1]

The European Society for Clinical Nutrition and Metabolism guidelines[2] recommend the use of parenteral nutrition when enteral feeding is not tolerated or is contraindicated (grade B recommendation) within 3–7 days following intensive care admission but recommend careful consideration of the optimal timepoint for supplemental parenteral nutrition for those patients not tolerating exclusive enteral nutrition (grade good practice point recommendation).

In the NUTRIREA-2 study,[1] consecutive patients were randomly assigned (1:1) to one of the two treatment groups, independently of clinical indication. Therefore, it is possible that some patients were assigned to enteral nutrition when this treatment was not clinically indicated (ie, absence of gastrointestinal integrity or function, or both), possibly affecting the results. Patients in the enteral group had significantly more episodes of vomiting and diarrhoea and major events, such as bowel ischaemia and acute colonic pseudo-obstruction,[1] possibly affecting mortality and secondary infections.

Enteral nutrition has been indicated to stimulate intestinal function either directly by supplying substrates for enterocyte oxidation, or indirectly, by promoting hormone secretion and limiting bacterial translocation.[3]

Data for enteral feeding highlight benefits in comparison with parenteral nutrition, such as lower infectious and non-infectious complications and associated costs.[4,5] Therefore, when deciding the most appropriate route of nutrient delivery, continuous clinical judgment rather than strict adherence to protocols should inform therapy in ventilated adults with shock.

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Authors' reply

We thank correspondents for their comments on the NUTRIREA-2 trial.[1] We agree with Simon Bourcier and Alain Combes that bowel ischaemia is challenging to diagnose and can be caused by different mechanisms, including non-occlusive mesenteric ischaemia and vessel obstruction. Moreover, we agree that the unblinded study design could have caused detection bias. These points were clearly acknowledged in the discussion. However, predefined criteria were used in the NUTRIREA-2 trial to diagnose bowel ischaemia. Importantly, the use of diagnostic tools, including CT scanning, CT angiography, angiography, magnetic resonance angiography, endoscopy, and surgery strongly limited the risk of detection bias. In the CALORIES trial,[2] which used similar predefined criteria of bowel ischaemia, 11 (0·9%) of 1195 patients in the enteral nutrition group had bowel ischaemia, compared with eight (0·7%) of 1188 patients in the parenteral nutrition group. The proportion of patients with bowel ischaemia in the parenteral nutrition CALORIES group was similar to that in the corresponding NUTRIREA-2 group. The higher frequency in our enteral nutrition group could be related to the greater illness severity, as only mechanically ventilated patients with shock were included, compared with unselected critically ill patients in the CALORIES trial.

As stated by Tetsuji Fujita, the amount of enteral nutrition delivered during the acute phase of critical illness could have an impact on gastrointestinal complications. When the NUTRIREA-2 trial was designed, data for this point were very scarce. To the best of our knowledge, the only large trial comparing hypocaloric to normocaloric enteral nutrition is the EDEN trial[3] with patients receiving invasive mechanical ventilation for acute lung injury. There was no between-group difference in ventilator-free days or mortality at day 60. Patients with hypocaloric feeding had fewer days with regurgitation, vomiting, and constipation, compared with those with full enteral feeding. There were no differences in other gastrointestinal complications between groups. Whether the enteral feeding route and the enteral-nutrition calorie target could have beneficial or deleterious effects on the gut mucosa of critically ill patients with shock is unclear.[4,5] Current guidelines recommend prokinetic drug therapy of gastroparesis before lowering the calorie target in patients intolerant to early enteral nutrition.[6]

Lastly, we disagree with Alessio Molfino and Alessandro Laviano's suggestion that some patients in the enteral nutrition group could have had contraindications to enteral feeding, thus explaining the higher frequency of bowel ischaemia in this group compared with the parenteral nutrition group. Non-inclusion criteria in the NUTRIREA-2 protocol consisted of active gastrointestinal bleeding; gastrointestinal tract surgery within the past month; and a history of gastrectomy, oesophagectomy, duodenopancreatectomy, bypass surgery, gastric banding, or short bowel syndrome. The European Society for Clinical Nutrition and Metabolism guidelines[6] on supplemental parenteral nutrition were supported only by low-level evidence and have been contradicted by the EPaNIC trial results.[7] The possibility that enteral nutrition might decrease the risk of infectious and non-infectious complications compared with parenteral nutrition is not supported by the results of the NUTRIREA-2 and CALORIES trials. The NUTRIREA-2 trial provides the first evidence that early enteral nutrition could promote gut ischaemia in patients with severe, critical illness, including shock. We are confident that this evidence is reliable and constitutes valid grounds for concern about adverse effects of enteral nutrition in patients with shock who are receiving mechanical ventilation. Whether the route or dose of feeding plays the main role in these adverse effects requires further investigation. The NUTRIREA-3 trial (NCT03573739), comparing hypocaloric and standard feeding, is ongoing and will provide additional data for this issue.

We declare no competing interests.

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