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Early Enteral Nutrition and Gastrointestinal Complications in Pediatric Patients on Extracorporeal Membrane Oxygenation

*‡Gema Pérez, *Elena González, *Laura Zamora, *†‡§Sarah N. Fernández, *†‡§Amelia Sánchez, ‡Jose María Bellón, *†‡§María José Santiago, and *†‡§María José Solana

ABSTRACT

Objectives: To assess the safety of enteral nutrition (EN) in children on extracorporeal membrane oxygenation (ECMO). To describe nutritional status and the characteristics of the nutritional support in this population.

Methods: A retrospective single-center analysis (2006–2016) including children <18 years on ECMO. Demographic data, nutritional status, characteristics of nutritional support, and development of gastrointestinal (GI) complications were recorded.

Results: One hundred children, with a median age of 9.7 months (interquartile range [IQR] 3.9–63.1) were enrolled. Undernutrition was prevalent among children on ECMO (33.3%) mainly in patients <2 years ($P = 0.042$). Most patients (64%) received EN at some point during ECMO therapy. EN was administered in the first 48 hours after ECMO initiation (48HEN) to 60.3% of the children.

Mortality rate in the Pediatric Intensive Care Unit was lower in patients who received EN as the initial artificial nutrition support (ANS) (37.7 vs 51%, $P = 0.005$) and in children on 48HEN (34% vs 50%, $P = 0.04$). In the logistic regression analysis, duration of ECMO support and low cardiac output indication were the only factors associated with mortality.

Although most patients on ECMO (45%) developed digestive complications, they were mostly mild, being constipation the most prevalent. In the logistic regression analysis, EN was not associated with an increase in GI complications ($P = 0.09$). Only three patients developed intestinal ischemia (one without EN and two on EN).

Conclusions: Undernutrition is prevalent among children on ECMO, mainly in infants <2 years. EN is not associated with severe gastrointestinal complications or higher mortality in these children.

Key Words: complications, enteral nutrition, extracorporeal membrane oxygenation, nutritional support, parenteral nutrition, pediatric intensive care

(*JPGN* 2022;74: 110–115)

What Is Known

- Enteral nutrition (EN) and early enteral nutrition (EEN) are safe in adult patients on extracorporeal membrane oxygenation (ECMO) support.
- Undernutrition is prevalent among pediatric patients on ECMO.

What Is New

- EN and 48HEN (EN administered within the first 48 hours after ECMO initiation) are safe in pediatric patients on ECMO, as gastrointestinal complications are mostly mild.
- No association was found between the use of EN and mortality.

The use of extracorporeal membrane oxygenation (ECMO) is becoming increasingly common in pediatric patients with severe respiratory or heart failure (1). Critically ill patients on ECMO support are at a high risk of developing digestive problems, since splanchnic circulation may be impaired favoring intestinal ischemia (2) and sepsis due to bacterial translocation (3).

Undernutrition is prevalent among pediatric patients on ECMO (4,5) and may have negative effects on prognosis (6–8), therefore, an adequate nutritional support is essential in these patients (5,9,10). EN support is common but not uniform among neonatal and pediatric patients receiving ECLS (11). Parenteral nutrition (PN) or late enteral nutrition (EN) is often administered to critically ill children on ECMO to prevent potential digestive complications.

Received April 5, 2021; accepted September 6, 2021.

From the *Pediatric Intensive Care Unit, Hospital General Universitario Gregorio Marañón, the †Maternal and Child Public Health Department. Universidad Complutense de Madrid, the ‡Gregorio Marañón Health Research Institute (IISGM), and the §Maternal and Child Health and Development Research Network (REDSAMID), Institute of Health Carlos III, Madrid, Spain.

Address correspondence and reprint requests to María José Santiago, MD, PhD, Pediatric Intensive Care Department, Gregorio Marañón University Hospital, Dr. Castelo 47, 28009 Madrid (e-mail: msanti20@ucm.es).

Source of Funding: This work was supported by Carlos III Health Institute (PI17/00248): Mother-Child Health and Development Network (Red SAMID)–RETICS funded by the PN I+D+I 2008–2011 (Spain), ISCIIISub-Directorate General for Research Assessment and Promotion, and the European Regional Development Fund (ERDF), ref. RD16/0022/0007.

The authors report no conflicts of interest.

DOI: 10.1097/MPG.0000000000003317

Some recent studies suggest that early EN (EEN) is safe in adult patients on ECMO support (12–15), but the evidence about its safety in neonates (16) and pediatric patients (17) is scarce. Moreover, the nutritional status of these patients and the development of gastrointestinal complications associated with EN, has not been assessed in any of the studies published so far.

The primary outcome of this study was to assess the development of gastrointestinal complications and mortality associated with the use of EN, including enteral nutrition started within the first 48 hours of ECMO support, in children on ECMO. The secondary outcomes were to analyze the nutritional status and type of nutritional support including the caloric and protein intake in this population.

PATIENTS AND METHODS

A retrospective study was carried out in the Pediatric Intensive Care Unit (PICU) of a tertiary hospital between September 2006 and 2016. All patients, neonates and children <18 years receiving ECMO in the pediatric intensive care unit were previously included in a prospective registry. The registry was approved by the Gregorio Marañon Institutional Review Board. Informed consent from the parents was obtained for all the patients included in the registry. The local Ethics Committee approved also this retrospective review.

The data collected included demographic and anthropometric data, nutritional status before ECMO support, diagnosis, length of PICU stay and mortality. Other data included were the reason for indication and type of ECMO, duration of therapy and data related to artificial nutrition support (ANS): type of ANS, type of formula administered, time to initiation of ANS, route of EN administration and use of EN within the first 48 hours of ECMO support (48HEN).

Moreover, information about digestive complications (abdominal distension, gastric residual volume, constipation, diarrhea, vomits, gastrointestinal bleeding, and intestinal ischemia) was collected.

Anthropometric (weight and height/length) was registered at PICU admission and nutritional status was assessed using an online tool (https://www.seghnp.org/) certified by the Spanish Society of Pediatric Gastroenterology to calculate the following scores: weight-for-height (WH) z score for children <2 years and body mass index (BMI) z score for children >2 years. Undernutrition was defined as a z score <-2 in any of these scores and overweight was defined as a z score >2. This cut-off point was selected following the American and European guidelines (18,19).

Energy targets were calculated using Schofield equations for basal metabolic rate and protein targets were taken as the lower range of requirement for age in critically ill children (18).

The following variables were collected: caloric and protein intake at the beginning and at day 7 of EN, time to nutrition initiation (hours), time to maximum nutrition delivery (hours) and maximum caloric (kcal kg^{-1} d^{-1}) and protein intake (g kg^{-1} d^{-1}).

Long-term ECMO support was defined as a duration of ECMO >7 days.

High gastric residual volume was considered when gastric content was >50% the volume of enteral nutrition administered in the previous 4 hours (20). Diarrhea was defined as the presence of >8 liquid stools in infants <3 months of age, >4 liquid stools in 3–12-month-old children, and more than two liquid stools in children >12 months (20). Constipation was defined as the absence of bowel movements 72 hours after the start of EN (21). Abdominal distension was considered if abdominal circumference on the sagittal plane was increased (22). Intestinal ischemia was defined as the occurrence of clinical signs of low digestive bleeding and/or poor abdominal wall perfusion concurrent to pathological findings on ultrasound or CT scan.

Categorical variables were expressed as frequencies and percentages. Continuous variables were presented as mean and standard deviation in case of normal distribution or as median and interquartile range when the variable was not normally distributed. Comparison of categorical variables was performed using χ^2 and Fisher exact test. Continuous variables were compared with Student t-test and median test for not normally distributed variables. Univariate and multivariate logistic regression models were performed to study the strength of the association with complications and mortality. As independent variables, we considered those that are clinically significant. After a first statistical evaluation, we limited the covariates to three in the complications model (ECMO duration, enteral nutrition, and high morphic dose). In the mortality model, five covariates (malnutrition, low cardiac output, ECMO duration, enteral nutrition, digestive complications) were necessary to maintain an adequate area under the receiver operator characteristic curve (area under curve = 0.85). Significance was set at a P value of <0.05. IBM SPSS Statistics 21.0 system (SPSS Inc, Chicago, USA) was used for statistical analysis.

RESULTS

During the study period, 100 critically ill children required ECMO support. Sixty-seven percent of them were male. The median age at the onset of ECMO therapy was 9.7 months (interquartile range [IQR] 3.9–63.1 months). Detailed demographic and clinical characteristics of the cohort are highlighted in Table 1.

The most prevalent diagnosis at admission was cardiac disease (93%), followed by respiratory failure (5%) and septic shock (2%).

ECMO therapy was veno-arterial in 98% of the cases. The most frequent reasons for ECMO support were inability to wean from extracorporeal membrane oxygenation after cardiac surgery

TABLE 1. Demographic characteristics of children on ECMO support

	Total group median [IQR]	Enteral nutrition, N = 64	No enteral nutrition, N = 36	*P*
Age (mo)	9.7 [3.9–63.1]	7.2 [3.6–35.4]	22 [4.2–127]	0.145
Weight (kg)	7.3 [4.8–16.7]	7.2[4.7–12]	8.7 [4.8–32]	0.532
Height (cm)	69 [58–102]	67 [57–95]	79 [61–123]	0.200
	% Total group	% Enteral nutrition	% No enteral nutrition	*P*
Cardiac disease	93%	91%	97%	0.213
Postoperatory period	65%	65.6%	63.9%	0.515
Cardiac arrest	24%	15.6%	38.9%	0.014
Undernutrition	33.3%	36.2%	28.6%	0.615
Exitus	49%	43.8%	58.3%	0.120

ECMO = extracorporeal membrane oxygenation; IQR = interquartile range.

TABLE 2. Characteristics of enteral and parenteral nutrition during ECMO support

	Enteral nutrition, $N = 64$, mean (SD)	Parenteral nutrition $N = 28$, mean (SD)	P
Time to nutrition initiation (h)	46.5 (40)	26.7 (24)	0.220
Time to maximum nutrition delivery (h)	33.8 (51.1)	60 (57.6)	0.097
Maximum caloric intake (kcal $kg^{-1} d^{-1}$)	53 (16)	49 (18)	0.311
Maximum protein intake (g $kg^{-1} d^{-1}$)	1.8 (0.85)	1.9 (0.88)	0.722
% Schofield	92 (35)	110 (36)	0.08

ECMO = extracorporeal membrane oxygenation; SD = standard deviation.

(28%) and non-postoperative low cardiac output (25%), followed by postoperative low cardiac output (17%), hypoxemia (13%), resuscitation (11%), arrhythmia (5%), and shock (1%). As many as 24% of children required ECMO in the setting of a cardiac arrest.

ECMO was performed with a centrifugal pump (Jostra Rotaflow HL20, Maquet, Germany) and hollow fiber oxygenators Quadrox-D and Quadrox-iD Pediatr (Jostra, Germany).

In 31 patients, ECMO support was necessary before PICU admission and was started in the operating room or catheterization laboratory. In the remaining 69 cases, the median time from PICU admission to ECMO therapy was 2 days (IQR 0.5–8 days). The median duration of ECMO therapy was 137.8 hours (IQR 73.9–226.1 hours) and the median length of PICU stay for survivors was 30 days (IQR 19.2–54.4 days).

The mortality rate of children requiring ECMO support was 49%. The leading cause of death was multiorganic failure (42.9%) followed by neurological complications (18.4%), adequacy of therapeutic effort (16.3%), massive bleeding (12.2%), cardiogenic shock (4.1%), arrhythmia after ECMO weaning (4.1%), and sepsis (2%). The use of EN was not associated with mortality ($P = 0.43$).

Nutritional Status of Children on Extracorporeal Membrane Oxygenation Support

The median weight at admission was 7.3 kg (IQR 4.8–16.7 kg) [median weight for age z score −1.4 (IQR −2.4/−0.4)]. Undernutrition was prevalent among children on ECMO at the onset of the therapy (33.3%) [median WH z score −1.9 (IQR −2.8/−0.9); median BMI z score −0.35 (IQR −1.9/0.9)] and was severe in 16% of the patients.

Undernutrition was more frequent in children <2 years as compared to older patients ($P = 0.042$).

Being undernourished was not associated with the development of gastrointestinal complications ($P = 0.68$), mortality ($P = 0.51$), or the need for prolonged ECMO support ($P = 0.32$).

Few children (5.3%) were overweight at the ECMO therapy onset. Being overweight was not associated with the development of gastrointestinal complications ($P = 0.37$), mortality ($P = 0.89$), or prolonged ECMO ($P = 0.1$).

Characteristics of the Artificial Nutritional Support of Children on Extracorporeal Membrane Oxygenation

At the onset of the ECMO support, 92% of patients were on intravenous fluid therapy. EN was used as the initial ANS in 45% of patients and PN in 47%. Eight percent of patients did not receive any nutritional support during ECMO therapy.

Most children (64%) received EN at some point during ECMO therapy (34% of them were on exclusive EN and 30% received supplementary PN) and 28% of patients received PN as a sole mode of nutritional support. 48HEN was administered to 60.3% of children on EN.

Mean time from ECMO onset to the initiation of EN was 46.5 ± 40 hours and mean time to achieve total EN was 1.41 ± 2.13 days (Table 2).

Transpyloric tube was the preferred method for EN delivery in these patients (97%) followed by continuous nasogastric tube (3% of the children).

The formulas used were Isosource Junior in 25% of the patients, standard artificial formula in 20.3%, hypercaloric formulas (Infatrini) in 14% and breast milk administered by feeding tube in 10.9% of the patients.

The mean of the maximum caloric and protein intake administered by the enteral and parenteral route within the first week after ECMO support initiation are detailed in Table 2. There were no statistically significant differences in the maximum caloric supply ($P = 0.31$) nor in the maximum protein delivery ($P = 0.72$) between fed children compared with patients on parenteral nutrition (Table 2).

Children on EN achieved 92% of the energy target calculated using Schofield equations while children on PN received 110% of the target. There were no statistically significant differences in the caloric intake measured as percentage of Schofield achieved between enteral and parenteral nutrition.

Outcomes

Twenty-six patients (26%) died during the ECMO therapy. Seventy-four patients (74%) were able to survive to ECMO weaning but 23 of them (31%) died during PICU admission. Mean survival of these patients was 36 (SD 62) days after ECMO weaning.

Mortality rate in the PICU was lower in patients who received EN as the initial ANS as compared to PN (37.7% vs 51%, $P = 0.005$). 48HEN was also associated with a lower mortality rate, as compared to enteral nutrition initiated after 48 hours of ECMO support (34% vs 50%, $P = 0.04$).

In the logistic regression analysis, duration of ECMO support and low cardiac output were the only factors associated with mortality in the PICU. More details are summarized in Table 3.

TABLE 3. PICU mortality logistic regression analysis

Variable	Odds ratio	95% CI	P
Malnutrition	1.99	0.58–6.85	0.273
Low cardiac output	9.5	2.2–41.6	0.003
ECMO Duration	1.01	1.003–1.013	0.001
Enteral Nutrition	0.35	0.13- 0.98	0.044
Digestive complications	1.36	0.49–3.81	0.557

95% CI = 95% confidence interval; CEC = extracorporeal circulation; ECMO = extracorporeal membrane oxygenation; PICU = Pediatric Intensive Care Unit.

TABLE 4. Gastrointestinal complications in patients on ECMO

GI complication	Patients without EN	Patients with EN	*P* value
Constipation	7 (17.5%)	24 (44.4%)	0.006
High gastric residual volume	3 (7.5%)	13 (22.8%)	0.046
Abdominal distension	4 (9.7%)	9 (16.1%)	0.367
Gastrointestinal bleeding	3 (7.5%)	7 (12.3%)	0.446
Intestinal ischemia	1 (2.5%)	2 (3.6%)	0.755
Diarrhea	0 (0%)	2 (3.5%)	0.226
Vomiting	0 (0%)	1 (1.8%)	0.390

ECMO = extracorporeal membrane oxygenation; EN = enteral nutrition; GI = gastrointestinal.

Gastrointestinal Complications

Forty-five patients on ECMO (45%) developed digestive complications, mostly mild. The most prevalent complication was constipation in 31 patients (33%), followed by high gastric residual volume in 16 children (16.5%), abdominal distension in 13 children (13.4%), gastrointestinal bleeding in 10 patients (10.3%), and intestinal ischemia in 3 of them (5.3%). Two patients developed diarrhea and one presented with vomiting.

There was an association between the use of EN and the development of constipation [24 patients with enteral (44.4%) vs 7 without EN (17.5%); $P = 0.006$] and high gastric residual volume [13 (22.8%) vs 3 (7.5%) without EN; $P = 0.046$]. There were no statistically significant differences between the use of EN and the occurrence of other digestive complications (Table 4).

48HEN in children on ECMO was not associated with an increase in the incidence of gastrointestinal complications ($P = 0.13$). Patients who developed digestive complications needed more time to reach total EN as compared to patients without gastrointestinal symptoms ($P = 0.028$). Gastrointestinal complications in children on ECMO receiving enteral nutrition within de first 48 hours and after 48 hours of ECMO initiation are detailed in Table 5.

The need for prolonged ECMO was associated with constipation (43.9% vs 24.5%; $P = 0.048$) but not with other types of gastrointestinal complications. Children who required muscle relaxants had also more constipation, although the differences were not statistically significant (35.9% vs 12.5%, $P = 0.056$).

The use of high doses of opioids did not increase the risk for gastrointestinal complications in patients on ECMO in univariate (46% vs 41%; $P = 0.67$) or logistic regression (95% confidence interval [CI] 0.26–2.13; $P = 0.586$).

Abdominal distension was more prevalent in patients who died ($P = 0.033$).

TABLE 5. Gastrointestinal complications in patients on early and late EN

GI complication	Patients with 48HEN	Patients with late EN	*P*
Constipation	13 (35.1%)	12 (50%)	0.249
High gastric residual volume	7 (18.4%)	6 (24%)	0.592
Abdominal distension	4 (10.8%)	6 (24%)	0.166
Digestive bleeding	4 (10.5%)	5 (20.8%)	0.262
Intestinal ischemia	1 (2.7%)	1 (4.1%)	0.754
Diarrhea	2 (5.2%)	0 (0%)	0.244
Vomiting	1 (2.7%)	0 (0%)	0.407

48HEN = enteral nutrition initiation in the first 48 hours on extracorporeal membrane oxygenation support; EN = enteral nutrition; GI = gastrointestinal.

TABLE 6. Complications logistic regression analysis

Variable	Odds ratio	95% CI	*P*
ECMO duration	1.006	1.01–1.011	0.023
Enteral nutrition	0.45	0.18–1.14	0.093
High morphic dose	0.75	0.26–2.13	0.586

95% CI = 95% confidence interval; ECMO = extracorporeal membrane oxygenation.

In the multivariable study (Table 6), the only factor affecting complications was the ECMO duration (95% CI 1.01–1.011; $P = 0.023$).

DISCUSSION

There is scarce data about the nutritional status, characteristics of nutritional support and the development of digestive complications in pediatric patients requiring ECMO support. To our knowledge, this is the largest study that has analyzed these factors in a large cohort of critically ill children on ECMO showing that undernutrition is prevalent and that enteral nutrition may be safe and beneficial in this population. Although it is a retrospective study, it provides interesting results that should be confirmed in future prospective studies.

The primary outcome of the present study was to describe the relationship between nutrition support and complications including mortality. Our data reflects that children on ECMO receiving EN did not develop severe gastrointestinal complications or higher mortality.

Historically, EN used to be avoided in patients with shock, as splanchnic circulation can be compromised resulting in mesenteric ischemia, necrotizing enterocolitis, gastrointestinal perforation, or gastrointestinal bleeding (23); however, most patients on ECMO stabilize within a few hours and inotropes can be withdrawn being considered as stable patients who can be fed (24).

Few studies suggest that EN can be safe in adult patients on ECMO (10,13–15) even when used early (14,25–27). In the pediatric field, there is scant data, although results seem to be favorable for neonates and infants (16,17,28,29). Indeed, the use of EN at day 5 during ECMO therapy has been associated with higher survival rates at discharge, as compared to exclusive PN (30). On the other hand, a recent retrospective study reported that EEN in ECMO patients reduced in-hospital and at 28-day mortality (31). Our results are consistent with previous studies (28–30) highlighting that EN is not only safe in children on ECMO but it can also decrease mortality when it is used as the initial type of ANS. Moreover, EN initiated within the first 48 hours of ECMO onset may also be beneficial as it was associated with lower mortality but not with a higher incidence of gastrointestinal complications.

EN may be associated with gastrointestinal complications (20,32–39) but they are usually not severe (40). Mild digestive complications have been reported in adult ECMO patients on EN (abdominal distension, high gastric residual volume, diarrhea, and constipation) (13,14).

The gastrointestinal complications in pediatric patients on ECMO are scarcely described in the literature. A study conducted by Hanekamp in neonates assisted with ECMO (16) revealed that the most frequent complication was high gastric residual volume. In pediatric patients, there is only one study that has analyzed it (17), showing that abdominal distension and high gastric residual volume were the most prevalent complications.

In our study, 45% of patients developed gastrointestinal complications, mainly constipation, high gastric residual volume, and abdominal distension. High gastric residual volume and

constipation were more frequent in the children who received EN. The incidence of high gastric residual volume and abdominal distension observed in our study was consistent with the one reported in previous studies (16,17), but higher than the one reported in other series of critically ill patients without ECMO (32,33). This inconsistency may be explained by the fact that ECMO patients are at a higher risk of developing gastrointestinal complications.

Our data reflects that children on ECMO receiving EN did not develop severe gastrointestinal complications or higher mortality suggesting that EN in these patients is safe and should be the preferred nutritional support if not contraindicated.

Transpyloric enteral nutrition can be useful for managing feeding intolerance in critically ill children (20,32,41–43) and can be used in patients receiving ECMO support (26,29,44,45). In our experience, transpyloric EN was used in most patients without complications. Therefore, it can be an alternative for pediatric ECMO patients with feeding intolerance.

The secondary outcome of our study was to describe the nutritional status of children on ECMO and to assess the caloric and protein delivery administered to these patients.

Our data are consistent with previous studies (5), showing that undernutrition is prevalent in pediatric patients on ECMO, especially in infants under the age of two. Therefore, close monitoring of the nutritional status of these patients and individualized nutritional support should be performed in this population.

Although undernutrition in critically ill children, and more specifically in children requiring ECMO support, has been associated with a poor prognosis (6–8), in our study, undernutrition was not associated with higher mortality or more gastrointestinal problems. Only children who needed prolonged ECMO support had more complications as reflected in the multivariable study. Nevertheless, prospective studies are needed to confirm these results.

Adequate nutritional support may contribute to improve the prognosis of critically ill children including those on ECMO (5,9). Enteral route is the preferred method to deliver artificial nutrition in PICU since it has multiple advantages (18), but due to a variety of barriers, parenteral nutrition is often employed as a sole mode of nutrient delivery or as supplementary. In our study, most children (64%) received EN at some point during ECMO therapy being the initial ANS in 45% of them. Thirty-four of the patients were on exclusive enteral nutrition and 30% received supplementary parenteral nutrition. Few patients (28%) were on exclusive PN. These results contrast with a previous report where only 44% of the children received EN at day 7 of ECMO being most of them (85%) on a combination of EN and PN (46).

In our study, mean time from ECMO onset to the initiation of ANS was 46.5 hours for EN and 26.7 hours for PN. Early administration of ANS after ECMO onset allowed patients to achieve total enteral or parenteral nutrition fast. This is an important fact as early nutrition support, may prevent cumulative and protein-energy deficit that can worsen outcomes in these populations.

Armstrong et al reported a median time of 6 days to the initiation of EN versus 1 day to the onset of PN (46). According to our results, time to ANS initiation was shorter in children on parenteral nutrition than in children on enteral nutrition reflecting the reluctance of PICU caregivers to fed children on ECMO for the risk of complications.

Energy requirements during ECMO remain unclear as the presence of more than one site of gas exchange makes indirect calorimetry technically challenging. Following the international guidelines, we estimated resting energy expenditure using the Schofield equation. In our cohort, energy delivery was similar to the target in both enteral and parenteral group and superior to previous reports (5,46). On the other hand, we did not find any differences in the maximum caloric and protein intake between the enteral and the parenteral group contrasting with previous data where PN provided the majority of calories and proteins (5).

Limitations

Our study has some limitations. First, it is a retrospective, single-center study so prospective, multicenter studies are needed to confirm our results. In addition, the influence of some factors such as the diagnosis, the severity of critical illness, and the use of vasoactive drugs on nutrition tolerance and the development of digestive complications were not assessed in this study.

CONCLUSIONS

Undernutrition is prevalent among pediatric patients on ECMO, mainly in patients under the age of two. Close monitoring of their nutritional status and individualized nutritional support may be crucial. EN, may be safe and beneficial in this population.

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