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ORIGINAL

Factors associated with acute mesenteric ischemia among critically ill ventilated patients with shock: a post hoc analysis of the NUTRIREA2 trial

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Abstract

Purpose: Acute mesenteric ischemia (AMI) is a rare, but life-threatening condition occurring among critically ill patients. Several factors have been associated with AMI, but the causal link is debated, most studies being retrospective. Among these factors, enteral nutrition (EN) could be associated with AMI, in particular among patients with shock. We aimed to study the factors independently associated with AMI in a post hoc analysis of the NUTRIREA-2 trial including 2410 critically ill ventilated patients with shock, randomly assigned to receive EN or parenteral nutrition (PN).

Methods: Post hoc analysis of the NUTRIREA-2 trial was conducted. Ventilated adults with shock were randomly assigned to receive EN or PN. AMI was assessed by computed tomography, endoscopy, or laparotomy. Factors associated with AMI were studied by univariate and multivariate analysis.

Results: 2410 patients from 44 French intensive care units (ICUs) were included in the study: 1202 patients in the enteral group and 1208 patients in the parenteral group. The median age was 67 [58–76] years, with 67% men, a SAPS II score of 59 [46–74], and a medical cause for ICU admission in 92.7%. AMI was diagnosed among 24 (1%) patients, mainly by computed tomography (79%) or endoscopy (38%). The mechanism of AMI was non-occlusive mesenteric ischemia ($n=12$), occlusive ($n=4$), and indeterminate ($n=8$). The median duration between inclusion in the trial and

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AMI diagnosis was 4 [1–11] days. Patients with AMI were older, had a higher SAPS II score at ICU admission, had higher plasma lactate, creatinine, and ASAT concentrations and lower hemoglobin concentration, had more frequently EN, dobutamine, and CVVHDF at inclusion, developed more frequently bacteremia during ICU stay, and had higher 28-day and 90-day mortality rates compared with patients without AMI. By multivariate analysis, AMI was independently associated with EN, dobutamine use, SAPS II score ≥ 62 and hemoglobin concentration ≤ 10.9 g/dL.

Conclusion: Among critically ill ventilated patients with shock, EN, dobutamine use, SAPS II score ≥ 62 and hemoglobin ≤ 10.9 g/dL were independently associated with AMI. Among critically ill ventilated patients requiring vasopressors, EN should be delayed or introduced cautiously in case of low cardiac output requiring dobutamine and/or in case of multiple organ failure with high SAPS II score.

Keywords: Acute mesenteric ischemia, Critically ill, Shock, Enteral nutrition, Parenteral nutrition

Introduction

Acute mesenteric ischemia (AMI) is a rare, but life-threatening condition among critically ill patients being associated with a high mortality rate [1]. In most cases of AMI occurring in the intensive care unit (ICU), the mechanism is related to low flow states with absence of mesenteric vascular occlusion, defining the non-occlusive mesenteric ischemia (NOMI) [2]. It is well established that the gut, and in particular the small bowel, is very sensitive to low flow state or hypoxia [3]. The diagnosis of AMI is difficult and often delayed in the ICU, in particular because of the inability of patients to indicate abdominal pain in case of deep sedation [4]. It is considered that the severity of shock per se could lead to NOMI among critically ill patients, in particular in case of mesenteric atherosclerosis [5]. In this context, enteral nutrition (EN) could lead to the development of AMI, or could impair a pre-existing AMI, by impairing the adequacy between oxygen delivery and demand to the gut [6]. Therefore, the the American Society for Parenteral and Enteral Nutrition (ASPEN), the European Society for Clinical Nutrition and Metabolism (ESPEN), the Society of Critical Care Medicine (SCCM), and the European Society of Intensive Care Medicine (ESICM) recommend that EN should be delayed among critically ill patients with uncontrolled shock [7–9]. On the other hand, EN is associated with beneficial effects on the gut mucosa of critically ill patients, avoiding villous atrophy, loss of gut barrier failure, and bacterial translocation, and could be safe among patients requiring low catecholamine dose [10–13]. Finally, factors associated with AMI among critically ill patients have been poorly studied, mainly by retrospective analyses. Recently, the NUTRIREA-2 study, evaluating the impact of the route of nutrition among critically ill ventilated patients with shock, identified that EN was associated with an increased risk of AMI compared with parenteral nutrition (PN), with 2% vs < 1% cases of AMI, respectively [14]. In this post hoc analysis of the NUTRIREA-2 trial, we aimed to study the factors associated with AMI in a population of critically ill ventilated patients with shock.

Take-home message

This study identified four factors associated with acute mesenteric ischemia among medical critically ill ventilated patients with shock: enteral nutrition, dobutamine use, SAPS II score ≥ 62, and hemoglobin concentration ≤ 10.9 g/dL This suggests that among critically ill ventilated patients with shock requiring vasopressors, enteral nutrition should be delayed in case of low cardiac output requiring dobutamine and/or in case of multiple organ failure with high SAPS II score.

Patients and methods

Study protocol

This was a post hoc analysis of the large randomized controlled NUTRIREA-2 trial (ClinicalTrials.gov NCT01802099) [14]. In this randomized, controlled, multicenter, open-label, parallel-group study done at 44 French ICUs, adults (18 years or older), expected to require more than 48 h of invasive mechanical ventilation and vasopressure support (adrenaline, dobutamine, or noradrenaline) via a central venous catheter for shock and to be started on nutritional support within 24 h after tracheal intubation (or within 24 h after ICU admission if intubation occurred before ICU admission), were randomly assigned (1:1) to either PN or EN, both targeting normocaloric goals (20–25 kcal/kg per day), within 24 h after intubation. In the parenteral group, PN was switched to EN at day 7, unless a contraindication to enteral feeding was identified. However, a switch toward EN was possible after 72 h among patients of the parenteral group in whom catecholamine had been weaned off for 24 h and plasma lactate concentration was less than

2 mmol/l. In the enteral group, PN was allowed only after day 8 in case of feeding intolerance and/or insufficient caloric intake. Exclusion criteria were invasive mechanical ventilation started more than 24 h earlier; surgery on the gastrointestinal tract within the past month; history of gastrectomy, esophagectomy, duodeno-pancreatectomy, bypass surgery, gastric banding, or short bowel syndrome; gastrostomy or jejunostomy; specific nutritional needs, such as pre-existing long-term home EN or PN; active gastrointestinal bleeding; treatment-limitation decisions; adult under legal guardianship; pregnancy; breastfeeding; current inclusion in a randomized trial designed to compare EN with PN; contraindication to PN (known hypersensitivity to egg or soybean proteins or to another component, inborn error in amino acid metabolism, or severe familial dyslipidemia affecting triglyceride levels).

Acute mesenteric ischemia and other complications

During ICU stay, the following variables were collected: bacteremia; AMI confirmed either on abdominal computed tomography, at digestive endoscopy, or during laparotomy. AMI was defined as any of the following predefined criteria: absent blood flow in one of the main arteries supplying the bowel (superior mesenteric artery, inferior mesenteric artery or celiac artery) with evidence of bowel wall compromise on an imaging study (computed tomography angiography, angiography, or magnetic resonance angiography), and/or presence of endoscopy criteria for colonic ischemia according to the Favier classification system (stage I, petechiae; stage II, petechiae and superficial ulcers; and stage III, necrotic ulcers and polypoid lesions), and/or evidence of bowel ischemia during surgery. AMI was classified according to the mechanism of vascular occlusion (occlusive, non-occlusive or unknown) as identified on abdominal computed tomography (CT) when contrast-enhanced injection was available. The delay between inclusion in the protocol and the diagnosis of AMI was recorded. 28-day mortality and 90-day mortality were also collected.

Statistical analyses

Nominal variables were expressed as number (percentage) and were compared with the Fisher's exact test. Continuous variables were expressed as median [interquartile range] and compared with the Mann– Whitney test. In a first time, the variables associated with AMI by univariate analysis ($p < 0.05$) were introduced in a logistic regression model to perform a multivariable analysis with a backward method. In a second time, continuous variables independently associated with AMI were dichotomized at a cutoff value identified according to the receiver operating characteristic (ROC) curve analysis and introduced in a second multivariable analysis. Statistical analyses were performed with IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp.

Results

Description of the study population

2410 patients were included in the study, with a mean age of 67 [58–76] years, with 67% men, and a Simplified Acute Physiology Score (SAPS) II of 59 [46–74]. A medical cause for ICU admission was found in 92.7% of the patients, and AMI was diagnosed in 24/2410 patients (1%) during ICU stay. AMI was found in 19/1202 (1.6%) of the patients in the EN group and 5/1208 (0.4%) in the PN group. The norepinephrine dose at inclusion was 0.44 [0.22–0.93] γ/kg/min in the 2266 (94%) receiving norepinephrine.

Description of the cases of AMI

The 24 cases of AMI are described in Table 1 and in the Supplementary Table. AMI diagnosis was mainly based upon computed tomography (79%) and digestive endoscopy (38%). The mean time between inclusion and diagnosis was 4 [1–11] days. The mechanism of AMI was NOMI in 50% (58% vs 20% in the EN and PN groups), occlusive in 17% (11% vs 40% in the EN and PN groups), and unknown in 33% (31% vs 40% in the EN and PN groups). Intestinal resection was performed in 54%, whereas conservative treatment was performed in 46%. Twenty-eight-day and 90-day mortality rates were 58% and 75%, respectively. The catecholamine dose was 0.79 [0.49–1.47] γ/kg/min, and 90% of the patients developing AMI had a catecholamine dose $\geq$ 0.3 γ/kg/min at inclusion. The caloric intake at day 4 among the patients under EN developing AMI was 1460 [1293–1849] kcal, and 15/16 (94%) received more than 20 ml/h on day 4.

Univariate analysis of factors associated with AMI

Univariate analysis of the variables associated with AMI appears in Table 2. Compared with patients without AMI, patients diagnosed with AMI were older, had a higher SAPS II score at ICU admission, had higher plasma lactate, creatinine, and aspartate aminotransferase (ASAT) concentrations and lower hemoglobin concentration, had more frequently EN, dobutamine and continuous veno-venous hemodiafiltration (CVVHDF) at inclusion, developed more frequently bacteremia during ICU stay, and had higher 28-day and 90-day mortality rates.

Table 1 Description of the 24 cases of acute mesenteric ischemia

Variables of AMI	*n* = 24
Diagnosis	
Computed tomography	19 (79)
Endoscopy	9 (38)
Colonoscopy	5 (21)
Stage III	4/5 (80)
Not available	1/5 (20)
Upper digestive endoscopy	3 (13)
Stage III	1/3 (33)
Stage I	1/3 (33)
Not available	1/3 (34)
Rectosimoidoscopy	1 (4)
Stage III	1/1 (100)
Arteriography	1 (4)
Strategy of diagnosis	
CT alone	12 (50)
CT + endoscopy	7 (30)
Endoscopy alone	2 (8)
Surgery alone	2 (8)
Arteriography alone	1 (4)
Time between inclusion and diagnosis (day)	4 [1–11]
Mechanism of AMI	
Non-occlusive	12 (50)
Occlusive	4 (17)
Unknown	8 (33)
Absence of CT	3 (38)
CT with written report unavailable	5 (62)
Intestinal resection	6 (75)
Treatment of AMI	
Intestinal resection	13 (54)
Conservative treatment	11 (46)
Prognosis	
28-day mortality rate	14 (58)
90-day mortality rate	18 (75)
NOMI	10/12 (83)
Unknown mechanism	7/8 (88)
Occlusive	1/4 (25)

Numbers are *n* (%) and median [interquartile range]

NOMI non-occlusive mesenteric ischemia; *AMI* acute mesenteric ischemia; *CT* computed tomography

Multivariate analysis of factors associated with AMI

Multivariate logistic regression analysis of variables associated with AMI appears in Table 3. The variables included in the model were age, lactate, creatinine, ASAT, hemoglobin, CVVHDF, dobutamine infusion, route of nutrition, and SAPS II score. By multivariate analysis, a higher SAPS II score (OR 1.04 [1.02–1.06]), use of EN (OR 4.28 [1.58–11.61]), dobutamine infusion (OR 2.78 [1.16–6.67]), and hemoglobin level at inclusion (OR 0.82 [0.69–0.96]) were independently associated with AMI. After dichotomization of the continuous variables, a SAPS II score ≥ 62 (OR 4.18 [1.55–11.30]), use of EN (OR 3.92 [1.45–10.60]), dobutamine infusion (OR 2.90 [1.21–6.94]), and hemoglobin ≤ 10.9 g/dL (OR 3.79 [1.40–10.29]) were independently associated with AMI.

Whereas the overall prevalence of AMI was 1% in the study, it was 3.8% among patients receiving both EN and dobutamine (Fig. 1), and 2.6% among patients receiving EN and having a SAPS II score > 62 (Fig. 2). No case of AMI was diagnosed among the 644 patients receiving PN and having a SAPS II score ≤ 62 (Fig. 2).

Discussion

In this post hoc analysis of a large randomized controlled trial including 2410 critically ill ventilated patients with shock receiving EN or PN, we identified four factors independently associated with AMI: the enteral route of nutrition, the use of dobutamine, a SAPS II score > 62, and a hemoglobin level at inclusion ≤ 10.9 g/dL. Most cases of AMI were related to NOMI and were diagnosed by computed tomography. The prognosis of patients with AMI was poor.

We found that 1% of critically ill ventilated patients with shock developed AMI. This result is concordant with the study of Mancl et al., who found that the prevalence of AMI was 0.9% in a retrospective study of 259 critically ill patients with vasopressors receiving EN [15]. In the study by Mancl et al., there was an inverse correlation between the norepinephrine dose and the EN tolerability [15], suggesting a possible link between the dose of vasopressor and the risk of NOMI, also suspected by us studying biomarkers of acute mesenteric ischemia [16]. Ohbe et al. also identified the possible importance of the catecholamine dose, early EN being safe among patients receiving less than 0.3 γ/kg/min of norepinephrine [13]. Similarly, in the current study, 90% of the patients developing AMI had more than 0.3 γ/kg/min of norepinephrine at inclusion. The overall prognosis of the patients developing AMI was poor, with a 28-day mortality rate of 58%, which was concordant with the results by Leone et al. describing a mortality rate of 58%, similar to us. Patients were aged 74 years in this study and 69 years in the study by Leone et al., confirming that AMI is a disease that should be strongly suspected among old patients presenting with shock [1].

The main result of this study is that we identified four independent factors associated with AMI. First, we identified that EN was associated with an increased risk of AMI compared with PN, with an odds ratio of 3.9. This result is logical in a population of critically ill patients with shock receiving early EN, because EN

Table 2 Univariate analysis of the variables associated with acute mesenteric ischemia among 2410 critically ill patients ventilated with shock

Variable	Absence of AMI *n* = 2386	AMI *n* = 24	*p* value
Clinical variables			
Age (year)	67 [58–77]	74 [66–78]	0.045
Male sex	1608 (67)	16 (67)	1.0
Body mass index	27 [23–31]	27 [22–30]	0.39
Biological variables			
Lactate (mmol/L)	2.6 [1.6–4.7]	4.7 [3–6.5]	0.002
ASAT (UI/L)	67 [34–194]	181 [51–463]	0.05
ALAT (UI/L)	43 [23–99]	57 [41–130]	0.15
Bilirubin (µmol/L)	13 [8–24]	15 [10–24]	0.40
Creatinine (µmol/L)	140 [88–237]	170 [141–216]	0.04
Hemoglobin (g/dL)	11 [9.3–12.8]	9.6 [8.2–10.7]	0.006
Variables of treatment			
Norepinephrine infusion	2245 (94)	21 (88)	0.17
Epinephrine infusion	198 (8)	4 (17)	0.14
Dobutamine infusion	342 (14)	8 (33)	0.02
PaO_2 (mmHg)	91 [71–133]	117 [68–186]	0.34
PEEP (cm H_2O)	6 [5–10]	5 [5–9]	0.24
CVVHDF the day of inclusion	462 (19)	10 (42)	0.02
Type of nutrition			
Enteral nutrition	1183 (50)	19 (79)	0.004
Parenteral nutrition	1203 (50)	5 (21)	
Caloric intake day of inclusion (kcal)	796 [350–1180]	743 [281–1067]	0.45
Variables of prognosis			
SAPS II score	60 [47–74]	73 [63–90]	< 0.001
Bacteremia	89 (4)	4 (17)	0.01
28-day mortality rate	842 (35)	14 (58)	0.03
90-day mortality rate	1019 (43)	18 (75)	0.003

Numbers are *n* (%) and median [interquartile range]

ALAT alanine aminotransferase; *AMI* acute mesenteric ischemia; *ASAT* aspartate aminotransferase; *CVVHDF* continuous venovenous hemodiafiltration; *SAPS II* simplified acute physiologic score; *PEEP* positive end-expiratory pressure

increases the work of the gut and could impair the balance between oxygen delivery and demand of the gut [2, 6, 17]. Interestingly, NOMI was the mechanism involved in 58% of the patients developing AMI under EN, and was involved in only 20% of the patients developing AMI under PN, reinforcing the link between EN and NOMI. Whereas EN is associated with beneficial effects on the gut mucosa, these effects could be counterbalanced by the occurrence of AMI in case of severe shock [10, 18]. Indeed, in an ancillary study of the NUTRIREA 2 trial, we identified that EN was associated with higher plasma intestinal fatty acid-binding protein (I-FABP) concentration at day 3 of nutrition compared with PN [18]. Since I-FABP is a biomarker of enterocyte necrosis, this result suggests that full EN could favor the development of mucosal ischemia. However, despite this signal regarding I-FABP concentration, we identified that EN was associated with a higher plasma citrulline concentration on day 3 compared with PN, suggesting a complex but globally beneficial effect of EN on gut mucosa. The second factor associated with AMI was the use of dobutamine, which had an odds ratio of 2.9. This result is concordant with the hypothesis that the main mechanism of AMI in the ICU is NOMI [19]. For the gut, not only the pressure matters, but also the flow: both hypotension and low flow states are associated with the development of NOMI [2, 20]. Therefore, this result suggests that after correction of hypotension using fluid challenge and vasopressors, the persistence of low cardiac output requiring infusion of dobutamine exposes the gut to a risk of ischemia. However, our data do not permit to exclude other mechanisms, including direct adverse effect of dobutamine on the gut or gut perfusion. The third factor associated

Table 3 Simple and multivariate logistic regression analyses of variables associated with acute mesenteric ischemia among 2410 critically ill ventilated patients with shock

Variables at inclusion	Simple model odds ratio [95% CI]	*p* value	Multiple model odds ratio [95% CI]	*p* value
First model with continuous variables				
SAPS II score	1.04 [1.02–1.06]	< 0.001	1.04 [1.02–1.06]	< 0.001
Route of nutrition		0.007		0.004
Parenteral nutrition	1		1	
Enteral nutrition	3.86 [1.44–10.38]		4.28 [1.58–11.61]	
Dobutamine infusion		0.01		0.02
No	1		1	
Yes	2.99 [1.27–7.04]		2.78 [1.16–6.67]	
Hemoglobin at inclusion (g/dL)	0.81 [0.68–0.95]	0.009	0.82 [0.69–0.96]	0.01
Second model with dichotomized variables				
SAPS II		0.002		0.005
< 62	1		1	
≥ 62	4.67 [1.74–12.56]		4.18 [1.55–11.30]	
Route of nutrition		0.007		0.007
Parenteral nutrition	1		1	
Enteral nutrition	3.86 [1.44–10.38]		3.92 [1.45–10.60]	
Dobutamine infusion				0.02
No	1		1	
Yes	2.99 [1.27–7.04]		2.90 [1.21–6.94]	
Hemoglobin at inclusion		0.009		0.009
> 10.9 g/dL	1		1	
≤ 10.9 g/dL	3.74 [1.39–10.04]		3.79 [1.40–10.29]	

SAPS 2 Simplified Acute Physiologic Score

with AMI was a SAPS II score > 62. This result suggests that the overall severity of the patient at ICU admission is a risk factor of AMI [1]. Since NOMI associates gut ischemia with kidney and liver ischemia [19], it is logical that AMI was associated with a higher SAPS II score, reflecting multiple organ failure. Finally, we identified that a hemoglobin level ≤ 10.9 g/dL was associated with an increased risk of AMI. Again, this result is concordant with the fact that AMI in the ICU is mainly related to NOMI. In this context, a reduction of hemoglobin level leads to a reduced transport of oxygen to the gut. Finally, three out of the four risk factors identified were related to the pathophysiology of NOMI: a reduction of oxygen delivery to the gut (reduced cardiac output with need of dobutamine use; reduced hemoglobin level) or an increased demand of oxygen by the gut (introduction of EN) leading to an imbalance between oxygen demand and delivery.

To the best of our knowledge, we report the largest prospective study dealing with the risk of AMI among critically ill patients with shock, with more than 2400 patients included. All diagnoses of AMI were confirmed using computed tomography, digestive endoscopy, or mesenteric arteriography. Most other studies dealing with AMI in the context of ICU were retrospective [1, 4]. In addition, Reintam et al. identified that the studies dealing with early enteral nutrition in patients with shock receiving vasopressors were prospective observational or retrospective, ranging between 9 and 1174 patients, with no randomized controlled trials [8].

From a clinical point of view, the results of this study could help to identify the subgroup of patients with shock in whom EN should be delayed or introduced cautiously. Indeed, no case of AMI was diagnosed among critically ill patients with shock receiving PN and having a SAPS II score ≤ 62 (Fig. 2). On the other hand, the prevalence of AMI was approximately 4% among patients with shock receiving EN and requiring dobutamine, and approximately 3% among patients receiving EN and having a SAPS II score > 62 (Figs. 1 and 2). Finally, among critically ill patients with shock under vasopressors, an evaluation of the risk of AMI could be performed before starting EN. As recommended by guidelines, this evaluation should take into account the kinetics of the vasopressor dose, but also the overall severity of the patient assessed by the SAPS II score and the need for dobutamine related

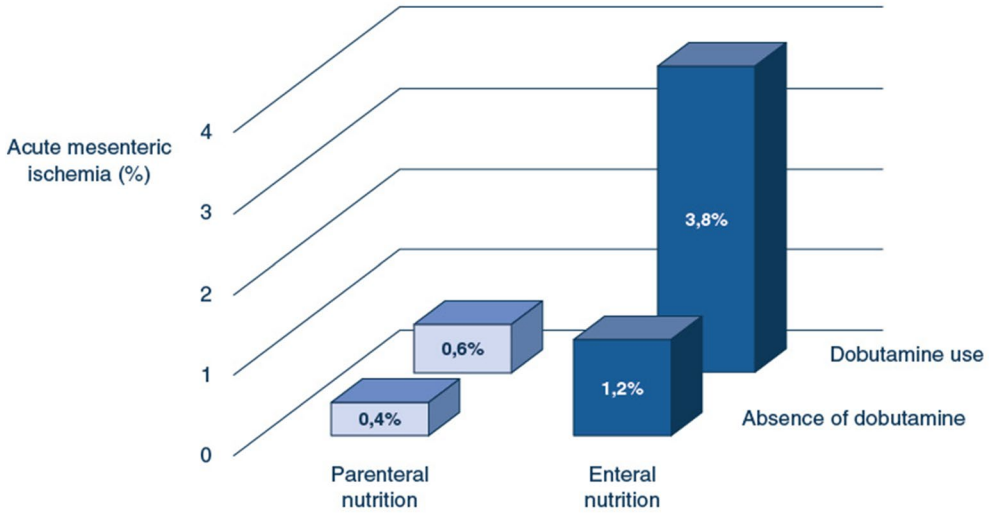

Fig. 1 Prevalence of acute mesenteric ischemia according to the route of nutrition and the dobutamine use

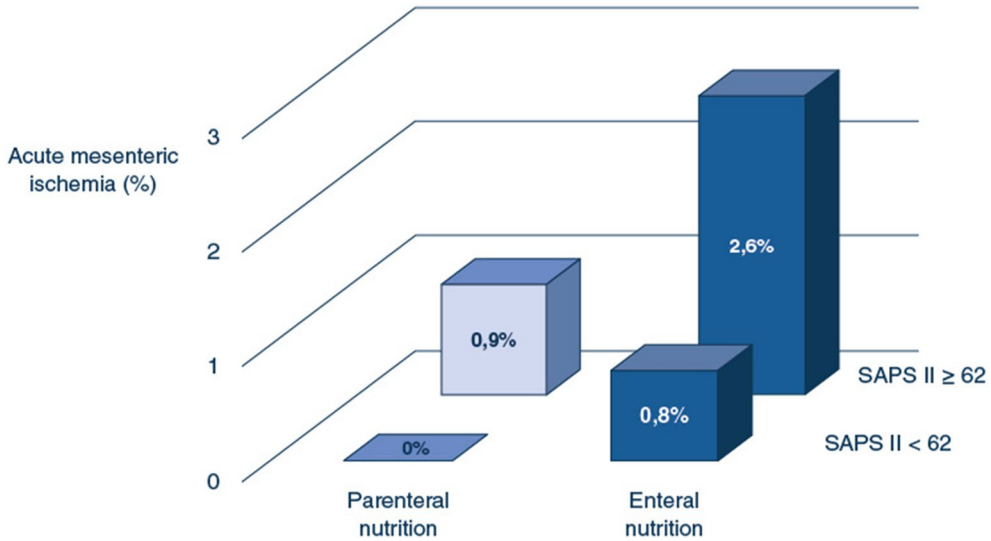

Fig. 2 Prevalence of acute mesenteric ischemia according to the route of nutrition and the SAPS 2 score

to low cardiac output. In case of increasing vasopressor dose, persistent low cardiac output requiring inotropic drugs, or multiple organ failure with high SAPS II score, EN should be probably delayed.

This study has several limitations. First, the search for AMI was based upon clinical judgment, and no systematic search of AMI was performed among patients. Therefore, it is likely that some cases of AMI have been underdiagnosed, in particular among the most severe patients dying early from multiple organ failure, and the 1% of AMI could be underestimated. Second, the strategy for the diagnosis of AMI was not protocolized in the study, since this was a post hoc analysis. However, most diagnoses were based upon abdominal computed tomography which is the best option for the diagnosis of AMI, or based upon digestive endoscopy which has a high specificity for the diagnosis of AMI. Third, to perform an exploratory analysis of AMI risk factors, many variables were included in the multivariate model, whereas the event of AMI was rare. As a rule of thumb, one covariate can be entered per ten events in a multivariate analysis [21]. Fourth, most of the patients included in this study were admitted to the ICU for a medical cause, and the risk factors identified could have been different among

post-surgical patients. Last, the prescribed dose of artificial nutrition was 25 kcal/kg/d. Lower amounts of EN may be associated with lower rates of AMI. Indeed, 94% of the patients developing AMI while under EN received more than 20 ml/h on day 4, suggesting that AMI is unlikely with trophic EN. Further studies are needed to explore this question.

In conclusion, we identified four factors associated with AMI among a population of medical critically ill ventilated patients with shock: EN, dobutamine use, SAPS II score > 62, and hemoglobin concentration ≤ 10.9 g/dL. NOMI was the main mechanism of AMI. Among critically ill ventilated patients with shock requiring vasopressors, EN should be delayed or introduced cautiously in case of low cardiac output requiring dobutamine and/or in case of multiple organ failure with high SAPS II score.

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1007/s00134-022-06637-w.

Abbreviations
AMI: Acute mesenteric ischemia; EN: Enteral nutrition; PN: Parenteral nutrition; ICU: Intensive care unit; NOMI: Non-occlusive mesenteric ischemia.

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Declarations

Conflicts of interest
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