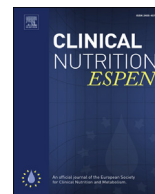




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Original article

Intestinal pathogen clearance in children with severe acute malnutrition is unrelated to inpatient morbidity

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SUMMARY

Background & aims: Children with Severe Acute Malnutrition (SAM) often suffer from diarrhea, which is associated with increased mortality. The contribution of intestinal bacteria, parasites and viruses to morbidity such as diarrhea in SAM remains poorly understood. To evaluate their association with clinical outcomes, we detected stool pathogens in children with SAM at hospital admission and after clinical stabilization prior to discharge.

Methods: 15 intestinal pathogens, fecal calprotectin and C-reactive protein (CRP) were determined at admission and after clinical stabilization in children aged 8–59 months ($n = 47$) hospitalized in Malawi for complicated SAM. Differences in fecal pathogens, intestinal and systemic inflammation, and clinical outcomes between time points were evaluated using the Wilcoxon Signed-Rank test or Wilcoxon rank-sum test.

Results: On admission pathogens were present in nearly all children and after clinical stabilization many were cleared with only 55% of children still harboring a pathogen (89% vs. 55%, $p = 0.001$). Nosocomial infections were infrequent. The pathogens *Giardia lamblia* and *Shigella* spp. were most likely to persist. After clinical stabilization, fecal calprotectin was higher in children harboring a pathogen (median (IQR): 383 mg/kg (903–149 mg/kg) vs 140 mg/kg (300–71 mg/kg), $p = 0.03$). CRP did not correlate with fecal calprotectin levels nor was it associated with pathogen detection. Presence of stool pathogens was not associated with clinical outcomes such as diarrhea.

Conclusions: Fecal pathogens were very common and cleared in most children with complicated SAM treated with antibiotics. The presence of stool pathogens after stabilization was associated with increased intestinal inflammation but not with clinical outcomes. (<http://www.isrctn.com/ISRCTN13916953>).

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Introduction

Worldwide severe acute malnutrition (SAM) results in unacceptably high mortality rates of up to half a million deaths in children under the age of 5 years annually [1]. Despite standardized treatment protocols, inpatient mortality reaches up to 30% in many hospitals [2–4]. Recently, we demonstrated that diarrhea is related to mortality in SAM [5]. Diarrhea, a common problem in children with SAM [4], has a broad differential diagnosis and may be

Abbreviations: CRP, C-reactive protein; SAM, Severe acute malnutrition.

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secondary to osmotic diarrhea, HIV enteropathy, environmental enteric dysfunction or an acute intestinal infection. In Malawi, (chronic) malnutrition is a serious problem with around 47% of children stunted [6]. The nationwide prevalence of diarrhea in children under five has decreased from 13% to 7% from 2000 to 2013 [7] but it remains a serious public health problem. Worldwide, children with malnutrition commonly harbor: pathogenic *Escherichia coli*, *Salmonella* spp., *Shigella* spp., rotavirus and *Cryptosporidium* spp. [8–10]. It is unclear how intestinal bacteria, viruses, and parasites are linked to morbidity (i.e., clinical relevant outcomes such as diarrhea) in children with SAM during inpatient rehabilitation. In addition, there is limited knowledge about nosocomial pathogen transfer during hospital stay and about the usefulness of the current treatment strategies aimed at clearing fecal pathogens.

Therefore, in 47 children with SAM, we evaluated 1) changes in pathogen prevalence during hospital admission and 2) the relation between pathogens and clinical outcomes (diarrhea and duration of stay).

Materials & methods

Study design and patient recruitment

We studied 47 children aged 8–59 months included in a previous randomized clinical trial that was designed to compare the outcomes of 3 commonly used WHO rehabilitation diets (<http://www.isrctn.com/ISRCTN13916953>). The three diets were isocaloric but varied in their composition of carbohydrate and fat ratios. From January to July 2013, this study aimed to recruit 90 children (6–60 months), who were admitted to the NRU Moyo House of Queen Elizabeth Central Hospital in Blantyre, Malawi due to complicated SAM or failing standardized appetite test with Ready to Use Therapeutic Food (RUTF). Complicated SAM was defined as having 1) nutritional bilateral edema in feet, legs, hands, arms and face and/or 2) mid-upper arm circumference (MUAC) less than 115 mm or a weight-for-height/length <-3 z score with medical complications or “danger signs” as described in the WHO guidelines [2,11]. These signs include cyanosis, respiratory distress, impaired consciousness, shock, hypoglycemia, convulsions, severe dehydration, profuse watery diarrhea, severe vomiting, and hypothermia. As determined by rapid antibody testing, HIV positive children (or exposed for children <18 months of age) were included in the original cohort. However, children were excluded if they 1) had been readmitted for SAM within the past year, 2) had a packed cell volume of $<15\%$, 3) had severe hemodynamic instability, 4) had unknown HIV status (because of testing refusal by caregiver), or 5) had severe neurologic symptoms such as convulsions [5]. From this cohort ($n = 90$), we additionally excluded children with: confirmed or clinically suspected malaria ($n = 7$), tuberculosis ($n = 3$) or insufficient or missing stool samples for analysis ($n = 33$) (Fig. 1). All children received treatment according to WHO guidelines with specific modifications required by Malawian Guidelines [2]. This consisted of 1) nutritional management, 2) treatment with broad-spectrum antibiotics (chloramphenicol and gentamicin initially), 3) anti-helminthic therapy with albendazole, 4) vitamin A and folic acid, and when clinically indicated 5) additional antibiotics (metronidazole or ciprofloxacin). During the first phase of nutritional management, i.e., clinical stabilization, children were provided with a low-energy and low-protein diet (F-75; 1.2 g protein/kg/day) until they showed improved appetite, or edema loss for children with kwashiorkor. Then, in transition phase, calorie intake was gradually increased and children received Chiponde (i.e., local name for RUTF) supplemented with F75 (75 kcal/100 mL), or F100 (100 kcal/100 mL). Children were discharged when capable of finishing their Chiponde feeds and when clinically stable (i.e., absence

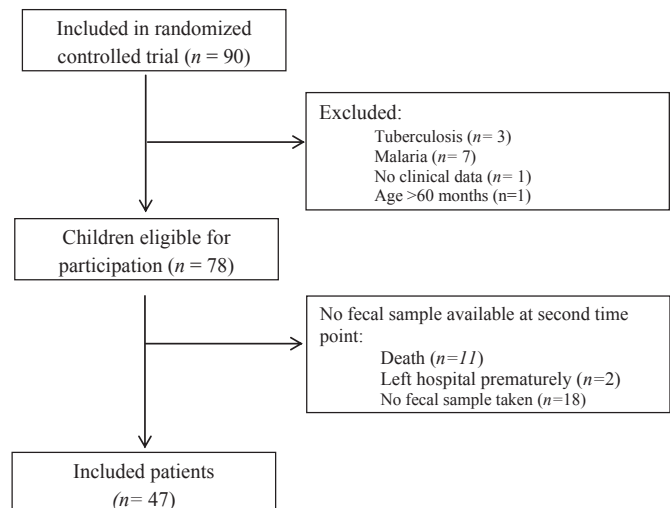


Fig. 1. Flow chart of severely malnourished children included in this study.

of danger signs as described by WHO guidelines). Caregivers provided written informed consent before patient enrollment and the study protocol was approved by the College of Medicine Research Ethics Committee of the University of Malawi, College of Medicine in Blantyre, Malawi and by the Research Ethics Board of SickKids in Toronto, Canada. The primary outcome of this study was the presence of fecal pathogens detected by PCR at hospital admission and after clinical stabilization. Secondary outcomes included clinical outcomes (diarrhea, duration of stay), fecal calprotectin as a marker of intestinal inflammation, and antimicrobial use.

Clinical data and stool collection

Anthropometric, demographic and daily clinical data were collected which included presence and degree of edema, appetite, stool consistency and frequency, antibiotic use and death or discharge. Diarrhea was defined as ≥ 3 loose or watery stools within the last 24 h and was assessed by maternal recall. Stool was obtained: 1) at admission and 2) after clinical stabilization prior to discharge. Stool was immediately cooled, homogenized and stored at -80°C .

Fecal pathogens, fecal calprotectin and C-reactive protein

Fifteen different fecal intestinal pathogens were assessed by polymerase chain reaction at the Hospital for Sick Children, Toronto, Canada, using the Gastrointestinal Pathogen Panel (Luminex Molecular Diagnostics, Toronto, Canada) with a sensitivity of 95% and specificity of 99% [5]. In short, nucleic acids were extracted from 100 to 150 mg of formed or 100 μL of loose stool by easyMAG extractor (bioMerieux, St. Laurent, Canada) and underwent multiplex PCR for: 1- *Salmonella* spp., 2- *Shigella* spp., 3- *Campylobacter jejuni/coli*, 4- *Yersinia enterocolitica* (pathogenic serotype only), 5- *E. coli* O157:H7, 6- non-O157 shiga-like toxin producing *E. coli*, 7- *Clostridium difficile* toxin A/B, 8- enterotoxigenic *E. coli* (ETEC), 9- *Vibrio cholerae*, 10- rotavirus A, 11- adenovirus 40/41, 12- norovirus GI/II, 13- *Giardia lamblia*, 14- *Entamoeba histolytica*, and 15- *Cryptosporidium parvum*. Fecal calprotectin, a measure of intestinal inflammation, was measured using a standard enzyme-linked immunoabsorbent assay by the University Medical Center Groningen, Clinical Laboratory in the Netherlands. C-reactive protein, a measure of systemic inflammation, was measured using standard

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