TECHNICAL REPORT

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FOOD AND NUTRITION TECHNICAL ASSISTANCE

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Randomized, Double-Blind, Placebo-Controlled Trial Evaluating the Need for Routine Antibiotics as Part of the Outpatient Management of Severe Acute Malnutrition

Mark J. Manary
Kenneth Maleta
Indi Trehan

March 2012

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THE SCIENCE OF IMPROVING LIVES

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Abbreviations and Acronyms

<	less than
>	greater than
°C	degrees Celsius
≥	greater than or equal to
≤	less than or equal to
ANOVA	analysis of variance
ART	antiretroviral therapy
COMREC	University of Malawi College of Medicine Research and Ethics Committee
CI	confidence interval
cm	centimeter(s)
DSMB	data and safety monitoring board
g	gram(s)
HAZ	height-for-age z-score
HIV	human immunodeficiency virus
IQR	interquartile range
kcal	kilocalorie(s)
kg	kilogram(s)
MAM	moderate acute malnutrition
mg	milligram(s)
ml	milliliter(s)
mm	millimeter(s)
MUAC	mid-upper arm circumference
PCP	pneumocystis pneumonia
PMPB	Pharmacy, Medicines and Poison Board (Malawi)
RUTF	ready-to-use therapeutic food
SAM	severe acute malnutrition
SD	standard deviation
TB	tuberculosis
U.S.	United States
US$	United States dollar
WHO	World Health Organization
WHZ	weight-for-height z-score

Abstract

Severe acute malnutrition (SAM) in children is defined as having a weight-for-height z-score (WHZ) < −3 (marasmus), bipedal pitting edema (kwashiorkor), or both (marasmic kwashiorkor). These diseases contribute to the deaths of 1 million children every year. Until recently, children with SAM were treated as inpatients in crowded hospital wards with milk-based therapy and routine antibiotics for all children. With the advent and widespread acceptance of peanut-based ready-to-use-therapeutic food (RUTF), standard therapy for SAM without medical complications is to treat these children at home, where the risk of nosocomial infection and the care burden on the family are much lower.

Even in the home setting, international guidelines continue to recommend that children receive a course of oral antibiotics at the start of their RUTF therapy for SAM. Because this places an additional burden on already taxed health systems and caregivers, because clinical experience has shown good recovery rates without antibiotics, and because the bacteria most likely to cause severe infections in these children are unlikely to be susceptible to most options for routine antibiotics, their routine use has been called into question. We thus undertook a rigorous prospective, double-blind, randomized, placebo-controlled clinical trial comparing nutritional recovery and mortality outcomes in children with SAM receiving 1 week of amoxicillin, cefdinir, or placebo, in addition to usual RUTF therapy. A total of 2,767 children were enrolled in the study.

The primary outcomes of interest were mortality and nutritional recovery (achieving WHZ ≥ −2 without edema) within six follow-up visits (scheduled every 2 weeks) of starting therapy. The recovery rates were 88.7%, 90.9%, and 85.1% for children that received amoxicillin, cefdinir, or placebo, respectively ($p < 0.001$ overall). The relative risk for recovery for the placebo group compared to the amoxicillin group was 0.96 (95% confidence interval [CI], 0.93–0.99) and for the placebo group compared to cefdinir was 0.94 (95% CI, 0.91–0.97). The mortality rates for the three groups were 4.8%, 4.1%, and 7.4%, respectively ($p = 0.003$ overall; relative risk for placebo compared to amoxicillin, 1.55, 95% CI, 1.07–2.24; relative risk for placebo compared to cefdinir, 1.80, 95% CI, 1.22–2.64). Stated differently, the routine addition of 1 week of amoxicillin to standard RUTF therapy for children with SAM without medical complications (and treated as outpatients) reduces the mortality rate by 36%, while the routine addition of 1 week of cefdinir reduces the mortality rate by 44%. Given the extremely large number of children that continue to develop SAM, incorporating routine antibiotics into the outpatient treatment regimen for SAM without medical complications has the potential to save the lives of thousands of children annually.

Introduction

The contribution of severe acute malnutrition (SAM) to the overall burden of childhood morbidity and mortality is enormous, with more than 20 million children severely wasted worldwide[1] and case fatality rates for hospitalized children as high as 50%.[1,2] Over the past decade, ready-to-use therapeutic food (RUTF) has made a profound impact on the treatment of SAM throughout the developing world. These peanut paste-based foods resist bacterial contamination because they contain very little water, do not require cooking, and are very energy dense.[3] These characteristics make RUTF ideal for use in places where food insecurity is common and hygiene is poor. Following years of primary management of SAM being based on providing fortified milk formulas in hospital settings,[4,5] recent international consensus guidelines now recommend RUTF in outpatient settings as the primary means of managing cases of SAM without medical complications.[6] While these outpatient regimens often have success rates equal to or better than the inpatient treatment regimens they have replaced,[7] further work remains to maximize the recovery rate and minimize the mortality rate.

A high prevalence of clinically significant infections, particularly bacteremia, in children hospitalized for severe malnutrition has been observed in a number of studies,[8-19] but this has been an inconsistent finding.[20,21] This clinical observation of a high infectious mortality among hospitalized malnourished children has motivated international consensus treatment guidelines to recommend routine antibiotics even for those treated as outpatients,[6] even though those treated as outpatients are presumably much less ill than those with medical complications that require inpatient care. Moreover, this recommendation for routine antibiotics is based only on expert opinion without an evidence base arising from any clinical trial.[22] In fact, retrospective data from therapeutic feeding programs would suggest that antibiotics are not necessary and perhaps even harmful in this setting.[23] This is not inconsistent with the findings from the treatment of other diseases that empiric antibiotics for apparently ill children, even in resource-limited developing world settings where diagnostics can be challenging, are not necessarily beneficial.[24]

Given that the majority of children with SAM will be managed in rural health posts throughout the developing world,[25,26] and given the complexity and costs associated with providing antibiotic therapy in addition to RUTF for all malnourished children in this setting and the retrospective evidence base that suggests antibiotics are unnecessary and perhaps even harmful in this setting, we conducted a clinical trial to test whether the routine administration of oral antibiotics as part of the outpatient management of SAM was beneficial.

Subjects and Methods

Study Area

Enrollment for the trial took place at 18 different therapeutic feeding clinics in rural southern Malawi, an area representative of agrarian sub-Saharan Africa. An estimated 11% of Malawi's adult population has HIV, and 53% of the children are moderately or severely stunted.[27] Rural children in this area come from families of subsistence farmers that rely on an annual harvest of maize as their staple crop[28] and consume minimal amounts of meat.[29]

The sites were located in six districts, identified based on census reports of severely malnourished children provided by the World Food Programme:

- Chikwawa District (Makhwila health center, Mitondo health post, Nkhate health post)
- Chiradzulu District (Namitambo health center, Thumbwe health center)
- Machinga District (Chamba health center, Chikweo health center, Chipolonga health post)
- Mulanje District (Chikonde village site, M'biza health center, Muloza health center, Namasalima health center, Namphungo health center, Ntonya village site)
- Phalombe District (Migowi health center)
- Zomba District (Chingale health center, Mayaka health center, Thondwe health center).

Subjects

A sample size of 2,700 children was estimated to be necessary for the study to have 80% power at a two-sided alpha level of 0.05 to detect both an improvement in the failure rate by 4 percentage points from an estimated baseline of 11%[30] and an improvement in the mortality rate by 3.5 percentage points from an estimated 8% baseline.

Children 6–59 months of age presenting to the selected therapeutic feeding/research clinics from December 22, 2009, to January 28, 2011, were screened for eligibility. Each child presenting had his or her weight measured to the nearest 5 g using a standard electronic scale, length measured to the nearest 0.2 cm using a rigid height board,[1] and mid-upper arm circumference (MUAC) measured using a standard insertion tape. In addition, kwashiorkor was diagnosed in children with bipedal pitting edema. To minimize inconsistency and subjectivity that comes with edema grading systems and in keeping with standard malnutrition references[4,6,31-34] that do not describe how to actually grade edema in children with kwashiorkor or marasmic kwashiorkor, no attempt was made to assign a grade to edema other than present or absent.

Children with edematous malnutrition (kwashiorkor) and/or severe wasting (marasmus, defined as a weight-for-height z-score [WHZ] < −3)[34] were identified and approached for enrollment in the study. Children were excluded if they had received any therapy for acute malnutrition in the prior month, if they had a chronic debilitating illness (excluding tuberculosis [TB] and HIV), or if they were allergic to any medication or foods. Of note, a therapeutic trial of three different supplementary foods for moderate acute malnutrition (MAM) was being concurrently conducted by our research team at the same sites. Children identified as having MAM (defined as WHZ between −2 and −3 without edema) were thus screened for eligibility for that trial.

Ethical Considerations

The study was approved by the University of Malawi College of Medicine Research and Ethics Committee (COMREC) and the Human Research Protection Office at Washington University in St. Louis. During the course of the study (on March 9, 2010), COMREC amended its approval to require the creation of an independent data and safety monitoring board (DSMB) to monitor adverse events and interim study outcomes and to require that approval be obtained from the Malawi government's Pharmacy, Medicines

[1] 0.7 cm was subtracted from the length of children 2 years and older to arrive at a comparable height.

and Poison Board (PMPB). The DSMB met twice during the course of the study to review interim results, but did not feel that the study needed to be ended early or modified from the original protocol. PMPB approval was also granted for the use of cefdinir in the context of the study since that medication was not previously approved for use in Malawi.

After screening, caregivers of eligible children were approached for verbal and written consent to participate in the study by one of six Malawian research nurses. Those that were ineligible or who did not consent continued to receive usual care as part of the therapeutic feeding program for SAM.[26]

Study Design and Interventions

This was a prospective, randomized, double-blinded, placebo-controlled clinical trial comparing nutritional and mortality outcomes for children with SAM treated as outpatients with or without antibiotics. All children received standardized nutrition counseling and RUTF at a dose of approximately 175 kcal per kg per day. Outpatient therapeutic feeding programs that provide antibiotics almost always provide either amoxicillin or cotrimoxazole, usually for 5–7 days.

A thorough search of the literature and discussion with colleagues in the malnutrition field yielded no consensus on which antibiotics to test in the study since no studies of the most common bacterial pathogens in children with SAM with medical complications had been performed. It was also a challenge to identify accurate recent data on antibiotic resistance patterns. We therefore selected the intervention antibiotics to use based on a group of patients that we believed was the closest match to the population of interest in this study.

These data came from a retrospective review of the medical records of the 4,322 children admitted to the pediatric nutritional rehabilitation unit at Queen Elizabeth Central Hospital in Blantyre, Malawi, from August 2005 to March 2008.[35] Among those 4,322 children, a total of 971 blood cultures had been performed on admission. Of these, 808 (83.2%) had no growth or grew organisms believed to be contaminants. A total of 33 (3.4%) grew Gram-positive organisms (mostly *Streptococcus pneumonia* with the occasional *Staphylococcus aureus*), 73 (7.5%) grew non-Typhoidal *Salmonella* species, and 57 (5.9%) grew other Gram-negative organisms (mostly enteric flora).

A review of the antibiotic sensitivity patterns of these isolates showed that the Gram-positive species were 27% sensitive to penicillin, 66% sensitive to erythromycin, 61% sensitive to chloramphenicol, 12% sensitive to cotrimoxazole, 50% sensitive to gentamicin, 24% sensitive to tetracycline, and 100% sensitive to ceftriaxone (a third-generation parenteral cephalosporin). Among the non-Typhoidal *Salmonella*, none were sensitive to ampicillin, 3% were sensitive to chloramphenicol, none were sensitive to cotrimoxazole, 97% were sensitive to gentamicin, 100% were sensitive to ceftriaxone, and 100% were sensitive to ciprofloxacin. Among the remaining Gram-negatives, 21% were sensitive to ampicillin, 27% were sensitive to chloramphenicol, 12% were sensitive to cotrimoxazole, 70% were sensitive to gentamicin, 76% were sensitive to ceftriaxone, and 87% were sensitive to ciprofloxacin.

Given the extremely high rates of cotrimoxazole resistance and our concern that resistance might be even more common in the years since that study due to increased availability of cotrimoxazole prophylaxis among HIV-infected and HIV-exposed patients, we did not believe it would be useful to test cotrimoxazole in this study. In light of the desire to test an intervention in common practice (for example, amoxicillin is recommended in the Malawi national guidelines for treatment of children with SAM), we elected to use amoxicillin in one study arm. However, given our prior retrospective study, which did not demonstrate improved outcomes in the amoxicillin group,[23] we felt it was important to also include a study arm to test an antibiotic that, despite its less demonstrated resistance, might have a better chance of "success." Perhaps the issue was not that antibiotics were not effective, but perhaps simply that the "wrong" antibiotics were not effective and that the "right" antibiotic might be useful in this context.[36]

Based on the resistance patterns listed above, our attention was drawn to ceftriaxone as remarkably effective across all three categories of bacteria. The recent availability of an oral formulation of cefdinir, another third-generation cephalosporin,[37] made this a realistic possibility. The fact that cefdinir can be

purchased at a relatively low cost in a flavored suspension form—important for palatability to children—from a generic drug manufacturer—important for affordability for local governments and aid organizations—made this a convincing choice.

Thus, one intervention group received oral amoxicillin (Sandoz GmbH) reconstituted suspension at a dose of 80–90 mg per kg per day divided into two daily doses; the second intervention group received oral cefdinir (Sandoz GmbH) reconstituted suspension at a dose of approximately 14 mg per kg per day divided into two daily doses. The control group received placebo to be administered twice per day. Caregivers were instructed to administer the medicine in addition to RUTF during the initial 7 days of therapy, although each received 8 days of medication to account for spillage or the child spitting up the medicine.

Both medications were purchased at cost from the St. Louis Children's Hospital Pharmacy. A 150 ml bottle of amoxicillin 250 mg per 5 ml suspension cost US$3.64, and a 100 ml bottle of cefdinir 125 mg per 5 ml suspension cost US$22.43. Thus, for a typical child weighing 7.5–8.0 kg at enrollment, the cost of the amoxicillin that would be dispensed was about US$2.67 and the cost of cefdinir was US$7.85. (For comparison, the cost of RUTF for that child would be just over US$1 per day of therapy.)

The trial was registered with the United States (U.S.) Clinical Trials Registry at http://clinicaltrials.gov with accession code NCT010000298.

Study Procedures

All children identified with SAM in the clinic were administered an appetite test, under the supervision of one of the research nurses, using 30 g of RUTF to verify whether the child had an appetite and was therefore an appropriate candidate for outpatient therapy. Locally produced RUTF[3] from Project Peanut Butter, Blantyre, Malawi, was used in this study; this food has proven safe in a number of studies and is as effective as commercially produced, imported RUTF.[38] Children that were anorexic or otherwise too ill to consume RUTF in the clinic were referred to the local health facility or district hospital for inpatient management. No child had an adverse reaction to the RUTF. Caregivers of children that met enrollment criteria were then approached for consent and given a baseline demographic and clinical questionnaire.

Block randomization lists were created using a computerized random number generator in permuted blocks of 54. Participating children were allocated to their study arm when their caregivers drew an opaque envelope containing one of nine coded letters corresponding to one of the three medication groups. The code was accessible only to specific pharmacy personnel at each clinic dedicated to the preparation and distribution of the medications. Caregivers, study nurses, and all study personnel involved in clinical assessments and data analysis were kept blinded to the intervention each child received. The allocation code was available only to the DSMB during the course of the study and to study investigators after completion of data analysis.

The medications and placebo were distributed in opaque plastic bottles with plastic syringes marked to indicate the dose of medication each child was to receive. After randomization and distribution of the medications and placebo, study nurses educated each child's caregiver on how to use the syringe to give the medications and supervised the administration of the first dose in the clinic. Caregivers were also provided with a pencil and a pictorial calendar for recording each dose given, with instructions to give the medication twice per day for 7 days.

Each child was discharged home with his/her study medication and a 2-week supply of RUTF, and caregivers were instructed not to allow any sharing of the RUTF with other children or adults. If there was a healthy twin or other child near the same age in the household with whom sharing might be suspected by the study nurses, an allotment of RUTF was also provided for the other child to limit this possibility. Children were brought back for up to six follow-up visits at 2-week intervals, at which time repeat anthropometric measurements were taken and caregivers were asked about the child's interim clinical and appetite history. At the first follow-up visit, study nurses assessed how much medication was given to the child by examining how much medication remained in the study bottle, examining how many doses were marked off on the dosing calendar, and considering the caregiver's verbal report.

Children that still had bipedal pitting edema and/or whose WHZ remained < –2 at follow-up visits were continued in the study and received nutrition counseling and another 2-week supply of RUTF. Any child whose clinical status was significantly worse during the course of the study or who remained malnourished (WHZ < −2 and/or with bipedal pitting edema) after six follow-up visits was referred to inpatient care. Children that did not return for follow-up visits were sought by community health workers at their homes and instructed to return to the clinic at the next opportunity; children that missed three consecutive visits were sought by the entire study team with the use of a 4-wheel drive vehicle. Children were considered to have recovered from SAM when their edema had resolved and they had a WHZ > −2. Study failures included children that dropped out and could not be found at home, children that had bilateral pitting edema and/or a WHZ < −2 after six follow-up visits, children that were hospitalized for any reason during the study, and children that died.

Statistical Analysis

Summary enrollment characteristics were calculated as *means* ± *standard deviation* (SD) for continuous measurements and as *n* (%) for dichotomous measures. Anthropometric indices were calculated using World Health Organization (WHO) standards.[34] The two primary comparison endpoints of interest in the study were rates of nutritional recovery and mortality rates in the three study arms. Secondary outcomes of interest included weight gain, length gain, tolerance of the medications, and time to recovery. Outcomes were also stratified by type of SAM (kwashiorkor, marasmus, or marasmic kwashiorkor) and by baseline characteristics, such as HIV status. Intention-to-treat analyses were used and all tests were two-sided. Dichotomous outcome variables were compared using the Fischer's exact test and the chi-square test, and continuous variables were compared by analysis of variance (ANOVA) and Student's t-test. The relative risk differences in outcomes among the three intervention arms were also computed. Survival analysis plots (Kaplan-Meier curves) comparing time to recovery were also generated and compared using the logrank statistic.

Results

Study Population

A total of 3,212 children were diagnosed with SAM from December 2009 to January 2011. After exclusion of ineligible children, 2,767 children with SAM remained (**Figure 1**; see **Annex 2** for all figures). No caregivers refused enrollment in the study. A total of 924 children were randomized to the amoxicillin group, 923 to the cefdinir group, and 920 to the placebo group. The number of children enrolled at each site in each arm of the study is shown in **Table 1** (see **Annex 1** for all tables).

Baseline characteristics of the enrolled children were similar in each intervention arm except for the age of the children at enrollment and the starting WHZ of children with marasmic kwashiorkor (**Table 2**). The median age of the enrolled children was 19.4 months (interquartile range [IQR], 13.4–26.9 months). More than 70% of the children had kwashiorkor, nearly 21% had marasmus, and almost 9% had marasmic kwashiorkor. Stunting was extremely common, with more than 80% having a height-for-age z-score (HAZ) < −2 and more than half < −3.

Less than a third of the children had been tested for HIV; of those, more than a fifth were HIV-positive, and less than a third of those were receiving antiretroviral therapy (ART). About three-quarters of the children's mothers had been tested for HIV, with 19% being HIV-positive; less than half of those were receiving ART. Access to health care in general was limited, with the median travel time (generally on foot, occasionally by bicycle for those able to afford one) to the nearest health center being approximately 60 minutes and the median travel time to the nearest shop that sells over-the-counter medications (generally analgesics and antipyretics) being approximately 15 minutes. More than 96% of the children were reported to have at least one acute infectious symptom (fever, cough, diarrhea, vomiting, and/or rash) in the prior 2 weeks, although more than 85% were reported to have a good appetite at the time of enrollment.

Study Interventions

Adherence to the intervention was excellent in each of the three study groups, with almost all children completing the entire 7-day course (**Table 3**). No reports of severe allergy or anaphylaxis were reported from any children in the study. A total of three presumed adverse drug reactions occurred: One child who received cefdinir developed oral thrush; one child who received cefdinir was reported to have bloody diarrhea, although this had resolved spontaneously by the time the child returned for follow-up; and one child who received amoxicillin developed a generalized rash. Children that received placebo had higher rates of cough and diarrhea reported at the first follow-up visit; caregivers of children that received amoxicillin reported cough least frequently, while children that received cefdinir had the least reported diarrhea.

Recovery and Mortality Outcomes

Overall, 88.3% of the children enrolled in the study recovered from SAM (**Table 4**). Children with marasmic kwashiorkor recovered much less frequently than children with either kwashiorkor or marasmus (65.6% versus 93.8% and 79.1%, respectively) and had much higher mortality (17.2% versus 3.3% and 7.4%, respectively). The proportion of children that recovered was significantly lower among those that received placebo (85.1%) than among those that received either amoxicillin (88.7%, $p = 0.02$) or cefdinir (90.9%, $p = 0.0001$). Subgroup analysis showed that, when stratified by type of SAM, children with kwashiorkor that received placebo recovered less frequently than those that received cefdinir (92.2% versus 95.2%, $p = 0.04$). Similarly, children with marasmus that received placebo also recovered less frequently than those that received cefdinir (74.4% versus 79.2%, $p = 0.02$).

The large proportion of failures in the placebo arm was predominantly due to excess mortality in these children rather than excess dropouts, hospitalization, or continued SAM at the end of the study period. The overall mortality rate was 5.4%, but was significantly higher for children that received placebo (7.4%)

than for those that received either amoxicillin (4.8%, p = 0.02) or cefdinir (4.1%, p = 0.003). Analysis of these numbers revealed some trends by type of SAM, but the numbers of deaths in these subgroups were too low to achieve enough statistical power.

Although the simple mean time to recovery did not differ among the three study arms (**Table 5**), Kaplan-Meier analysis showed that the rates of recovery were significantly different among the three study arms when considering all types of SAM together (**Figure 2**, logrank p = 0.01). However, when stratified by type of SAM, this sub-analysis did not demonstrate statistical significance (**Figures 3–5**), although each stratified sub-analysis does demonstrate a trend toward cefdinir providing the highest and quickest chances for recovery, followed by amoxicillin, followed by placebo.

Growth outcomes are also presented in **Table 5**. Weight gain during the first 4 weeks of therapy (or 2 weeks for children followed for only 2 weeks) was significantly higher among those children that received cefdinir than among those that received placebo (3.9 g/kg/day versus 3.1 g/kg/day, p = 0.002). These differences in weight gain were also seen specifically in children with kwashiorkor. Children that received amoxicillin or cefdinir also had greater increases in MUAC, both overall and in the kwashiorkor and marasmic kwashiorkor subsets. Differences in length gain between the three groups were not identified to a level of statistical significance.

Enrollment Characteristics Related to Recovery

Demographic characteristics at the time of enrollment among children that recovered, children that failed therapy (including those that died, dropped out, were hospitalized, or remained malnourished), and children that died during the course of therapy are presented in **Table 6**. Children that recovered were significantly older than children that did not recover and children that died. Children that recovered were also significantly more likely to have their father be alive and in the home. Children that died were significantly more likely than children that recovered to live closer to their nearest health center, as measured by the primary caregiver's assessment of the time it took to travel to the health center. Children that recovered were also significantly less likely to still be breastfeeding, although this may be confounded by the fact that these children were older on average. Among those children that had already stopped breastfeeding, those that recovered had breastfed for approximately 2 months longer than those that did not recover or died.

Baseline clinical characteristics at the time of enrollment are presented in **Table 7**. As seen earlier in **Table 4**, children with kwashiorkor that received RUTF and any of the study interventions recovered at significantly higher rates than those with marasmus and especially those with marasmic kwashiorkor. Among children with marasmus and marasmic kwashiorkor, those with the lowest MUAC and WHZ at enrollment were most likely to fail therapy or die during the study. Children with the most stunting, an excellent marker of chronic malnutrition,[1] also had the highest rates of failure and death.

Table 8 compares some of the subjects' medical histories, based on whether they recovered from SAM, failed therapy, or died during the study. HIV infection or exposure, especially without being on ART, is an obvious factor in mortality and failure to recover from SAM in this study population. While this finding is almost certainly real, the absolute numerical findings in **Table 8** must be approached with the reminder that the rate of HIV testing among these children is quite low overall. The test results thus seem likely to reflect a strong referral bias in health centers with limited resources: The most chronically ill children and children not responding to usual therapy for acute illnesses are the ones usually referred for testing, and many HIV-infected children whose infection has not yet progressed to an advanced clinical stage are not being tested.

Table 9 shows that cough, diarrhea, and vomiting in the 2 weeks prior to enrollment in therapy for SAM is correlated with failure to recover or death. Despite the observed appetite test that all subjects took part in, under the supervision of the study nurses, a caregiver report of poor appetite appears predictive of failure to recover. **Table 10** shows that children that are most likely to fail therapy or die during treatment continue to present with fever, cough, diarrhea, and vomiting when they return for follow-up.

The exact day of death was available for 128 of the 150 children that died (85%). Among these 128 children, the mean time from enrollment to death was 27.5 ± 23.3 days. The median time was 20 days (IQR 10–40 days), with a minimum of 0 days and maximum of 105 days. The group of children that received amoxicillin had the highest percentage of early deaths and the cefdinir group had the lowest (**Table 4**). Comparing children that died “early” (less than 21 dayss after enrollment) compared to those that died “late” (more than 21 days after enrollment), the groups had similar baseline demographic and clinical characteristics, except that children that died earlier were more likely to be male and had stopped breastfeeding at an earlier age (**Table 11**). The two groups also had similar medical histories and recent symptoms at enrollment (**Table 12**) and similar symptoms at their first follow-up visit (**Table 13**).

Discussion

Despite the great strides that have been made in the treatment of SAM over the last several years with the advent and widespread usage of RUTF for the community-based management of SAM, 10%–15% of children still do not recover from their episode of SAM.[26] Those children that do not recover have a high risk of linear growth faltering, cognitive stunting, and, most importantly, a markedly increased risk of mortality from acute infectious diseases.[39,40] Given the extremely high incidence of SAM annually,[1,41] the recovery and mortality rates currently achieved using optimal therapy remain unacceptably high,[42] particularly in the areas of highest HIV prevalence.[43] In these resource-limited settings, expensive interventions for such high-burden diseases should generally not be recommended on a large scale without appropriate clinical trial evidence as to their efficacy. The well-described adverse effects from indiscriminate antibiotic use specifically[44,45] provides further motivation for their judicious use.

The international consensus guideline for the community-based management of SAM recommends that children with SAM "need to receive a short course of basic oral medication to treat infections,"[6] although there is no trial evidence to suggest that this is helpful[22] and observational evidence suggests it may in fact be harmful.[23] Should routine antibiotics indeed be unnecessary, treatment protocols for SAM could be simplified and made less expensive, theoretically allowing more children in more places to be treated. We conducted this prospective, randomized, double-blind, placebo-controlled trial to provide the first rigorous trial evidence to evaluate the effects of routine antibiotics in the community-based management of SAM.

Among the 2,767 children with SAM randomized to 1 week of oral amoxicillin, cefdinir, or placebo in addition to standard nutrition therapy with RUTF, children that received antibiotics did indeed demonstrate marked improvements in the primary study outcomes of nutritional recovery and mortality. While 85.1% of children taking placebo recovered, 88.7% of the children that received amoxicillin and 90.9% of the children that received cefdinir recovered (**Table 4**). This corresponds to a 24% (95% confidence interval [CI], 4%–40%) reduction in the failure rate when amoxicillin is added to RUTF therapy and a 39% (95% CI, 21%–53%) reduction when cefdinir is added to RUTF therapy. Moreover, the decrease in the failure rates was primarily driven by a large decrease in mortality, with 4.8% and 4.1% of children that received amoxicillin and cefdinir, respectively, dying during the study, compared to 7.4% who received placebo. This corresponds to a 36% (95% CI, 7%–55%) reduction in mortality when given amoxicillin and a 44% (95% CI, 18%–62%) reduction in mortality with cefdinir.

These results provide clear evidence to support the recommendation for routine oral antibiotics as part of the outpatient management of SAM. Although the differences between amoxicillin and cefdinir did not reach statistical significance given our sample size, a clear trend emerged: Cefdinir improved the recovery rate compared to amoxicillin by 21% (95% CI, −7%–42%) and decreased the mortality rate by 14% (95% CI, −34%–45%). Secondary study outcomes (**Table 5**) are generally consistent with these findings as well, with the time to recovery and rates of growth being better among those children that received cefdinir and worse among those that received amoxicillin.

Children with marasmic kwashiorkor fared consistently worse than those with either just marasmus or just kwashiorkor (**Tables 4** and **5**). While some experts recommend that all children with marasmic kwashiorkor be referred for inpatient care,[25,33] others do not specifically make this recommendation in cases where the child has a good appetite,[26] and current international consensus guidelines do not specifically address this population of children with SAM.[6,34] Given the continued high mortality rates associated with inpatient care for malnutrition[17,43] and the logistical and financial difficulties associated with admitting all children with marasmic kwashiorkor to a hospital as soon as they present for care, it is likely that in most settings in sub-Saharan Africa these children will continue to be managed as outpatients first if they demonstrate a good appetite. Our results confirm the clinical sense that children with marasmic kwashiorkor are at particularly high-risk and warrant aggressive care, perhaps including earlier and/or more frequent follow-up. Furthermore, if the availability of antibiotics for malnourished children is limited, one strategy may be to reserve them for children with marasmic kwashiorkor or marasmus, as the relative benefit for children with kwashiorkor alone appears smaller.

It is not surprising that HIV infection severely hampers a child's ability to recover from SAM.[47-49] Only 32% of the children in this study had been tested for HIV, and of those found to be HIV-positive, only 31% were receiving ART. Given our limited sample of children that had been tested for HIV, we found a high number of infected children that failed therapy or died during the study (**Table 8**), significantly more so if they were not receiving ART, providing further evidence for the need to provide integrated HIV and malnutrition care in this setting.[43]

Given that this study was conducted in rural sub-Saharan Africa in a stable, subsistence farming population with a heavy burden of food insecurity and HIV, these results may not necessarily be applicable to other populations of malnourished children, such as those that might be found in refugee or natural disaster settings. Nevertheless, given the uniquely worsening malnutrition situation in sub-Saharan Africa,[46] it can be argued that the malnourished children in this region remain a high priority for study.

We pursued an aggressive strategy to minimize the dropout rate during this study. We provided *chitenjes* (traditional cloths) to caregivers of children that completed the study (successfully or not), paid village health workers to seek out and gather information on children that did not return for follow-up, used cell phone and text-messaging technology to provide reminders and encouragement to village health workers as they tracked missing children,[50] and had the study researchers and nurses make home visits for any children that the village health workers were unable to find. Almost all of the children that we found using these aggressive methods had in fact died or were so ill that they needed to be hospitalized, thereby accounting for our relatively higher percentage of deaths during the course of this study compared to other recent studies in Malawi,[30,51,52] in which similar methods were not used and children not tracked were likely to have been simply categorized as dropouts. Almost all of the children that could not be tracked had moved away, lived across the border in Mozambique, or lived in a remote location inaccessible to our study team's vehicle. Given the very low dropout rate we were able to achieve in our study (2.2%) and the fact that the trend in dropouts mirrored the overall recovery and mortality trends (i.e., most dropouts in the placebo group and least in the cefdinir group), we can surmise that the dropouts were indeed quite likely to be children that failed therapy.

We provided caregivers with their intervention medications in a liquid suspension form in an opaque amber bottle fitted with a bottle adapter and an oral syringe individually marked with the appropriate dose. An experienced research nurse demonstrated to the caregiver how to dose and administer the intervention. These steps were taken in an attempt to minimize dosing errors and maximize the caregivers' ability to effectively administer the medication.[53] Providing this degree of resources in an operational setting is admittedly unlikely in many settings at this time, but we believe that this type of intervention during the study was necessary to most rigorously test the effectiveness of the interventions themselves rather than leaving this to the unpredictability of caregiver compliance.

No serious adverse events were noted from the receipt of antibiotics and, in fact, the rates of typical antibiotic side effects (most notably diarrhea) were lower among children that received antibiotics (**Table 3**). This reflects both the safety of these medications and perhaps even the specific mechanism of their effectiveness in the malnutrition armamentarium, i.e., decreasing the rates of bacterial pneumonia and dehydrating diarrhea in these immunocompromised children.

The exact mechanism of the effectiveness of antibiotics in this study remains an open—and likely unanswerable—question in this population without large-scale invasive studies that are unlikely ever to be performed. The mucosal barriers (both respiratory and intestinal) are known to be diminished among patients in this setting,[54] especially malnourished children[55,56] and those with HIV.[57] The types of bacteria most commonly found in surveillance studies of bacteremia among malnourished children[13] corroborates the notion that the significant invasive bacterial infections among these children are due to translocation across these compromised mucosal surfaces. Given recent information about the antibiotic resistance patterns for these most commonly translocating bacteria in this setting,[58-61] β-lactam antibiotics—particularly third-generation cephalosporins, such as cefdinir—seem to be the optimal choice for severely malnourished children.

The drug dosing we used in this study is the standard dosing recommended for appropriately nourished children in resource-rich settings. Since severely malnourished children are known to demonstrate altered pharmacokinetics,[62,63] it might be reasonable to further study what dosing in these children leads to maximal recovery rates.

Ultimately, what is evident is that, although these severely malnourished children have SAM without medical complications—in that they are clinically stable enough to qualify for outpatient therapy[6]—they nevertheless are susceptible enough to bacterial infections to warrant the routine inclusion of antibiotics as part of their nutrition therapy. Although we did not perform a cost-benefit analysis for the addition of antibiotics, the excellent "value" that is provided by the community-based management of SAM[64-66] almost certainly remains even with this additional cost. The evidence from this rigorous study is strong enough that policy makers, ministries of health, and nongovernmental organizations working with severely malnourished children should make plans to include routine antibiotics as part of their case-management of these children.

Annex 1. Tables

Table 1. Listing of Study Sites and the Number of Children Enrolled in Each Study Group

Study Site	Amoxicillin (n = 924)	Cefdinir (n = 923)	Placebo (n = 920)	Total (N = 2,767)
Chikwawa District				
Makhwila (weekly site)	75	60	73	208
Mitondo	31	35	31	97
Nkhate	45	39	43	127
Chiradzulu District				
Namitambo	28	44	32	104
Thumbwe	30	32	24	86
Machinga District				
Chamba	39	44	45	128
Chikweo	36	39	38	113
Chipolonga	22	15	23	60
Mulanje District				
Chikonde	46	52	44	142
M'biza (weekly site)	137	131	130	398
Muloza	69	66	75	210
Namasalima	33	46	41	120
Nampuhungo	57	47	43	147
Ntonya	34	30	31	95
Phalombe District				
Migowi	39	37	35	111
Zomba District				
Chingale	43	43	58	144
Mayaka (weekly site)	125	131	118	374
Thondwe	35	32	36	103

Table 2. Baseline Characteristics of Children Enrolled in the Study

Variable	Amoxicillin* (n = 924)	Cefdinir* (n = 923)	Placebo* (n = 920)
Demographic Characteristics			
Male	432 (47)	449 (49)	436 (47)
Age (months)	20.6 ± 9.7[A]	21.7 ± 10.3[A]	20.9 ± 9.8
Twin	55 (6)	49 (5)	40/919 (4)
Mother as primary caregiver	855/923 (93)	843 (91)	843 (92)
Mother alive	900 (97)	894 (97)	885 (96)
Father alive	876 (95)	871 (94)	871 (95)
Father in home	654 (71)	645 (70)	669 (73)
Number of children under 5 in home	1.6 ± 0.7	1.6 ± 0.7	1.5 ± 0.7
Distance to nearest health center (minutes)	85 ± 52	85 ± 56	82 ± 51
Distance to nearest shop that sells medicines (minutes)	24 ± 25	25 ± 29	24 ± 27
Currently breastfeeding	444 (48)	399 (43)	431 (47)
Age stopped breastfeeding (months)	19.3 ± 7.7	19.7 ± 8.5	19.1 ± 8.0
Clinical Characteristics			
Kwashiorkor	649 (70)	664 (72)	632 (69)
Marasmic kwashiorkor	78 (8)	73 (8)	93 (10)
MUAC (cm)	10.7 ± 1.1	10.7 ± 0.9	10.7 ± 1.1
WHZ	−3.75 ± 0.64	−3.56 ± 0.53	−3.71 ± 0.66
Marasmus	197 (21)	186 (20)	195 (21)
MUAC (cm)	10.9 ± 1.1	11.0 ± 1.1	10.9 ± 1.1
WHZ	−3.42 ± 0.55	−3.49 ± 0.58	−3.44 ± 0.59
HAZ	−3.13 ± 1.63	−3.23 ± 1.64	−3.21 ± 1.47
HAZ ≤ −2	725/917 (79)	756/915 (83)	756/910 (83)
HAZ ≤ −3	490/917 (53)	509/915 (56)	504/910 (55)
Axillary temperature (°C)	36.4 ± 0.94	36.4 ± 0.86	36.4 ± 0.88
Medical History			
Ever been hospitalized for any reason	102/923 (11)	116/922 (13)	107/919 (12)
Ever been hospitalized for malnutrition	28/922 (3)	36/918 (4)	30 (3)
On TB treatment	2 (0.2)	2 (0.2)	5 (0.5)
Child has had HIV test done	299/923 (32)	277/922 (30)	298 (32)
Tested HIV-positive	61/298 (20)	60/277 (22)	67/296 (23)
HIV-positive on ART	20/60 (33)	16/59 (27)	20/64 (31)
HIV-positive on pneumocystis pneumonia (PCP) prophylaxis	30/60 (50)	32/60 (53)	39/65 (60)
Mother has had HIV test done	691/922 (75)	687/921 (75)	689/917 (75)
Tested HIV-positive	121/688 (18)	131/684 (19)	136/688 (20)
HIV-positive on ART	49/117 (42)	59/128 (46)	64/129 (50)
Known HIV-reactive or -exposed	132 (14)	140 (15)	148 (16)
Kwashiorkor	82/132 (62)	88/140 (63)	79/148 (63)
Marasmic kwashiorkor	17/132 (13)	21/140 (15)	30/148 (20)
Marasmus	33/132 (25)	31/140 (22)	39/148 (27)
Recent Symptoms			
At least one infectious symptom in prior 2 weeks	897 (97)	894 (97)	887 (96)
Fever in prior 2 weeks	580/908 (64)	561/915 (61)	569/906 (63)
Cough in prior 2 weeks	503/917 (55)	470/921 (51)	472/915 (52)
Diarrhea in prior 2 weeks	427/918 (47)	445/923 (48)	436/914 (48)
Vomiting in prior 2 weeks	239/919 (26)	250/922 (27)	243/917 (26)
Rash in prior 2 weeks	64/901 (7)	76/904 (8)	74/899 (8)
Reported to have a good appetite	791/913 (87)	775/916 (85)	780/912 (86)

* Values are presented as number (%), number/total number (%), or mean ± SD.
All pairwise comparisons with $p > 0.05$ except for the following:
[A] $p = 0.02$ for age at enrollment for amoxicillin vs. cefdinir
[B] $p = 0.04$ for WHZ for amoxicillin vs. cefdinir

Table 3. Tolerance of Study Intervention Administered as Assessed at First Follow-Up Visit

Variable	Amoxicillin* (n = 924)	Cefdinir* (n = 923)	Placebo* (n = 920)
Number of children that took all 7 days of intervention	865/879 (98)	887/897 (99)	865/872 (99)
Fever since enrollment	309/876 (35)	339/889 (38)	337/870 (39)
Cough since enrollment	239/874 (27)[A,B]	280/889 (31)[A]	301/871 (35)[B]
Diarrhea since enrollment	322/878 (37)[C]	282/889 (32)[C,D]	352/871 (40)[D]
Vomiting since enrollment	114/877 (13)	124/890 (14)	137/872 (16)
Rash since enrollment	43/865 (5)	31/872 (4)	37/857 (4)
Reported to have a good appetite since enrollment	865/879 (98)	883/893 (99)	855/871 (98)

* Values are presented as number/total number (%).
All pairwise comparisons with $p > 0.10$ except for the following:
[A] $p = 0.06$ for cough since enrollment for amoxicillin vs. cefdinir
[B] $p = 0.001$ for cough since enrollment for amoxicillin vs. placebo
[C] $p = 0.03$ for diarrhea since enrollment for amoxicillin vs. cefdinir
[D] $p = 0.0002$ for diarrhea since enrollment for cefdinir vs. placebo

Table 4. Primary Study Outcomes by Intervention Group and Type of SAM

Type of SAM *Outcome* Detailed Outcome	**Amoxicillin***	**Cefdinir***	**Placebo***	**Total***
Overall	**n = 924**	**n = 923**	**n = 920**	**N = 2,767**
Recovered	*820 (88.7)[A]*	*839 (90.9)[B]*	*783 (85.1)[A,B]*	*2,442 (88.3)*
Failed	*104 (11.3)*	*84 (9.1)*	*137 (14.9)*	*325 (11.7)*
Died	44 (4.8)[C]	38 (4.1)[D]	68 (7.4)[C,D]	150 (5.4)
Early Death**	24/35 (68.6)[E,F]	13/33 (39.4)[E]	29/60 (48.3)[F]	66/128 (51.6)
Dropout	20 (2.2)	15 (1.6)	25 (2.7)	60 (2.2)
Hospitalized	26 (2.8)	15 (1.6)	22 (2.4)	63 (2.3)
Remained with SAM	14 (1.5)	16 (1.7)	22 (2.4)	52 (1.9)
Kwashiorkor	**n = 649**	**n = 664**	**n = 632**	**N = 1,945**
Recovered	*610 (94.0)*	*632 (95.2)[G]*	*583 (92.2) [G]*	*1,825 (93.8)*
Failed	*39 (6.0)*	*32 (4.8)*	*49 (7.8)*	*120 (6.2)*
Died	15 (2.3)[H]	18 (2.7)[I]	32 (5.1)[H,I]	65 (3.3)
Early Death**	8/14 (57.1)	7/15 (46.7)	13/28 (46.4)	28/57 (49.1)
Dropout	9 (1.4)	5 (0.8)	7 (1.1)	21 (1.1)
Hospitalized	12 (1.8)[J]	5 (0.8)[J]	8 (1.3)	25 (1.3)
Remained with SAM	3 (0.5)	4 (0.6)	2 (0.3)	9 (0.5)
Marasmic Kwashiorkor	**n = 78**	**n = 73**	**n = 93**	**N = 244**
Recovered	*54 (69.2)*	*51 (69.9)*	*55 (59.1)*	*160 (65.6)*
Failed	*24 (30.8)*	*22 (30.1)*	*38 (40.9)*	*84 (34.4)*
Died	12 (15.4)	9 (12.3)	21 (22.6)	42 (17.2)
Early Death**	5/8 (62.5)	4/9 (44.4)	11/18 (61.1)	20/35 (57.1)
Dropout	6 (7.7)	5 (6.8)	6 (6.5)	17 (7.0)
Hospitalized	4 (5.1)	4 (5.5)	7 (7.5)	15 (6.1)
Remained with SAM	2 (2.6)	4 (5.5)	4 (4.3)	10 (4.1)
Marasmus	**n = 197**	**n = 186**	**n = 195**	**N = 578**
Recovered	*156 (79.2)*	*156 (83.9)[K]*	*145 (74.4)[K]*	*457 (79.1)*
Failed	*41 (20.8)*	*30 (16.1)*	*50 (25.6)*	*121 (20.9)*
Died	17 (8.6)	11 (5.9)	15 (7.7)	43 (7.4)
Early Death**	11/13 (84.6)	2/9 (22.2)	5/14 (35.7)	18/36 (50.0)
Dropout	5 (2.5)[L]	5 (2.7)	12 (6.2)[L]	22 (3.8)
Hospitalized	10 (5.1)	6 (3.2)	7 (3.6)	23 (4.0)
Remained with SAM	9 (4.6)	8 (4.3)	16 (8.2)	33 (5.7)

* Values are presented as number (%).
** "Early Death" is defined as less than 21 days from time of enrollment. (Information on date of death is available for 128 of 150 deaths.)
All pairwise comparisons with p > 0.10 except for the following:
[A] p = 0.02 for amoxicillin vs. placebo recovery overall
[B] p = 0.0001 for cefdinir vs. placebo recovery overall
[C] p = 0.02 for amoxicillin vs. placebo death overall
[D] p = 0.003 for cefdinir vs. placebo death overall
[E] p = 0.03 for amoxicillin vs. cefdinir early death overall
[F] p = 0.09 for amoxicillin vs. placebo early death overall
[G] p = 0.04 for cefdinir vs. placebo recovery in kwashiorkor
[H] p = 0.01 for amoxicillin vs. placebo death in kwashiorkor
[I] p = 0.03 for cefdinir vs. placebo death in kwashiorkor
[J] p = 0.09 for amoxicillin vs. cefdinir hospitalization in kwashiorkor
[K] p = 0.02 for cefdinir vs. placebo recovery in marasmus
[L] p = 0.09 for amoxicillin vs. placebo dropout in marasmus

Table 5. Secondary Study Outcomes by Intervention Group and Type of SAM

Outcome by Type of SAM	Amoxicillin*	Cefdinir*	Placebo*	Total*
Overall				
Time to recovery (days)	29.6 ± 18.7 (820)	29.1 ± 18.7 (839)	29.6 ± 18.9 (783)	29.4 ± 18.8
Weight gain** (g/kg/day)	3.4 ± 4.0 (883)[A,B]	3.9 ± 6.3 (897)[A,C]	3.1 ± 4.1 (873)[B,C]	3.5 ± 4.9
Length gain*** (mm/day)	0.20 ± 0.45 (883)	0.22 ± 0.44 (897)[D]	0.18 ± 0.44 (873)[D]	0.20 ± 0.44
MUAC gain*** (mm/day)	0.27 ± 0.42 (878)[E]	0.28 ± 0.42 (888)[F]	0.22 ± 0.41 (866)[E,F]	0.26 ± 0.42
Kwashiorkor				
Time to recovery (days)	26.4 ± 16.0 (610)	26.8 ± 17.6 (632)	26.6 ± 16.9 (583)	26.6 ± 16.9
Weight gain** (g/kg/day)	2.7 ± 3.4 (636)	3.2 ± 6.7 (649)[G]	2.5 ± 3.4 (614)[G]	2.8 ± 4.8
Length gain*** (mm/day)	0.21 ± 0.48 (636)	0.24 ± 0.47 (649)	0.20 ± 0.48 (614)	0.22 ± 0.48
MUAC gain*** (mm/day)	0.26 ± 0.45 (633)[H]	0.26 ± 0.42 (642)[I]	0.21 ± 0.42 (609)[H,I]	0.25 ± 0.43
Marasmic Kwashiorkor				
Time to recovery (days)	43.8 ± 20.8 (54)	38.7 ± 17.1 (51)	40.5 ± 18.1 (55)	41.0 ± 18.9
Weight gain** (g/kg/day)	4.1 ± 3.4 (65)	4.9 ± 4.3 (67)[J]	3.6 ± 5.1 (76)[J]	4.2 ± 4.4
Length gain*** (mm/day)	0.17 ± 0.38 (65)	0.15 ± 0.26 (67)	0.13 ± 0.30 (76)	0.15 ± 0.32
MUAC gain*** (mm/day)	0.22 ± 0.33 (63)[K]	0.34 ± 0.42 (66)[K,L]	0.19 ± 0.37 (75)[L]	0.25 ± 0.38
Marasmus				
Time to recovery (days)	37.3 ± 22.8 (156)	35.2 ± 20.9 (156)	37.7 ± 22.6 (145)	36.7 ± 22.2
Weight gain** (g/kg/day)	5.6 ± 5.3 (182)	6.0 ± 4.7 (181)[M]	4.9 ± 5.0 (183)[M]	5.5 ± 5.1
Length gain*** (mm/day)	0.15 ± 0.33 (182)[N]	0.21 ± 0.35 (181)[N]	0.16 ± 0.32 (183)	0.17 ± 0.34
MUAC gain*** (mm/day)	0.32 ± 0.37 (182)	0.34 ± 0.41 (180)	0.28 ± 0.38 (182)	0.31 ± 0.39

* Values reported as mean ± SD (number of subjects).
** Weight gain calculated from enrollment until second follow-up visit (or first follow-up visit for children that graduated at first follow-up or did not return for second follow-up).
*** Length and MUAC gains calculated from enrollment until final study visit.
All pairwise comparisons with $p > 0.10$ except for the following:

[A] $p = 0.09$ for amoxicillin vs. cefdinir weight gain overall
[B] $p = 0.07$ for amoxicillin vs. placebo weight gain overall
[C] $p = 0.002$ for cefdinir vs. placebo weight gain overall
[D] $p = 0.06$ for cefdinir vs. placebo length gain overall
[E] $p = 0.01$ for amoxicillin vs. placebo MUAC gain overall
[F] $p = 0.002$ for cefdinir vs. placebo MUAC gain overall
[G] $p = 0.02$ for cefdinir vs. placebo weight gain in kwashiorkor
[H] $p = 0.04$ for amoxicillin vs. placebo MUAC gain in kwashiorkor
[I] $p = 0.03$ for cefdinir vs. placebo MUAC gain in kwashiorkor
[J] $p = 0.09$ for cefdinir vs. placebo weight gain in marasmic kwashiorkor
[K] $p = 0.07$ for amoxicillin vs. cefdinir MUAC gain in marasmic kwashiorkor
[L] $p = 0.03$ for cefdinir vs. placebo MUAC gain in marasmic kwashiorkor
[M] $p = 0.03$ for cefdinir vs. placebo weight gain in marasmus
[N] $p = 0.09$ for amoxicillin vs. cefdinir length gain in marasmus

Table 6. Enrollment Demographic Characteristics of Children That Recovered from SAM, Failed Treatment, and Died during Treatment for SAM

Demographic Characteristic	Recovered* (N = 2,442)	Failed* (N = 325)	Died* (N = 150)
Male	1,167 (48)	150 (46)	68 (45)
Age (months)	21.4 ± 10.0[A,B] (n = 2,427)	18.6 ± 9.6[A] (n = 315)	18.4 ± 10.2[B] (n = 147)
Twin	128 (5)	16/324 (5)	6 (4)
Mother as primary caregiver	2,248/2,441 (92)	293 (90)	135 (90)
Mother alive	2,367 (97)	312 (96)	144 (96)
Father alive	2,322 (95)[C,D]	296 (91)[C]	134 (89)[D]
Father in home	1,754 (72)[E,F]	214 (66)[E]	96 (64)[F]
Number of children under 5 in home	1.6 ± 0.7	1.5 ± 0.6	1.5 ± 0.7
Distance to nearest health center (minutes)	84 ± 53[G] (n = 2,441)	83 ± 56 (n = 323)	75 ± 49[G] (n = 148)
Distance to nearest shop that sells medicines (minutes)	24 ± 28 (n = 2,440)	23 ± 24 (n = 319)	21 ± 23 (n = 146)
Currently breastfeeding	1,091 (45)[H,I]	183 (56)[H]	79 (53)[I]
Age stopped breastfeeding (months)	19.7 ± 8.0[J,K] (n = 13,30)	17.4 ± 8.5[J] (n = 136)	17.6 ± 8.9[K] (n = 69)

* Values are presented as number (%), number/total number (%), or mean ± SD.
All pairwise comparisons of recovered vs. failed and recovered vs. died with $p > 0.10$ except for the following:

[A] $p < 0.0001$ for age at enrollment in recovered vs. failed
[B] $p = 0.0003$ for age at enrollment in recovered vs. died
[C] $p = 0.004$ for father alive in recovered vs. failed
[D] $p = 0.004$ for father alive in recovered vs. died
[E] $p = 0.03$ for father in home in recovered vs. failed
[F] $p = 0.49$ for father in home in recovered vs. died
[G] $p = 0.04$ for distance to nearest health center in recovered vs. died
[H] $p < 0.0001$ for still breastfeeding in recovered vs. failed
[I] $p = 0.07$ for still breastfeeding in recovered vs. died
[J] $p = 0.002$ for breastfeeding stop age in recovered vs. failed
[K] $p = 0.04$ for breastfeeding stop age in recovered vs. died

Table 7. Enrollment Clinical Characteristics of Children That Recovered from SAM, Failed Treatment, and Died during Treatment for SAM

Clinical Characteristic	Recovered* (N = 2,442)	Failed* (N = 325)	Died* (N = 150)
Kwashiorkor	1,825 (74.7)[A,B]	120 (36.9)[A]	65 (43.3)[B]
MUAC (cm)	12.9 ± 1.3[C,D] (n = 1,823)	12.4 ± 1.5[C] (n = 118)	12.2 ± 1.4[D] (n = 64)
WHZ	−1.22 ± 1.00[E,F]	−1.56 ± 1.19[E]	−1.69 ± 0.99[F]
Marasmic kwashiorkor	160 (6.6)[G,H]	84 (25.8)[G]	42 (28.0)[H]
MUAC (cm)	11.0 ± 0.9[I,J] (n = 157)	10.2 ± 1.1[I]	10.3 ± 1.2[J]
WHZ	−3.53 ± 0.52[K,L]	−3.95 ± 0.70[K]	−3.97 ± 0.74[L]
Marasmus	457 (18.7)[M,N]	121 (37.2)[M,O]	43 (28.7)[N,O]
MUAC (cm)	11.1 ± 1.0[P,Q]	10.4 ± 1.1[P,R]	10.0 ± 1.0[Q,R]
WHZ	−3.38 ± 0.53[S,T]	−3.72 ± 0.63[S]	−3.84 ± 0.73[T]
HAZ	−3.13 ± 1.59[U,V] (n = 2,427)	−3.68 ± 1.47[U] (n = 315)	−3.78 ± 1.38[V] (n = 147)
HAZ ≤ −2	1,957/2,427 (81)[W,X]	280/315 (89)[W]	136/147 (93)[X]
HAZ ≤ −3	1,280/2,427 (53)[Y,Z]	223/315 (71)[Y]	110/147 (75)[Z]
Axillary temperature (°C)	36.4 ± 0.88[AA] (n = 2,413)	36.5 ± 0.96[AA] (n = 315)	36.5 ± 0.93 (n = 146)

* Values are presented as number (%), number/total number (%), or mean ± SD.
All pairwise comparisons of recovered vs. failed and recovered vs. died with $p > 0.10$ except for the following:

[A] $p < 0.0001$ for kwashiorkor in recovered vs. failed
[B] $p < 0.0001$ for kwashiorkor in recovered vs. died
[C] $p = 0.0002$ for kwashiorkor MUAC in recovered vs. failed
[D] $p < 0.0001$ for kwashiorkor MUAC in recovered vs. died
[E] $p = 0.0004$ for kwashiorkor WHZ in recovered vs. failed
[F] $p = 0.0002$ for kwashiorkor WHZ in recovered vs. died
[G] $p < 0.0001$ for marasmic kwashiorkor in recovered vs. failed
[H] $p < 0.0001$ for marasmic kwashiorkor in recovered vs. died
[I] $p < 0.0001$ for marasmic kwashiorkor MUAC in recovered vs. failed
[J] $p < 0.0001$ for marasmic kwashiorkor MUAC in recovered vs. died
[K] $p < 0.0001$ for marasmic kwashiorkor WHZ in recovered vs. failed
[L] $p < 0.0001$ for marasmic kwashiorkor WHZ in recovered vs. died
[M] $p < 0.0001$ for marasmus in recovered vs. failed
[N] $p = 0.004$ for marasmus in recovered vs. died
[O] $p = 0.08$ for marasmus in failed vs. died
[P] $p < 0.0001$ for marasmus MUAC in recovered vs. failed
[Q] $p < 0.0001$ for marasmus MUAC in recovered vs. died
[R] $p = 0.02$ for marasmus MUAC in failed vs. died
[S] $p < 0.0001$ for marasmus WHZ in recovered vs. failed
[T] $p < 0.0001$ for marasmus WHZ in recovered vs. died
[U] $p < 0.0001$ for HAZ in recovered vs. failed
[V] $p < 0.0001$ for HAZ in recovered vs. died
[W] $p = 0.0005$ for HAZ < −2 in recovered vs. failed
[X] $p = 0.0005$ for HAZ < −2 in recovered vs. died
[Y] $p < 0.0001$ for HAZ < −3 in recovered vs. failed
[Z] $p < 0.0001$ for HAZ < −3 in recovered vs. died
[AA] $p = 0.03$ for axillary temperature in recovered vs. failed

Table 8. Recent Medical History at Time of Enrollment of Children That Recovered from SAM, Failed Treatment, and Died during Treatment for SAM

Medical History	Recovered* (N = 2,442)	Failed* (N = 325)	Died* (N = 150)
Ever been hospitalized for any reason	280/2,440 (11)	45/323 (14)	21/149 (14)
Ever been hospitalized for malnutrition	79/2435 (3)	15 (5)	5 (3)
On TB treatment	5 (0.2)[A]	4 (1.2)[A]	1 (0.7)
Child has had HIV test done	702/2,441 (29)[B,C]	172/324 (53)[C,D]	57/149 (38)[B,D]
Tested HIV-positive	107/700 (15)[E,F]	81/171 (47)[E]	31/57 (54)[F]
HIV-positive on ART	41/107 (38)[G]	15/76 (20)[G]	7/31 (23)
HIV-positive or -exposed on PCP prophylaxis	85/126 (67)[H]	38/81 (47)[H]	20/33 (61)
Mother has had HIV test done	1830/2,438 (75)	237/322 (74)	109/148 (74)
Tested HIV positive	298/1,824 (16)[I,J]	90/236 (38)[I]	46/109 (42)[J]
HIV-positive on ART	141/287 (49)[K]	31/87 (36)[K]	19/44 (43)
Child and/or mother known HIV-positive	310 (13)[L,M]	110 (34)[L]	49 (33)[M]
Kwashiorkor	218/1,825 (12)[N,O]	31/120 (26)[N]	14/65 (22)[O]
Marasmic kwashiorkor	35/160 (22)[P,Q]	33/84 (39)[P]	17/42 (40)[Q]
Marasmus	57/457 (12)[R,S]	46/121 (38)[R]	18/43 (42)[S]

* Values are presented as number (%), number/total number (%), or mean ± SD.
All pairwise comparisons of recovered vs. failed and recovered vs. died with $p > 0.10$ except for the following:

[A] $p = 0.01$ for being on TB treatment in recovered vs. failed
[B] $p < 0.0001$ for having had HIV test done in recovered vs. failed
[C] $p = 0.02$ for having had HIV test done in recovered vs. died
[D] $p = 0.003$ for having had HIV test done in failed vs. died
[E] $p < 0.0001$ for having a positive HIV test in recovered vs. failed
[F] $p < 0.0001$ for having a positive HIV test in recovered vs. died
[G] $p < 0.009$ for being on ART in recovered vs. failed
[H] $p = 0.004$ for being on PCP prophylaxis in recovered vs. failed
[I] $p < 0.0001$ for mother having had a positive HIV test in recovered vs. failed
[J] $p < 0.0001$ for mother having had a positive HIV test in recovered vs. died
[K] $p = 0.03$ for mother being on ART in recovered vs. failed
[L] $p < 0.0001$ for known HIV-reactive or -exposed recovered vs. failed
[M] $p < 0.0001$ for known HIV-reactive or -exposed recovered vs. died
[N] $p < 0.0001$ for known HIV-reactive or -exposed kwashiorkor recovered vs. failed
[O] $p = 0.03$ for known HIV-reactive or -exposed kwashiorkor recovered vs. died
[P] $p < 0.007$ for known HIV-reactive or -exposed marasmic kwashiorkor recovered vs. failed
[Q] $p = 0.02$ for known HIV-reactive or -exposed marasmic kwashiorkor recovered vs. died
[R] $p < 0.0001$ for known HIV-reactive or -exposed marasmus recovered vs. failed
[S] $p < 0.0001$ for known HIV-reactive or -exposed marasmus recovered vs. died

Table 9. Recent Symptoms at Time of Enrollment of Children That Recovered from SAM, Failed Treatment, and Died during Treatment for SAM

Recent Symptom	Recovered* (N = 2,442)	Failed* (N = 325)	Died* (N = 150)
At least one infectious symptom in prior 2 weeks	2,361 (97)	317 (98)	146 (97)
Fever in prior 2 weeks	1,507/2,409 (63)	203/320 (63)	93/148 (63)
Cough in prior 2 weeks	1,250/2,432 (51)[A,B]	195/321 (61)[A]	96/147 (65)[B]
Diarrhea in prior 2 weeks	1,135/2,432 (47)[C,D]	173/323 (54)[C]	84/149 (56)[D]
Vomiting in prior 2 weeks	630/2,434 (26)[E,F]	102/324 (31)[F,G]	61/149 (41)[E,G]
Rash in prior 2 weeks	178/2,390 (7)[H]	36/314 (11)[H]	16/143 (11)
Reported to have a good appetite	2,086/2,419 (86)[I,J]	260/322 (81)[I,K]	110/149 (74)[J,K]

* Values are presented as number (%), number/total number (%), or mean ± SD.
All pairwise comparisons of recovered vs. failed and recovered vs. died with $p > 0.10$ except for the following:
[A] $p < 0.002$ for cough in prior 2 weeks recovered vs. failed
[B] $p = 0.001$ for cough in prior 2 weeks recovered vs. died
[C] $p = 0.02$ for diarrhea in prior 2 weeks recovered vs. failed
[D] $p = 0.03$ for diarrhea in prior 2 weeks recovered vs. died
[E] $p = 0.04$ for vomiting in prior 2 weeks recovered vs. failed
[F] $p < 0.0001$ for vomiting in prior 2 weeks recovered vs. died
[G] $p < 0.05$ for vomiting in prior 2 weeks failed vs. died
[H] $p = 0.02$ for rash in prior 2 weeks recovered vs. failed
[I] $p = 0.01$ for good appetite recovered vs. failed
[J] $p < 0.0001$ for good appetite recovered vs. died
[K] $p = 0.09$ for good appetite failed vs. died

Table 10. Symptoms and Temperature at First Follow-Up Visit of Children That Recovered from SAM, Failed Treatment, and Died during Treatment for SAM

Recent Symptom	Recovered* (N = 2,442)	Failed* (N = 325)	Died* (N = 150)
At least one infectious symptom since enrollment	1,581/2,429 (65)[A,B]	165/211 (78)[A]	59/72 (82)[B]
Fever since enrollment	884/2,424 (36)[C,D]	101/211 (48)[C]	36/72 (50)[D]
Cough since enrollment	735/2,425 (30)[E,F]	85/209 (41)[E]	35/72 (49)[F]
Diarrhea since enrollment	848/2,428 (35)[G,H]	108/210 (51)[G]	41/72 (57)[H]
Vomiting since enrollment	329/2,428 (14)[I]	46/211 (22)[I]	15/72 (21)
Rash since enrollment	96/2,388 (4)[J]	15/206 (7)[J]	5/69 (7)
Reported to have a good appetite	2,398/2,433 (99)[K]	203/210 (97)[K]	70/72 (97)
Axillary temperature (°C)	36.2 ± 0.79 (n = 2,408)	36.2 ± 0.92 (n = 206)	36.2 ± 0.88 (n = 71)

* Values are presented as number (%), number/total number (%), or mean ± SD.
All pairwise comparisons of recovered vs. failed and recovered vs. died with $p > 0.10$ except for the following:
[A] $p = 0.002$ for at least one infectious symptom since enrollment recovered vs. failed
[B] $p = 0.005$ for at least one infectious symptom since enrollment recovered vs. died
[c] $p = 0.001$ for fever since enrollment recovered vs. failed
[D] $p = 0.03$ for fever since enrollment recovered vs. died
[E] $p = 0.003$ for cough since enrollment recovered vs. failed
[F] $p = 0.002$ for cough since enrollment recovered vs. died
[G] $p < 0.0001$ for diarrhea since enrollment recovered vs. failed
[H] $p = 0.0002$ for diarrhea since enrollment recovered vs. died
[I] $p = 0.001$ for vomiting since enrollment recovered vs. failed
[J] $p = 0.04$ for rash since enrollment recovered vs. failed
[K] $p = 0.07$ for good appetite since enrollment recovered vs. failed

Table 11. Enrollment Demographic and Clinical Characteristics of Children That Died Early (< 21 Days after Enrollment) vs. Died Late (> 21 Days after Enrollment) during Treatment for SAM

Demographic and Clinical Characteristics	Early Death* (N = 66)	Late Death* (N = 62)	p value (if p ≤ 0.10)
Male	34/66 (52)	22/62 (35)	0.077
Age (months)	18.0 ± 9.3 (n = 64)	18.2 ± 10.7 (n = 61)	–
Twin	2 (3)	3 (5)	–
Mother as primary caregiver	57 (86)	58 (94)	–
Mother alive	64 (97)	60 (97)	–
Father alive	58 (88)	56 (90)	–
Father in home	44 (67)	41 (66)	–
Number of children under 5 in home	1.6 ± 0.8	1.5 ± 0.6	–
Distance to nearest health center (minutes)	75 ± 51 (n = 65)	76 ± 49 (n = 61)	–
Distance to nearest shop that sells medicines (minutes)	19 ± 25 (n = 64)	22 ± 19 (n = 61)	–
Currently breastfeeding	31 (47)	38 (61)	–
Age stopped breastfeeding (months)	14.9 ± 7.6 (n = 35)	20.0 ± 9.6 (n = 24)	0.029
Kwashiorkor	28/57 (49.1)	29/57 (50.9)	–
MUAC (cm)	12.0 ± 1.1	12.4 ± 1.8 (n = 28)	–
WHZ	−1.88 ± 0.75	−1.49 ± 1.16	–
Marasmic kwashiorkor	20/35 (57.1)	15/35 (42.9)	–
MUAC (cm)	10.3 ± 1.3	10.3 ± 1.2	–
WHZ	−4.07 ± 0.89	−3.72 ± 0.36	–
Marasmus	18/36 (50.0)	18/36 (50.0)	–
MUAC (cm)	10.0 ± 0.9	10.0 ± 1.1	–
WHZ	−3.96 ± 0.84	−3.76 ± 0.63	–
HAZ	−3.73 ± 1.37 (n = 64)	−3.72 ± 1.32 (n = 61)	–
HAZ ≤ −2	61/64 (95)	55/61 (90)	–
HAZ ≤ −3	48/64 (75)	43/61 (70)	–
Axillary temperature (°C)	36.4 ± 1.1 (n = 64)	36.6 ± 0.8 (n = 60)	–

* Values are presented as number (%), number/total number (%), or mean ± SD.

Table 12. Recent Medical History and Symptoms of Children That Died Early (< 21 Days after Enrollment) vs. Died Late (> 21 Days after Enrollment) during Treatment for SAM

Medical History and Recent Symptoms	Early Death* (N = 66)	Late Death* (N = 62)	p value (if p ≤ 0.10)
Ever been hospitalized for any reason	10 (15)	7/61 (11)	–
Ever been hospitalized for malnutrition	2 (3)	3 (5)	–
On TB treatment	0 (0)	1 (2)	–
Child has had HIV test done	23 (35)	24 (39)	–
Tested HIV-positive	11/23 (48)	12/24 (50)	–
HIV-positive on ART	1/11 (9)	3/12 (25)	–
HIV-positive or -exposed on PCP prophylaxis	6/11 (55)	9/14 (64)	–
Mother has had HIV test done	49/65 (75)	42/61 (69)	–
Tested HIV-positive	16/49 (33)	20/42 (48)	–
HIV-positive on ART	9/15 (60)	6/19 (32)	–
Child and/or mother known HIV-positive	17 (26)	21 (32)	–
Kwashiorkor	4/28 (14)	7/29 (24)	–
Marasmic kwashiorkor	7/20 (35)	6/15 (40)	–
Marasmus	6/18 (33)	8/18 (44)	–
At least one infectious symptom in prior 2 weeks	64 (97)	62 (100)	–
Fever in prior 2 weeks	41/65 (63)	39/61 (64)	–
Cough in prior 2 weeks	41/65 (63)	41/60 (68)	–
Diarrhea in prior 2 weeks	39 (59)	34/61 (56)	–
Vomiting in prior 2 weeks	30 (45)	23/61 (38)	–
Rash in prior 2 weeks	5/65 (8)	8/58 (14)	–
Reported to have a good appetite	18 (74)	46 (75)	–

* Values are presented as number (%) or number/total number (%).

Table 13. Symptoms and Temperature at First Follow-Up Visit of Children That Died Early (< 21 Days after Enrollment) vs. Died Late (> 21 Days after Enrollment) during Treatment for SAM

Recent Symptom	Early Death* (N = 66)	Late Death* (N = 62)	p value (if p ≤ 0.10)
At least one infectious symptom since enrollment	8/9 (89)	42/53 (79)	–
Fever since enrollment	5/9 (56)	23/53 (43)	–
Cough since enrollment	4/9 (44)	25/53 (47)	–
Diarrhea since enrollment	4/9 (44)	29/53 (55)	–
Vomiting since enrollment	3/9 (33)	8/53 (15)	–
Rash since enrollment	0/9 (0)	4/50 (8)	–
Reported to have a good appetite	9/9 (100)	52/53 (98)	–
Axillary temperature (°C)	36.2 ± 0.4 (n = 9)	36.2 ± 0.8 (n = 53)	–

* Values are presented as number (%) or number/total number (%) or mean ± SD.

Annex 2. Figures

Figure 1. Enrollment, Randomization, and Outcomes of Study Patients

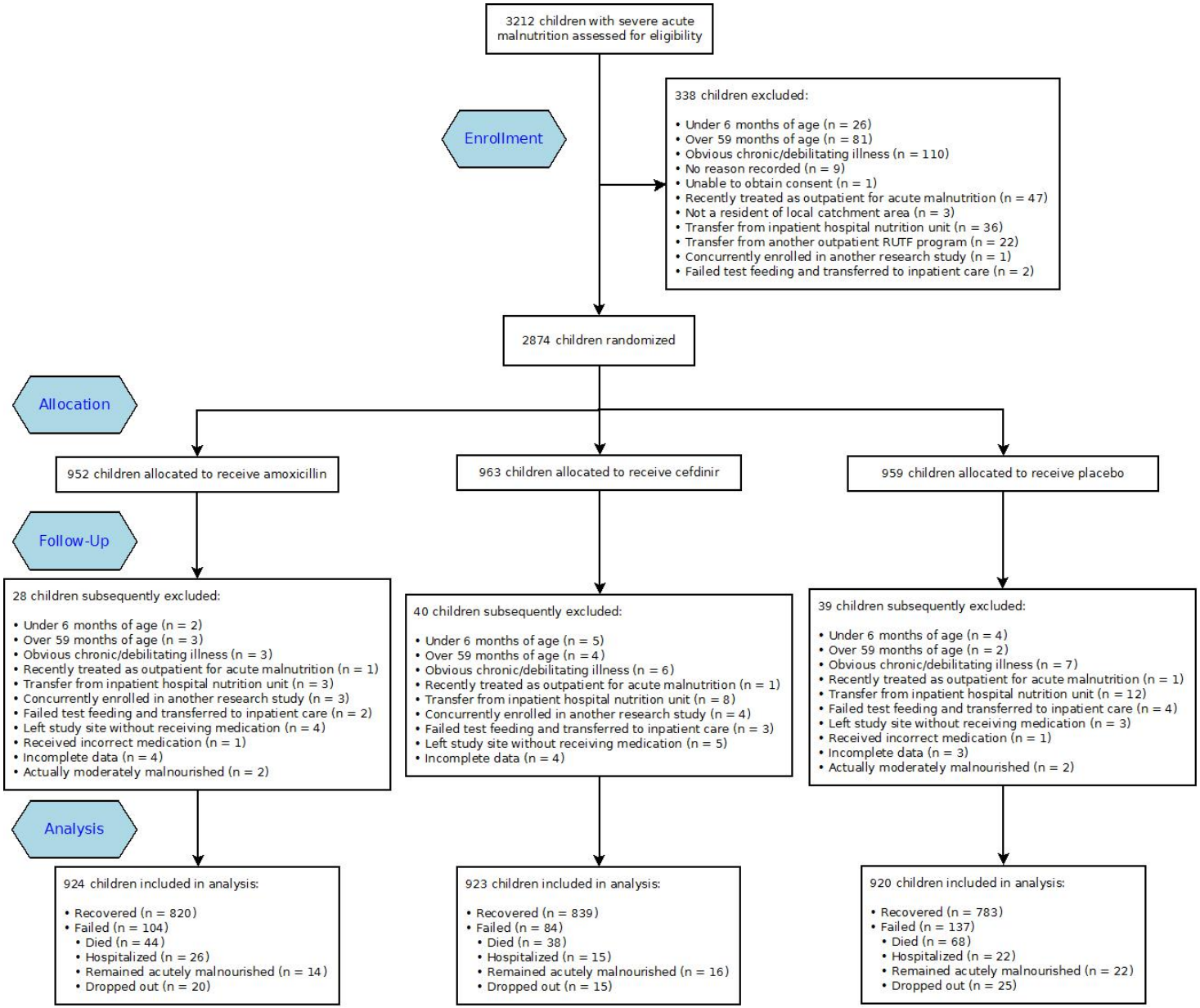
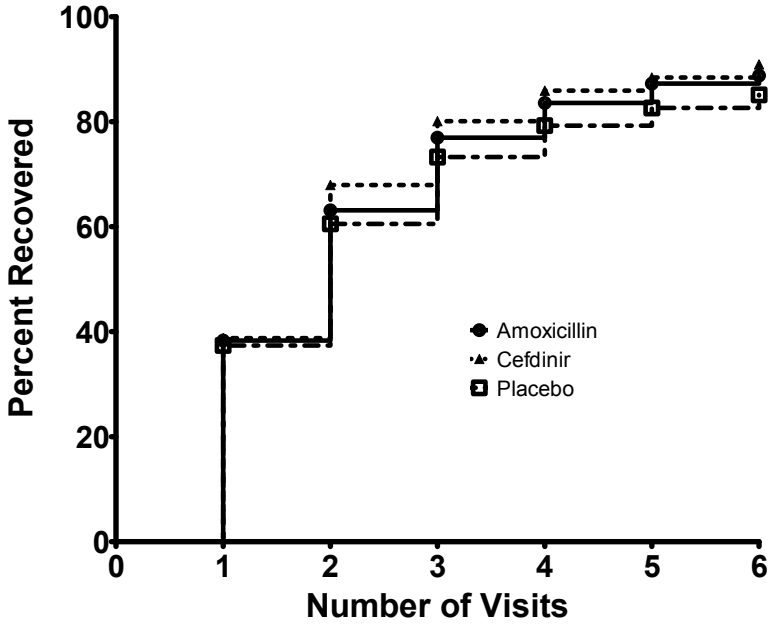
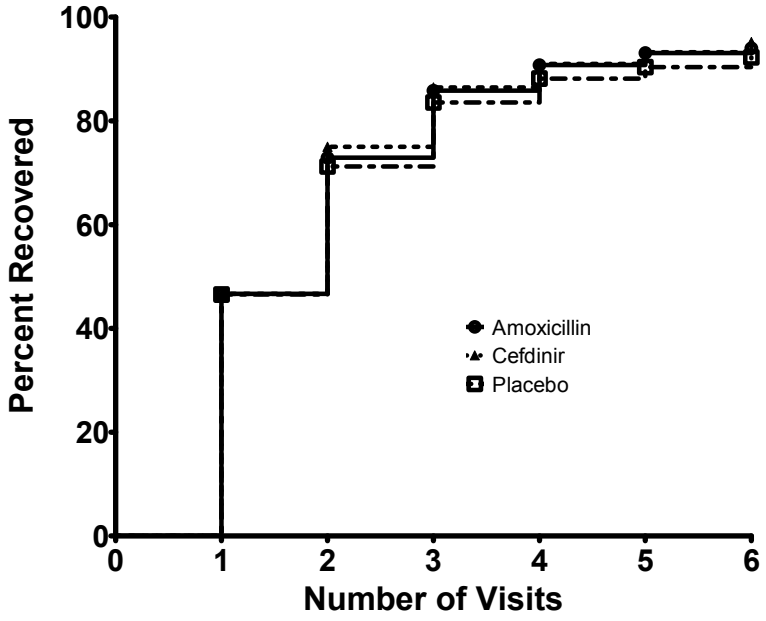


Figure 2. Survival Analysis for All Children in Study*



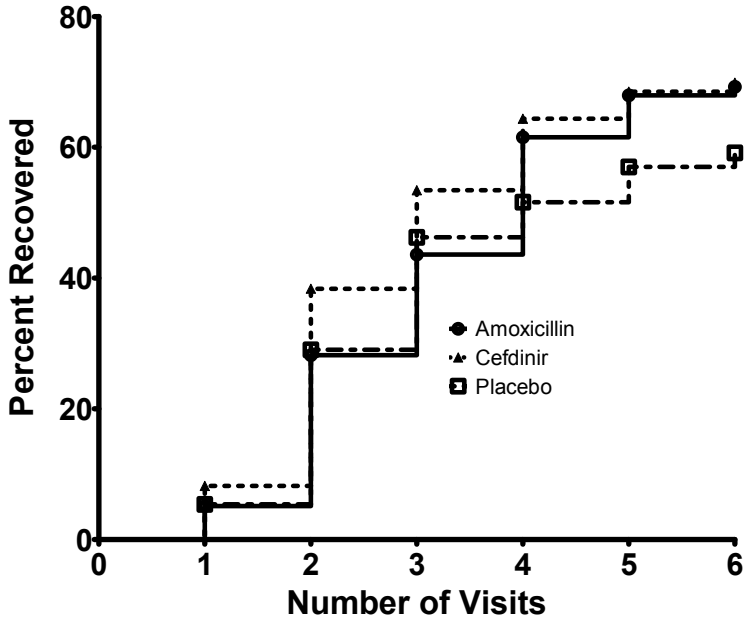
* Logrank p = 0.012

Figure 3. Survival Analysis for Children with Kwashiorkor*



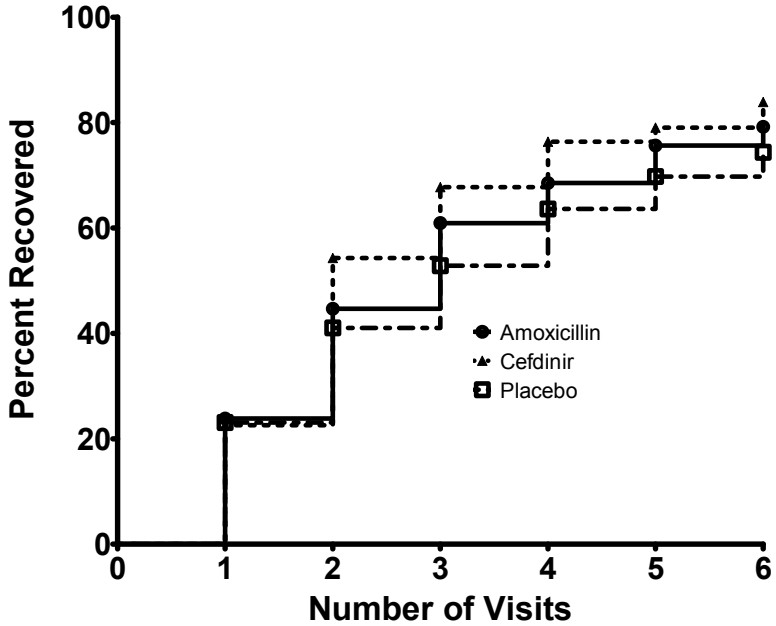
* Logrank p = 0.43

Figure 4. Survival Analysis for Children with Marasmic Kwashiorkor*



* Logrank p = 0.37

Figure 5. SurvivalAnalysis for Children with Marasmus*



* Logrank p = 0.088

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