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Pancreatic Enzyme Replacement Therapy in Children with Severe Acute Malnutrition: A Randomized Controlled Trial

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Objective To assess the benefits of pancreatic enzyme replacement therapy (PERT) in children with complicated severe acute malnutrition.

Study design We conducted a randomized, controlled trial in 90 children aged 6-60 months with complicated severe acute malnutrition at the Queen Elizabeth Central Hospital in Malawi. All children received standard care; the intervention group also received PERT for 28 days.

Results Children treated with PERT for 28 days did not gain more weight than controls (13.7 ± 9.0% in controls vs 15.3 ± 11.3% in PERT; $P = .56$). Exocrine pancreatic insufficiency was present in 83.1% of patients on admission and fecal elastase-1 levels increased during hospitalization mostly seen in children with nonedematous severe acute malnutrition ($P < .01$). Although the study was not powered to detect differences in mortality, mortality was significantly lower in the intervention group treated with pancreatic enzymes (18.6% vs 37.8%; $P < .05$). Children who died had low fecal fatty acid split ratios at admission. Exocrine pancreatic insufficiency was not improved by PERT, but children receiving PERT were more likely to be discharged with every passing day ($P = .02$) compared with controls.

Conclusions PERT does not improve weight gain in severely malnourished children but does increase the rate of hospital discharge. Mortality was lower in patients on PERT, a finding that needs to be investigated in a larger cohort with stratification for edematous and nonedematous malnutrition. Mortality in severe acute malnutrition is associated with markers of poor digestive function. *(J Pediatr 2017;190:85-92).*

Trial registration ISRCTN.com: 57423639.

Although childhood mortality globally decreased by 53% between 1990 and 2015, 16 000 children under the age of 5 died every day in 2015.[1] Sub-Saharan Africa has the highest share of global under-5 mortality (47%).[1] Undernutrition, as defined by low weight for height (weight for height ≤-2 SD), contributes to approximately 45% and severe wasting (weight for height <-3 SD) to 7.8% of these deaths.[2,3] Even if World Health Organization treatment protocols are followed rigorously, case fatality rates remain high, which underlines the urgent need for better treatment strategies.[3-5]

Severe diarrhea is common in children with severe acute malnutrition and greatly increases mortality.[6-8] Diarrhea in children with severe acute malnutrition is not only caused by infections[9] and intestinal epithelial dysfunction relating to malabsorption,[10] but also by impaired digestion. The exocrine pancreas plays a central role in nutrient digestion by secreting digestive enzymes. Exocrine pancreatic insufficiency in conditions such as cystic fibrosis is linked with nutrient malabsorption, poor nutritional status, and mortality.[11] Several "classic" studies, mostly performed between 1940 and 1980, have suggested that children with severe acute malnutrition also have exocrine pancreatic insufficiency.[12-23] We have confirmed these findings recently using contemporary techniques and showed that the prevalence of exocrine pancreatic insufficiency was 93% in Malawian children with severe acute malnutrition.[24] Also, those with the edematous form of severe acute malnutrition (ie, presenting with nutritional bilateral pitting edema) had more severe exocrine pancreatic insufficiency than those with nonedematous severe acute malnutrition (ie, severe wasting).[24]

FE-1	Fecal elastase-1
FFA	Free fatty acids
NRU	Nutrition rehabilitation unit
PERT	Pancreatic enzyme replacement therapy
TG	Triglycerides

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In children with exocrine pancreatic insufficiency with other underlying etiologies than severe acute malnutrition,[25-27] it is standard clinical practice to start pancreatic enzyme replacement therapy (PERT)[28,29] with the aim of restoring nutritional status by improved digestion.

The benefits of using PERT to treat children with severe acute malnutrition have not been thoroughly investigated. One study, performed in 1988 by Sauniere et al,[30] attempted to assess PERT as a potential treatment. The study did not report improvements of pancreatic function but was limited by a small sample size (n = 7 and n = 8), inadequate dosage, and short duration of PERT treatment.

The primary objective of this study was to assess the effect of PERT on weight gain among children hospitalized for severe acute malnutrition. Secondary objectives were to compare the effect of PERT on exocrine pancreatic function as assessed by fecal elastase-1 (FE-1) levels, duration of hospital stay and, mortality and digestive function assessed by fecal content of free fatty acids (FFA) and triglycerides (TG).

Methods

This prospective, randomized, single-blinded pilot study (OPTIMISM trial) was conducted at the nutrition rehabilitation unit (NRU) in the Pediatric Department of Queen Elizabeth Central Hospital in Blantyre, Malawi (ISRCTN57423639). The study was approved by the Malawi College of Medicine Research and Ethics Committee (COMREC nr P.11/12/1306) and conducted according to guidelines of Good Clinical Practice, which are based on the principles of the Declaration of Helsinki.[31]

Between February and September 2014, we screened children with complicated severe acute malnutrition, that is, those with signs of severe clinical illness and/or poor appetite[32] who were admitted to the NRU. Parents and guardians were informed about the study both verbally and with printed information in Chichewa or English. Before performing any research procedures, written consent was obtained, and for those unable to read or write the information was read to them in Chichewa. Consent was confirmed through a signature or thumbprint by the parent or guardian, and witnessed by a staff member of the study. All staff were fully trained before starting the study. All authors had access to the study data and reviewed and approved the final manuscript.

Inclusion criteria were children aged 6-60 months, admitted to hospital with a diagnosis of severe acute malnutrition. Severe acute malnutrition was defined according to World Health Organization standards, by any of the following: a weight for height below -3 SD (nonedematous severe acute malnutrition or marasmus), a mid-upper arm circumference of less than 115 mm (nonedematous severe acute malnutrition or marasmus), or the presence of bilateral edema (edematous severe acute malnutrition or kwashiorkor).[33] Patients were excluded if they had malaria (assessed by a positive blood smear), or signs suggestive of severe underlying systemic illness such as sepsis, severe pneumonia, or severe diarrhea.

An independent researcher prepared sealed envelopes using a computerized randomization program[34] and these were used to assign patients to treatment groups. The study was stratified for HIV status to ensure equal distribution of HIV reactive patients between groups.

For all children admitted to the NRU, a thick blood film was examined for parasitemia and hematocrit counts. All patients were offered an HIV antibody test with appropriate counseling before and after. During hospital stay, all children were treated according to national and World Health Organization guidelines.[32,35] Baseline characteristics were obtained and health questionnaires completed. Appetite, gastrointestinal losses, degree of edema, hydration state, and vital signs were recorded daily. The presence and severity of diarrhea, defined as having 3 or more loose or watery stools per day,[36] was assessed using standardized departmental pro-forma. An assigned nurse recorded daily weight; she was both unaware of treatment groups and not involved in the everyday care of the study patients (single blinded). Body weight was measured using a Marsden 4201 digital scale, which was calibrated daily. Supine length was taken using a measuring board.

Intervention

Patients assigned to the PERT group were prescribed 3000 U of lipase/kg of bodyweight to be taken 3 times a day with an upper limit dose of 10 000 U lipase/kg bodyweight per day.[37] Each PERT capsule contains enteric-coated mini-microspheres of porcine-derived lipase (10 000 PhEur units), amylase (8000 PhEur units) and protease (600 PhEur units). PERT was administered immediately before a feed. To enhance intake, capsules were opened and granules mixed into a spoonful of apple sauce (pH <5.5). This acidity avoids the dissolution of the protective enteric coating of the granules. PERT intake was monitored. Serious adverse events, defined as skin rash, pruritus or urticaria, anaphylaxis, or any episode of clinical deterioration accompanied by shock or respiratory distress (respiratory rate >60/min) or oxygen requirement (O_2 saturation <94%) or impaired consciousness (Blantyre coma score <4) or hypoglycemia (serum glucose of <3 mmol/L), were recorded and would lead to patient withdrawal from the study; 1 child in the PERT group was withdrawn because of urticaria.

Laboratory Investigations

Fecal samples were obtained on admission, day 14, and day 28 and homogenized before storage at -80 °C. To measure exocrine pancreatic insufficiency, FE-1 levels were determined in stool using an enzyme-linked immunosorbent assay (pancreatic elastase enzyme-linked immunosorbent assay, Bioserv Diagnostics GmbH, Rostock, Germany) at the clinical laboratory of the University Medical Center Groningen in the Netherlands. Exocrine pancreatic insufficiency was defined as FE-1 levels of less than 200 μg/g of stool, and severe exocrine pancreatic insufficiency as less than 100 μg/g of stool.[38,39] Digestive function was measured by split ratios of FFAs and TG on admission and day 28. This ratio can reflect failed fatty acid breakdown (ie, a high proportion of TG in total fecal fatty acids) and/or failed absorption (ie, a high proportion of FFA in total

fecal fatty acids).[40] FFA and TG were measured with Fourier transform infrared spectroscopy using a simple hexane extraction procedure for stool.[41] Briefly, an aliquot of the extracted hexane layer was directly injected into the measurement cell of the spectrophotometer, a BioRad Excalibur Series, Model FTS 3000. Split ratios were then calculated by (1) converting FFA and TG from grams to moles (using the molecular weight of oleic acid for FFA [282.46 g/mol] and 3 times the weight of oleic acid for TG [847.38 g/mol]), (2) calculating total fatty acids in feces by the sum of FFA and TG, and (3) obtaining the split ratio by dividing FFA by total fatty acids.

Statistical Analyses

Sample size calculations were based on estimates derived from a large cohort of children previously admitted to the NRU. That cohort showed a mean weight gain of 13.9 ± 11.0%, which was calculated using the difference between the lowest weight recorded during hospital stay and a follow-up weight obtained after 28 days. The present study aimed to detect 10% difference in weight gain between the intervention and control groups. Assuming a standard deviation of 11.0, 26 patients would be required in each arm of the study ($\alpha = .05$, $\beta = 0.1$). Because this study was designed to guide a future trial, we aimed to include 50 patients in each group to attain 99.5% power to detect a 10% effect of PERT on weight gain and insure against contingencies. For the calculation of weight change, weight after 28 days was compared with the lowest weight during hospital stay instead of weight on admission because children with edematous malnutrition will initially lose their edema and, therefore, weight.

An interim analysis was performed after 50% of patients were included in the study; mortality between both arms was assessed by an independent monitor. Pearson's χ^2 test and a 1% significance threshold level was used. The detection of a statistically significant mortality increase in the intervention group would have led to the immediate termination of the trial.

Data were collected on standardized forms, entered into an Access 2013 database and analyzed with Stata (StataCorp LP, Release 13, College Station, TX)[42] and with R (R Core Team, Version 3.2.3, Vienna, Austria) statistical software. The baseline characteristics of the study participants in both groups were compared as appropriate using the Fisher exact test, 2-way ANOVA or logistic regression. A 2-way ANOVA with or without correcting for HIV status was used to test for group differences in percent weight gain. Because nonedematous and edematous severe acute malnutrition display distinct clinical and biochemical characteristics, we also conducted a subanalysis for these groups. We used generalized linear models to analyze group differences and mixed effects models when needing to account for repeated measures. The competitive risk analysis was done to determine if time to discharge and time to death differed between treatment groups using the cmprsk R-package.[43] This analysis produces an incidence function that indicates the cumulative probability of either being discharged or dying as treatment progresses.

Results

Between February 24, 2014, and September 30, 2014, a total of 430 children were admitted to the NRU with severe acute malnutrition and 90 provided consent and were randomized to receive PERT as a supplement over standard care or to receive standard care only. Overall, 25 children died (27.8%) and 59 (65.6%) completed the 28-day follow-up (**Figure 1**). Patient

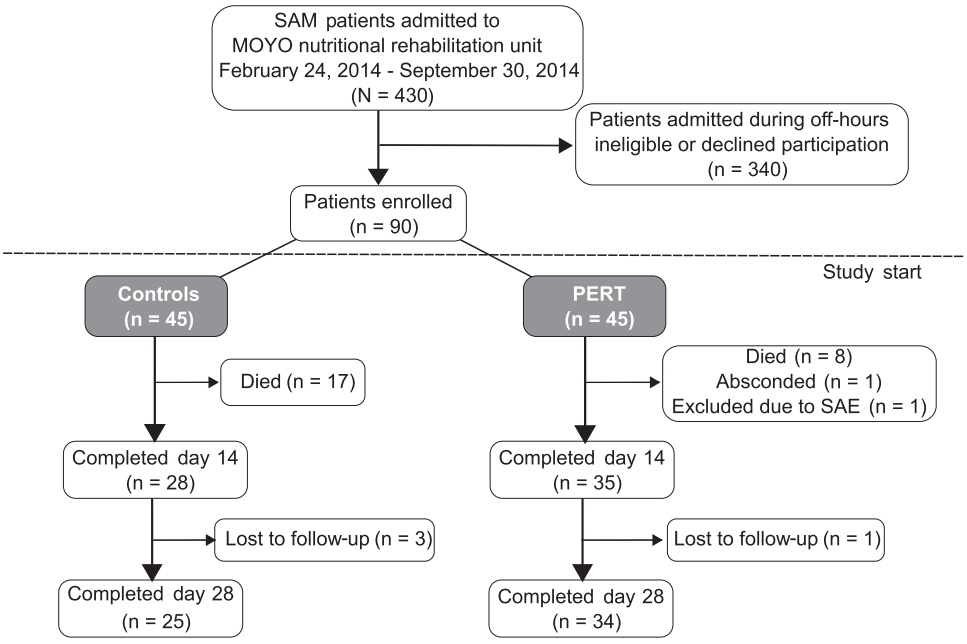

Figure 1. Flowchart of patient enrolment, randomization, and follow-up for the OPTIMISM study. *SAE*, Serious adverse event; *SAM*, Severe acute malnutrition.

Table I. Characteristics of patients randomized to receive standard treatment or PERT intervention

	All Patients N = 90	Control n = 45	PERT n = 45	*P*
Male	50 (56%)	25 (56)	25 (56)	.99
Age, months*	21.3 ± 11.8	20.0 ± 12.2	22.7 ± 11.4	.3
HIV reactive	41 (46)	21 (47)	20 (44)	.99
Edematous	51 (57)	20 (44)	31 (69)	.03
MUAC, cm*	11.4 ± 1.7	11.2 ± 1.8	11.5 ± 1.7	.5
Nonedematous	10.2 ± 1.1	10.2 ± 1.1	10.2 ± 1.1	.9
Edematous	12.3 ± 1.6	12.5 ± 1.7	12.1 ± 1.6	.3
Weight for age, *z*-score*	-3.6 ± 1.7	-3.6 ± 1.8	-3.5 ± 1.6	.7
Nonedematous	-4.6 ± 1.0	-4.5 ± 1.0	-4.8 ± 1.0	.5
Edematous	-2.7 ± 1.7	-2.5 ± 2.0	-2.9 ± 1.5	.4
Weight for length, *z*-score*	-2.7 ± 1.8	-2.9 ± 1.8	-2.6 ± 1.8	.5
Nonedematous	-3.9 ± 1.2	-3.9 ± 1.3	-3.9 ± 1.0	.99
Edematous	-1.8 ± 1.6	-1.5 ± 1.4	-1.9 ± 1.7	.3
Breastfeeding, yes	41 (46)	24 (53)	17 (38)	.2
Duration of illness before admission, days†	7 (3.8-28)	7 (3.5-21)	14 (4-28)	.4
Diarrhea, yes	31 (34)	14 (31)	17 (38)	.7
Fever on admission (>37.5°C‡)	9 (10)	4 (9)	5 (11)	.99
Hemoglobin, g/dL*	8.9 ± 1.9	9.2 ± 1.4	8.5 ± 2.4	.1

MUAC, mid-upper arm circumference.
Values are presented as n (%), means and standard deviations (*), or median and IQR (†). ‡Fever cutoff for axillary temperature. Differences between groups were tested using either Fisher Exact test, 2-way ANOVA, or logistic regression. Significance threshold was considered to be $P < .05$.

characteristics on admission are described in **Table I**. Despite randomization, the PERT group had a higher percentage of children with edematous malnutrition than the control group (69% vs 44%; $P = .03$). The number of children lost to follow-up (n = 6; 6.7%) did not differ between groups (**Figure 1**). The main comorbidities on admission were gastroenteritis and pneumonia, and were evenly prevalent in both groups.

After 28 days, the control group showed an average weight gain of 13.7 ± 9.0%, which did not differ from the PERT group (15.3 ± 11.3%; $P = .56$; **Figure 2**). Edematous patients receiving PERT did not lose weight faster ($P = .2$) than edematous patients in the control group. HIV status also did not influence weight change after 28 days of treatment. Changes in age- and sex-corrected weight-for-height *z*-scores also did not show any group differences.

Overall levels of FE-1 were markedly reduced in children with severe acute malnutrition at hospital admission (**Figure 3**; available at www.jpeds.com). Among admitted patients, 83% showed evidence of pancreatic insufficiency (FE-1 <200 μg/g of stool), whereas 69% showed severe pancreatic insufficiency (FE-1 <100 μg/g of stool; **Table II**; available at www.jpeds.com). Children with edema had lower FE-1 levels with a median of 32 μg/g of stool (IQR, 23-61) compared with 110 μg/g of stool (IQR, 48-228; $P = .002$) in children without edema (**Figure 3**). Consequently, pancreatic insufficiency was significantly more prevalent in patients with edematous malnutrition compared with those with the nonedematous form (exocrine pancreatic insufficiency in edematous malnutrition, n = 36 [97%] vs nonedematous malnutrition, n = 22 [69%; $P = .002$]; and severe exocrine pancreatic insufficiency in edematous malnutrition, n = 33 [89%] vs nonedematous malnutrition, n = 15 [47%, $P < .001$]; **Table II**). These relationships were not modulated by HIV status or by the presence of diarrhea (which has been associated with misleadingly low FE-1 results[44]). After 28 days, overall FE-1 levels in children treated for severe acute malnutrition increased from 42 μg/g (IQR, 24-96) to 168 μg/g (IQR, 72-256; $P < .0001$). The prevalence of exocrine pancreatic insufficiency in children that completed the study decreased from 83% to 55% and severe exocrine pancreatic insufficiency decreased from 69% to 35%, irrespective of PERT ($P < .6$). When analyzing FE-1 levels by nutritional diagnosis, FE-1 level increased more in children with

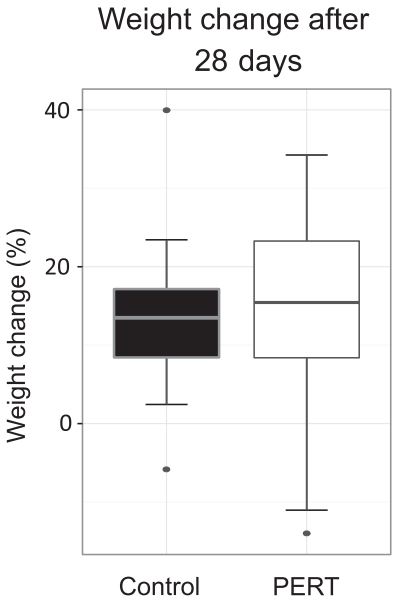

Figure 2. Percentage of weight change in children with severe acute malnutrition after 28 days of PERT treatment (n = 34) or standard care (n = 25). Boxplots summarize the median (midline) and IQRs (upper and lower boxes). Differences in mean weight change was tested between groups using 2-way ANOVA ($P = .56$).

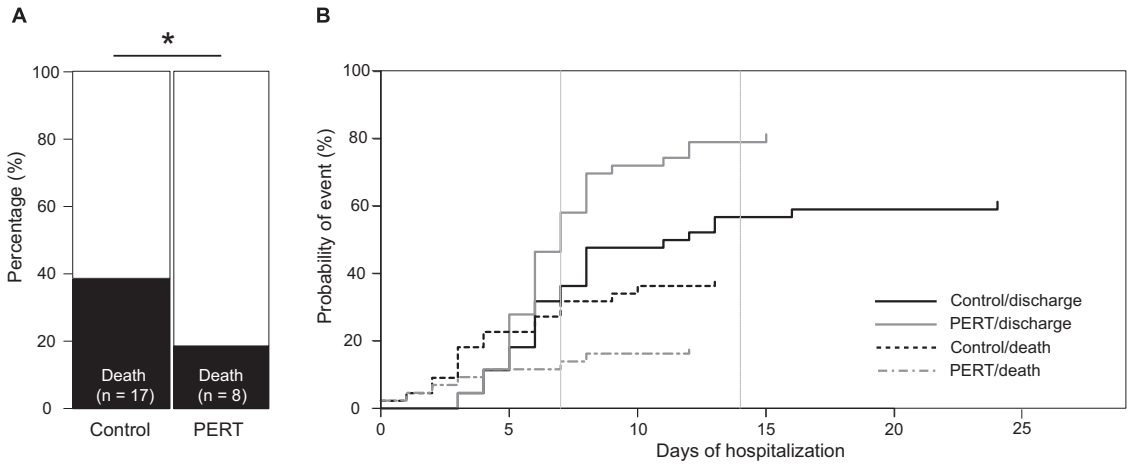

Figure 4. Mortality in children treated with either PERT or standard of care. **A,** Percentage of mortality in each group. Black boxes indicate the percentage of children who died; white boxes indicate the percentage of those that survived. Group differences were tested with logistic regression. **B,** Cumulative incidence curves representing the probability of discharge or death at any given day of hospitalization. Group differences were tested with competitive risk analysis which showed that the rate of discharge differed between controls and children receiving PERT ($P = .02$), whereas the rate of mortality at any given day was not significantly different ($P = .051$); difference in discharge rate was still significant between groups ($P < .05$) after accounting for edema status. The different line types indicate the cumulated incidence of discharge or death in the Control or PERT treated groups as detailed by the legend. *$P < .05$.

nonedematous severe acute malnutrition, 312.5 µg/g of stool (IQR, 223.8-371.2) compared with children with edema, who only reached 102.5 µg/g of stool (IQR, 49.8-238; $P < .002$; **Figure 3**). Most children with edematous severe acute malnutrition still showed signs of exocrine pancreatic insufficiency after 28 days of treatment (68%) and almost one-half (46%) had severe exocrine pancreatic insufficiency.

Although this trial was not powered to detect differences in mortality between the treatment groups, mortality was significantly lower in the PERT treated group (PERT, n = 8/43 [18.6%] vs controls, n = 17/45 [37.8%]; $P < .05$; **Figure 4**). The number of days between admission and death did not differ between the intervention and control groups (4.6 ± 4.1 days vs 4.9 ± 3.5 days; $P = .8$) and neither did the number of days to discharge and death (6.7 ± 2.6 days vs 7.7 ± 4.6; $P = .14$). The competitive risk analysis suggested that, compared with controls, children receiving PERT had a higher probability of being discharged on every passing day of treatment ($P = .02$; **Figure 4**).

FE-1 levels at admission were not associated with mortality, nor did they differ between the intervention and control group (**Figure 5**; available at www.jpeds.com). However, split ratios of fatty acids measured in stool collected at admission were significantly lower in children who died compared with those that survived with respective medians of 69% (IQR, 52-100) and 98% (IQR, 82-100; $P = .002$; **Figure 5**). Split ratios did not differ with nutritional diagnosis, diarrhea, or treatment groups because children who survived all showed split ratios of nearly 100% already (**Table III**; available at www.jpeds.com). Mortality was not influenced by HIV status ($P = .72$). Children who died were younger (15.5 ± 9.3 months vs 23.6 ± 12.1 months) and had lower mid-upper arm circumference (10.5 ± 1.7 cm vs 11.7 ± 1.6 cm).

Discussion

This study shows that PERT treatment of exocrine pancreatic insufficiency in children with complicated severe acute malnutrition does not improve weight gain after 28 days of treatment. Mortality in the intervention group was significantly lower, although this trial was not powered to detect such a finding. Supplementation with PERT may be associated with an increased rate of hospital discharge. Malnourished children showed improvement of pancreatic function unrelated to PERT treatment, but this was mostly seen in children with nonedematous severe acute malnutrition.

Previous studies have demonstrated the high prevalence of exocrine pancreatic insufficiency in children with severe acute malnutrition.[12-24] Sauniere et al[30] reported on the use of pancreatic enzymes in children with edematous severe acute malnutrition, but the study was small. Their placebo-controlled intervention consisted of giving porcine pancreatic powder 3 times daily for 5 days to 8 children in Ivory Coast and for 28 days to 8 Senegalese patients. No differences were found in concentrations of pancreatic enzymes in duodenal fluid. This study was limited by its small sample size, short treatment of patients from the Ivory Coast, and inclusion of only children with edematous severe acute malnutrition. Also, clinical outcomes were not described. Our study emphasizes clinical outcomes relevant to daily practice, examines a larger cohort, and includes both the edematous and nonedematous forms of severe acute malnutrition.

Our primary outcome, weight change in children with severe acute malnutrition, did not differ between the intervention and control groups as described in patients with cystic fibrosis.[11] This finding may be due to several reasons. The clinical use of PERT in children with cystic fibrosis aims to help maintain healthy nutritional status and growth, whereas we aimed to use PERT as an aid to recovery from a severely malnourished state. Another issue may be compliance. Throughout the hospital stay, PERT intake was monitored closely by clinical staff. However, PERT intake after discharge was evaluated only through guardian reporting and counting of empty blister packets brought back on follow-up visits. Alternatively, we cannot rule out that 28 days of PERT may not be long enough to affect weight change. The time frame was chosen as a trade-off to avoid the loss to follow-up frequently encountered in low-resource settings. Finally, our study population was severely ill; children with complicated severe acute malnutrition suffer from severe acute illness and often present with important comorbidities such as pneumonia, tuberculosis, or HIV infection. Focusing on impaired digestion to improve weight change may be too limited an approach to have a significant clinical impact in children with complicated severe acute malnutrition. Thus, weight change is likely not the ideal primary outcome and short-term weight gain might not be realistic irrespective of the intervention. It is a heterogenous parameter and weight might take longer to improve; many of the patients in our study were very wasted and severely ill.

In this study, exocrine pancreatic insufficiency was assessed by FE-1 as a marker of pancreatic function. Exocrine pancreatic insufficiency can be diagnosed by direct and/or indirect tests of exocrine pancreatic function.[27,44] Direct tests are not routine in clinical practice because they are invasive, require both exogenous hormonal stimulation, and intubation of the pancreatic duct to measure the enzyme activity of pancreatic secretions.[44] Less invasive, indirect tests measure pancreatic enzymes or their substrate or byproducts in stool, serum, or breath.[44] Measuring FE-1 in the stool is the most widely used indirect pancreatic function test; it has good specificity and sensitivity (86%-100%) to diagnose severe exocrine pancreatic insufficiency and is currently recommended as a screening tool.[39,44,45] In line with previous studies that investigated exocrine pancreatic insufficiency in severe acute malnutrition, we found that pancreatic function improved with nutritional rehabilitation.[12,13,15,19-22,24,46] However, pancreatic function was not normalized, even after 28 days of treatment, especially in the edematous group. Our study showed that the recovery pattern of pancreatic function differs between children with edematous or nonedematous severe acute malnutrition. Children who presented with edema at hospital admission showed more severe exocrine pancreatic insufficiency and only minimal improvements were achieved. These children may require specific and longer medical treatment to recover. Future treatment programs should consider having specific treatment modalities between the 2 different phenotypes of severe acute malnutrition.

As a biomarker for gastrointestinal digestion, we measured fecal FFA and TG to calculate the fatty acid split ratio. However, the gold standard for diagnosing fat malabsorption (steatorrhea) is to quantitatively measure stool fat via a traditional biochemical assay.[47] A coefficient of fat absorption can be calculated, but this requires 3 days of feces collection with records of all dietary intake. A 3-day collection of feces was not feasible in our setting. This test is also known to lack specificity to differentiate between syndromes of malabsorption and maldigestion.[48] FFA and TG and split ratios on admission and after 28 days of treatment did not differ between groups. Split ratios also did not vary with edema status, diarrhea, or HIV reactivity. Most children showed high split ratios; split ratios were only found to be lower in children who died. However, based on split ratios alone we cannot conclude failed absorption because we have not taken into account the intake and output of fat and numerous other factors in severe acute malnutrition that influence this, such as impaired bile homeostasis, enteropathy, and small intestine bacterial overgrowth.[49,50]

Mortality was significantly lower in children who received PERT (17%) compared with children receiving standard of care (37%). Our treatment groups differed in the proportion of edematous and nonedematous malnutrition. In the past, different mortality rates have been described between nonedematous malnutrition and edematous malnutrition, although not consistently.[24,51] We therefore cannot clearly conclude that our finding for differences in mortality are explained by a difference in phenotypical characteristics with more children with marasmus in the control group. The fact that the number of days between death in the 2 groups is similar also provides no insight into the mechanism behind the lower mortality in the PERT group.

Both the lower mortality as well as the significant increase in earlier hospital discharge rate in the intervention group stresses the possible beneficial effect of PERT early in the management of children with severe acute malnutrition, although this was not evident by our primary outcome. This finding could have important implications for the future management of severe acute malnutrition and, therefore, merits further investigation in a larger cohort with stratification for severe acute malnutrition phenotype.

A novel finding was that low split ratios on admission were significantly associated with mortality and this was mostly driven by high levels of TG measured on admission in the stool of children who died. Because we have not taken into account the fat intake and output, we cannot confirm based on split ratios alone that children who die are failing to digest and absorb fatty acids, but this seems likely to be the case. Failing to process TG into FFAs that can be absorbed may be an acute marker of death and calculating the split ratio from levels of FFA and TG in a single stool sample may be a valuable marker of the digestive function. The breakdown of TG into FFAs and monoglycerides depends on several processes, such as the emulsification of fats by bile acids produced by the liver and lipases secreted by the pancreas. Impaired bile acid homeostasis has been described recently in children with severe acute malnutrition by our group.[49] Together with the high prevalence of exocrine pancreatic insufficiency, this shows that the diges-

tive system is severely impaired and likely contributes to mortality.

The inpatient mortality rate for our NRU was high, but previous studies have reported similar rates around 20%-30%.[51-53] Since the development of the Community-based Management of Acute Malnutrition guidelines, less acutely ill children now receive adequate management in district hospitals and are no longer referred to NRUs like ours.[4] Therefore, children admitted to hospital with malnutrition are those that are critically sick and at high risk of mortality.

Our study has several strengths. First, the follow-up rates were high (93%). Second, we tracked weight, our primary outcome, on a daily basis during hospital admission. Third, the study was single blinded because the nurse weighing the children was unaware of treatment allocation. In addition, our study examined the effects of PERT on relevant clinical outcomes that are routinely used in low-resource settings. However, in addition to issues already discussed, our study would have gained from a longer follow-up, which would have helped to evaluate recovery of the pancreas function in children with and without edema.

In conclusion, our study showed that PERT does not improve weight gain in children with complicated severe acute malnutrition, mortality is lower in the intervention group treated with pancreatic enzymes, and that markers of maldigestion are associated with higher mortality, exocrine pancreatic insufficiency shows modest improvement after 28 days of nutritional rehabilitation, but this mostly in children with nonedematous severe acute malnutrition and this improvement was not related to PERT, and the rate of discharge from hospital may be influenced by PERT. A larger cohort is needed to confirm our findings focusing on the effect of PERT on mortality. If the current results are confirmed PERT should be considered as an additional treatment available for children with severe acute malnutrition worldwide. ■

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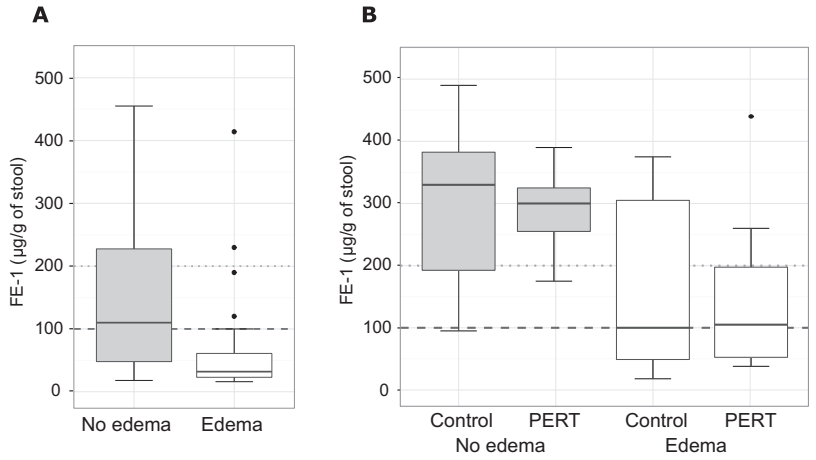

Figure 3. Concentration levels of FE-1 in patients with severe acute malnutrition with or without edema at **A,** admission (nonedematous, n = 32; edematous, n = 39) and **B,** after 28 days of PERT (nonedematous, n = 14; edematous, n = 31) or standard care (control: nonedematous, n = 25; edematous, n = 20). Boxplots summarize the median (midline) and IQRs (upper and lower box). Group differences were tested using generalized linear models with a gamma error structure. **P* < .05.

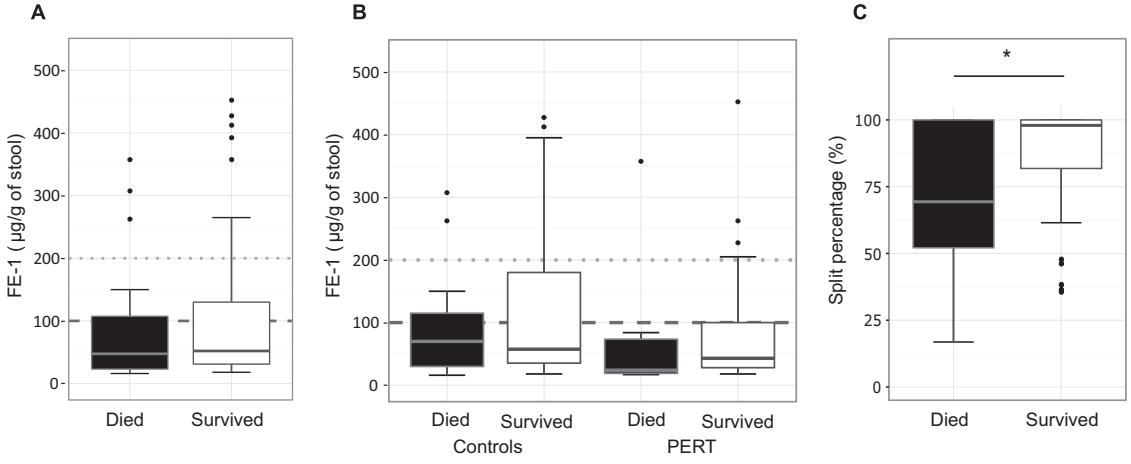

Figure 5. The relationship between mortality and fecal markers in children with severe acute malnutrition. **A,** Concentration of FE-1 at admission in patients with severe acute malnutrition who died or survived and **B,** split by PERT or standard of care treatment groups. **C,** Difference in split ratios at admission between children who died versus those who survived. Boxplots summarize the median (midline) and IQRs (upper and lower box). Group differences in levels of FE-1 were tested using generalized linear models with a gamma error structure; differences in split ratios were tested using binomial logistic regression. **P* < .05.

Table II. Clinical grade of exocrine pancreatic insufficiency as determined by abnormal FE-1 levels measured in patients with severe acute malnutrition presenting with or without edema who received PERT treatment for 28 days or the standard of care

FE-1 levels	n	Clinical cutoff (μg/g)	All patients, n/N (%)	n	Controls, n/N (%)	n	PERT, n/N (%)	*P*
At admission								
All	71	<200	59/71 (83)	35	28/35 (80)	36	31/36 (86)	.5
		<100	49/71 (69)		22/35 (63)		27/36 (75)	.3
Nonedematous	32	<200	22/32 (69)	21	15/21 (71)	11	7/11 (64)	.7
		<100	15/32 (47)		9/21 (43)		6/11 (55)	.7
Edematous	37	<200	36/37 (97)	14	13/14 (93)	25	24/25 (96)	.99
		<100	33/37 (89)		13/14 (93)		21/25 (84)	.6
28 Days after admission								
All	40	<200	22/40 (55)	16	7/16 (44)	24	15/24 (63)	.3
		<100	14/40 (35)		5/16 (31)		9/24 (38)	.7
Nonedematous	12	<200	3/12 (25)	7	2/7 (29)	5	1/5 (20)	.99
		<100	1/12 (8)		1/7 (14)		0/5 (0)	.99
Edematous	28	<200	19/28 (68)	9	5/9 (56)	19	14/19 (74)	.4
		<100	13/28 (46)		4/9 (44)		9/19 (47)	.99

Number of patients with or without edema that show either exocrine pancreatic insufficiency or severe pancreatic insufficiency as determined by abnormal levels of FE-1. Children with FE-1 levels below the clinical cutoff of <200 μg/g of stool show signs of pancreatic insufficiency, those with levels of <100 μg/g have severe pancreatic insufficiency. Differences in proportions between treatment groups were tested by Fisher's exact test and $P < .05$ was used as the significance threshold.

Table III. FFA and triglyceride levels with calculated split ratios on admission and after 28 days of patients with severe acute malnutrition with or without edema who received PERT or the standard of care

	All patients		Controls		PERT		
	n	Median (IQR)	n	Median (IQR)	n	Median (IQR)	*P* value
Admission							
All patients							
FFA (g/kg)	78	16.2 (5.0-34.4)	38	20.6 (10.2-45.8)	40	12.2 (4.4-24.6)	.2
TG (g/kg)		0.6 (0-7.6)		0.4 (0-5.7)		1.1 (0-10.1)	.99
Split ratio (%)		94 (73-100)		98 (78-100)		87 (70-100)	.4
Nonedematous							
FFA (g/kg)	33	20.6 (4.5-47.8)	22	25.1 (13.3-58.9)	11	14.4 (3.8-24.3)	.2
TG (g/kg)		0.6 (0-6.7)		0.85 (0-10.4)		0 (0-4.3)	.3
Split ratio (%)		98 (81-100)		94 (75-100)		100 (84-100)	.6
Edematous							
FFA (g/kg)	45	12.3 (5.1-25.7)	16	16.3 (8.9-28.5)	29	12.1 (5-24.5)	.9
TG (g/kg)		0.6 (0-7.7)		0 (0-2.6)		1.5 (0-15.1)	.7
Split ratio (%)		90 (67-100)		100 (80-100)		85 (62-100)	.3
28 Days after admission							
All patients							
FFA (g/kg)	45	10 (2.7-20)	22	10.8 (2.7-32.6)	23	9.4 (3.2-15.1)	.2
TG (g/kg)		0.4 (0-0.6)		0 (0-0.4)		0.4 (0-0.9)	.7
Split ratio (%)		99 (88-100)		100 (93-100)		96 (84-100)	.2
Nonedematous							
FFA (g/kg)	16	26.2 (2.9-44.1)	11	17.7 (2.7-42.6)	5	34.5 (17.8-45.8)	.5
TG (g/kg)		0 (0-0.4)		0 (0-0.4)		0 (0-1.2)	.8
Split ratio (%)		100 (94-100)		100 (87-100)		100 (97-100)	.3
Edematous							
FFA (g/kg)	29	6.5 (2.5-11.9)	11	10 (3.4-18)	18	5.4 (2.1-10.2)	.1
TG (g/kg)		0.4 (0-0.8)		0 (0-0.5)		0.4 (0-0.8)	.2
Split ratio (%)		97 (84-100)		100 (97-100)		91 (83-100)	.07

Values are presented as median and IQR. Differences between treatment groups were tested with generalized linear models with a binomial error structure.