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Antibiotics as part of the management of severe acute malnutrition

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Abstract

Background

Severe acute malnutrition contributes to 1 million deaths among children annually. Adding routine antibiotic agents to nutritional therapy may increase recovery rates and decrease mortality among children with severe acute malnutrition treated in the community.

Methods

In this randomized, double-blind, placebo-controlled trial, we randomly assigned Malawian children, 6 to 59 months of age, with severe acute malnutrition to receive amoxicillin, cefdinir, or placebo for 7 days in addition to ready-to-use therapeutic food for the outpatient treatment of uncomplicated severe acute malnutrition. The primary outcomes were the rate of nutritional recovery and the mortality rate.

Results

A total of 2767 children with severe acute malnutrition were enrolled. In the amoxicillin, cefdinir, and placebo groups, 88.7%, 90.9%, and 85.1% of the children recovered, respectively (relative risk of treatment failure with placebo vs. amoxicillin, 1.32; 95% confidence interval [CI], 1.04 to 1.68; relative risk with placebo vs. cefdinir, 1.64; 95% CI, 1.27 to 2.11). The mortality rates for the three groups were 4.8%, 4.1%, and 7.4%, respectively (relative risk of death with placebo vs. amoxicillin, 1.55; 95% CI, 1.07 to 2.24; relative risk with placebo vs. cefdinir, 1.80; 95% CI, 1.22 to 2.64). Among children who recovered, the rate of weight gain was increased among those who received antibiotics. No interaction between type of severe acute malnutrition and intervention group was observed for either the rate of nutritional recovery or the mortality rate.

Conclusions

The addition of antibiotics to therapeutic regimens for uncomplicated severe acute malnutrition was associated with a significant improvement in recovery and mortality rates. (Funded by the Hickey Family Foundation and others; ClinicalTrials.gov number, NCT01000298.)

Introduction

The contribution of severe acute malnutrition to the overall burden of childhood morbidity and mortality is enormous, with more than 20 million children with severe wasting worldwide,[1] an untold number with kwashiorkor, and case fatality rates among hospitalized children that are as high as 50%.[1,2] For decades, the primary management for severe acute malnutrition was based on inpatient rehabilitation with fortified milk formulas.[3] However, international consensus guidelines now recommend the use of ready-to-use therapeutic food (RUTF) — usually a fortified spread consisting of peanut paste, milk powder, oil, sugar, and a micronutrient supplement — in outpatient settings as the preferred management for uncomplicated cases of severe acute malnutrition.[4] Despite the markedly better outcomes observed with this revised outpatient regimen,[5] 10 to 15% of children still do not recover, even in the context of rigorously controlled clinical trials. Even modest improvements in recovery and mortality rates could mean thousands of lives saved annually.

Many studies,[6-15] but not all,[16,17] have shown a high prevalence of clinically significant infections among children hospitalized for severe malnutrition. This observation has led to treatment guidelines recommending the use of routine antibiotic agents even for children treated as outpatients,[4] although outpatients are presumably much less likely to have a systemic infection than are patients with complicated cases that require inpatient care. This recommendation for the use of routine antibiotics is based on expert opinion and has not been directly tested in a clinical trial[18]; and observational data suggest that antibiotics are unnecessary and perhaps even harmful in children with uncomplicated severe acute malnutrition (i.e., children with good appetite and noclinical signs of sepsis).[19]

Most children with severe acute malnutrition can now be treated in rural health posts throughout the developing world.[20,21] Providing antibiotic therapy in addition to RUTF for all malnourished children in this setting would not only be complex and costly but arguably unnecessary or even harmful.[19] We conducted a prospective clinical trial to determine whether the routine administration of oral antibiotics as part of the outpatient management of severe acute malnutrition in children in Malawi was associated with improved outcomes. Rural Malawi is representative of agrarian sub-Saharan Africa and populated primarily by subsistence

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farmers.[22] An estimated 11% of the adult population in Malawi is infected with the human immunodeficiency virus (HIV), and 53% of the children are stunted (height-for-age z score of less than –2).[23]

Methods

Study population and eligibility

We enrolled children from December 2009 through January 2011 at 18 feeding clinics in rural Malawi. Each child's weight, length, and mid-upper-arm circumference were measured. Children who were 6 to 59 months of age, with edema (indicative of kwashiorkor), a weight-for-height z score of less than −3 (indicative of marasmus),[24] or both (marasmic kwashiorkor), were eligible for enrollment. Each eligible child was given a 30-g test feeding of RUTF[25] under the supervision of a nurse to verify that the child was an appropriate candidate for outpatient therapy. Children who were too ill to consume the test dose in the clinic were hospitalized for inpatient management. Detailed descriptions of the study methods are provided in the Supplementary Appendix and the study protocol, both of which are available with the full text of this article at NEJM.org.

Study oversight

The study was approved by ethics boards of the University of Malawi, Washington University in St. Louis, and the Malawi government. A data and safety monitoring board monitored adverse events and interim study outcomes. Caretakers of eligible children provided informed oral and written consent before enrollment. Antibiotics were purchased at cost from the St. Louis Children's Hospital Pharmacy. RUTF was purchased at cost from Project Peanut Butter, which is based in Blantyre, Malawi. The first and last authors vouch for the accuracy and completeness of the data and analyses reported, as well as the fidelity of the report to the study protocol.

Study design and interventions

This randomized, double-blind, placebo-controlled clinical trial compared nutritional and mortality outcomes among children with uncomplicated severe acute malnutrition who received treatment as outpatients with or without antibiotics. All children received standardized counseling and RUTF that provided approximately 175 kcal per kilogram of body weight per day. One group received 80 to 90 mg of amoxicillin suspension per kilogram per day, divided into two daily doses; the second group received approximately 14 mg of cefdinir suspension per kilogram per day, divided into two daily doses. A suspension of 250 mg of amoxicillin per 5 ml was used, and the dose to be given to each child was based on a rounded amount that could be given by the field research pharmacist using the markings on a plastic syringe; a similar rounding of medication dose was used for cefdinir. The control group received placebo twice daily. Caretakers were instructed to administer the study drug in addition to RUTF during the initial 7 days of therapy.

Study procedures

Participants were assigned to their study group when caregivers drew an opaque envelope containing one of nine coded letters corresponding to one of the three intervention groups. Caregivers and study personnel involved in clinical assessments and data analysis were unaware of the intervention ssignments. Medications and placebo were distributed in opaque plastic bottles, with a plastic syringe marked with the appropriate dose for the child. After distribution of the study interventions, nurses instructed each caretaker in the use of the syringe to give the study medications and supervised the administration of the first dose in the clinic.

After enrollment and caretaker instruction, each child was discharged home with the assigned study medication and a 2-week supply of RUTF.[25] If the household included a healthy child who was close in age to the participant and with whom the food might be shared, an extra allotment of RUTF was provided. Children were scheduled for follow-up visits at 2-week intervals, at which time anthropometric measurements were repeated; caretakers were also asked about the child's interim history and adherence to the assigned intervention.

Children who continued to have bipedal pitting edema or a weight-for-height z score below −2 at follow-up visits[24] remained in the study and received nutritional counseling and another 2-week supply of RUTF. Any child whose condition substantially deteriorated during the study or who was still malnourished after six follow-up visits was referred for inpatient care. Children who did not return for follow-up visits were visited at home by community health workers and a member of the study team. Children were considered to have recovered when they were without edema and had a weight-for-height z score of −2 or higher. Children who withdrew from the study, were still malnourished after six follow-up visits, were hospitalized for any reason during the study, or died were considered to have had treatment failure.

Statistical analysis

The primary end points were the nutritional recovery and mortality rates in the three study groups. We calculated that a sample of 900 children in each group would provide the study with 80% power at an alpha level of 0.05 to detect a reduction of 4 percentage points in the rate of treatment failure from an estimated baseline of 11%[26] and a reduction of 3.5 percentage points in the mortality rate from an estimated baseline of 8%.

In addition, one prespecified subgroup analysis was conducted to evaluate the interaction between type of severe acute malnutrition and the intervention received, again with the use of recovery and mortality rates as the primary end points. This interaction was evaluated in a multiple logistic regression model that included baseline characteristics that were significantly correlated with the primary outcomes in a univariate analysis.

Secondary outcomes of interest included weight gain, length gain, whether the antibiotics were associated with increased rates of adverse events, and time to recovery. Intention-to-treat analyses were used, and all tests were two-sided. Dichotomous outcomes were compared with the use of the chi-square test and Fisher's exact test; continuous variables were compared by means of Student's t-test and analysis of variance. The relative-risk ratios for the outcomes in the three intervention groups were also computed, and Kaplan–Meier plots of time to recovery and time to death were prepared.

Results

Study population

A total of 3212 children with severe acute malnutrition were identified from December 2009 through January 2011; after the exclusion of ineligible children, the study included 2767 children (Fig. S1 in the Supplementary Appendix). Baseline characteristics of the enrolled children were similar among the three groups (Table 1, and Table S1 in the Supplementary Appendix).

Table 1. Selected Baseline Characteristics of Children Enrolled in the Study.*

Characteristic	Amoxicillin (N=924)	Cefdinir (N=923)	Placebo (N=920)
Age — mo	20.6±9.7†	21.7±10.3	20.9±9.8
Mother as primary caretaker — no./total no. (%)	855/923 (92.6)	843/923 (91.3)	843/920 (91.6)
Current breast-feeding — no. (%)	444 (48.1)	399 (43.2)	431 (46.8)
Kwashiorkor — no. (%)	649 (70.2)	664 (71.9)	632 (68.7)
Marasmic kwashiorkor			
No. of children (%)	78 (8.4)	73 (7.9)	93 (10.1)
Mid-upper-arm circumference — cm	10.7±1.1	10.7±0.9	10.7±1.1
Weight-for-height z score	−3.75±0.64†	−3.56±0.53	−3.71±0.66
Marasmus			
No. of children (%)	197 (21.3)	186 (20.2)	195 (21.2)
Mid-upper-arm circumference — cm	10.9±1.1	11.0±1.1	10.9±1.1
Weight-for-height z score	−3.42±0.55	−3.49±0.58	−3.44±0.59
Height-for-age z score			
Mean score	−3.13±1.63	−3.23±1.64	−3.21±1.47
−2 or lower — no./total no. (%)	725/917 (79.1)	756/915 (82.6)	756/910 (83.1)
−3 or lower — no./total no. (%)	490/917 (53.4)	509/915 (55.6)	504/910 (55.4)
HIV test performed — no./total no. (%)			
Children tested	299/923 (32.4)	277/922 (30.0)	298/920 (32.4)
HIV-seropositive	61/298 (20.5)	60/277 (21.7)	67/296 (22.6)
HIV-seropositive and receiving ART	20/60 (33.3)	16/59 (27.1)	20/64 (31.3)
HIV-seropositive or HIV-exposed and receiving PCP prophylaxis	30/60 (50.0)	32/60 (53.3)	39/65 (60.0)
Mothers tested	691/922 (74.9)	687/921 (74.6)	689/917 (75.1)
HIV-seropositive	121/688 (17.6)	131/684 (19.2)	136/688 (19.8)
HIV-seropositive and receiving ART	49/117 (41.9)	59/128 (46.1)	64/129 (49.6)
Known HIV infection or exposure — no. (%)	132 (14.3)	140 (15.2)	148 (16.1)
Children with kwashiorkor	82/132 (62.1)	88/140 (62.9)	79/148 (53.4)
Children with marasmic kwashiorkor	17/132 (12.9)	21/140 (15.0)	30/148 (20.3)
Children with marasmus	33/132 (25.0)	31/140 (22.1)	39/148 (26.4)
≥1 infectious symptom in previous 2 wk — no./total no. (%)	780/924 (84.4)	772/923 (83.6)	756/920 (82.2)
Fever	580/908 (63.9)	561/915 (61.3)	569/906 (62.8)
Cough	503/917 (54.9)	470/921 (51.0)	472/915 (51.6)
Diarrhea	427/918 (46.5)	445/923 (48.2)	436/914 (47.7)
Good appetite reported — no./total no. (%)	791/913 (86.6)	775/916 (84.6)	780/912 (85.5)

* Plus–minus values are means ±SD. Baseline characteristics were similar among the groups except as noted. ART denotes antiretroviral therapy, HIV human immunodeficiency virus, and PCP *Pneumocystis jiroveci* pneumonia.
† P<0.05 for the comparison with cefdinir.

Study interventions and adverse events

A total of 924 children were randomly assigned to the amoxicillin group, 923 to the cefdinir group, and 920 to the placebo group. Caregivers for more than 98% percent of the children reported that the child completed the entire 7-day course of the study regimen (Table S2 in the Supplementary Appendix).

No cases of severe allergy or anaphylaxis were identified. A total of three adverse events that were presumed to be drug reactions were reported: a generalized papular rash in a child who received amoxicillin, thrush in a child who received cefdinir, and bloody diarrhea that resolved spontaneously while treatment continued in a child who received cefdinir. Children who received placebo had higher rates of cough and diarrhea reported at the first follow-up visit than those who received an antibiotic agent; caretakers of children who received amoxicillin reported cough least frequently, whereas children who received cefdinir had the lowest rate of reported diarrhea (Table S2 in the Supplementary Appendix).

Nutritional recovery and mortality rates

Overall, 88.3% of the children enrolled in the study recovered from severe acute malnutrition (Table 2). Children with marasmic kwashiorkor recovered less frequently and had higher mortality rates than children with either kwashiorkor or marasmus. The proportion of children who recovered was significantly lower among those who received placebo than among those who received either amoxicillin (3.6 percentage points lower; 95% confidence interval [CI], 0.6 to 6.7) or cefdinir (5.8 percentage points lower; 95% CI, 2.8 to 8.7). Deaths accounted for the largest proportion of children who did not recover in each study group and for each type of severe acute malnutrition. The overall mortality rate was 5.4%, but the rate was significantly higher among children who received placebo than among those who received either amoxicillin (relative risk, 1.55; 95% CI, 1.07 to 2.24) or cefdinir (relative risk, 1.80; 95% CI, 1.22 to 2.64). No significant differences in the causes of death, as reported by verbal autopsy (i.e., a structured investigation of events leading to the death), were identified among the three study

Table 2. Recovery and Growth Outcomes, According to Intervention Group and Type of Severe Acute Malnutrition.*

Outcome	Amoxicillin	Cefdinir	Placebo	Placebo vs. Amoxicillin: Relative Risk (95% CI)	Placebo vs. Amoxicillin: P Value	Placebo vs. Cefdinir: Relative Risk (95% CI)	Placebo vs. Cefdinir: P Value	Amoxicillin vs. Cefdinir: Relative Risk (95% CI)	Amoxicillin vs. Cefdinir: P Value	Placebo vs. Amoxicillin and Cefdinir: Relative Risk (95% CI)	Placebo vs. Amoxicillin and Cefdinir: P Value
Overall											
No. of children	924	923	920								
Did not recover — no. (%)	104 (11.3)	84 (9.1)	137 (14.9)	1.32 (1.04–1.68)	0.02	1.64 (1.27–2.11)	<0.001	1.24 (0.94–1.62)	0.14	1.46 (1.19–1.80)	<0.001
Died	44 (4.8)	38 (4.1)	68 (7.4)	1.55 (1.07–2.24)	0.02	1.80 (1.22–2.64)	0.003	1.16 (0.76–1.77)	0.57	1.66 (1.22–2.27)	0.002
Withdrew from the study	20 (2.2)	15 (1.6)	25 (2.7)								
Were hospitalized	26 (2.8)	15 (1.6)	22 (2.4)								
Continued to have severe acute malnutrition	14 (1.5)	16 (1.7)	22 (2.4)								
Kwashiorkor											
No. of children	649	664	632								
Did not recover — no. (%)	39 (6.0)	32 (4.8)	49 (7.8)	1.29 (0.86–1.94)	0.23	1.61 (1.04–2.48)	0.04	1.25 (0.79–1.97)	0.39	1.43 (1.01–2.04)	0.06
Died	15 (2.3)	18 (2.7)	32 (5.1)	2.19 (1.20–4.01)	0.01	1.87 (1.06–3.29)	0.03	0.85 (0.43–1.68)	0.73	2.01 (1.25–3.25)	0.005
Withdrew from the study	9 (1.4)	5 (0.8)	7 (1.1)								
Were hospitalized	12 (1.8)	5 (0.8)	8 (1.3)								
Continued to have severe acute malnutrition	3 (0.5)	4 (0.6)	2 (0.3)								
Marasmic kwashiorkor											
No. of children	78	73	93								
Did not recover — no. (%)	24 (30.8)	22 (30.1)	38 (40.9)	1.33 (0.88–2.01)	0.20	1.36 (0.89–2.08)	0.19	1.02 (0.63–1.65)	1.00	1.34 (0.95–1.89)	0.13
Died	12 (15.4)	9 (12.3)	21 (22.6)	1.47 (0.77–2.79)	0.25	1.83 (0.89–3.76)	0.11	1.25 (0.56–2.79)	0.64	1.62 (0.94–2.81)	0.12
Withdrew from the study	6 (7.7)	5 (6.8)	6 (6.5)								
Were hospitalized	4 (5.1)	4 (5.5)	7 (7.5)								
Continued to have severe acute malnutrition	2 (2.6)	4 (5.5)	4 (4.3)								
Marasmus											
No. of children	197	186	195								
Did not recover — no. (%)	41 (20.8)	30 (16.1)	50 (25.6)	1.23 (0.86–1.77)	0.28	1.59 (1.06–2.39)	0.02	1.29 (0.84–1.98)	0.29	1.38 (1.01–1.90)	0.05
Died	17 (8.6)	11 (5.9)	15 (7.7)	0.89 (0.46–1.73)	0.85	1.30 (0.61–2.76)	0.55	1.46 (0.70–3.03)	0.33	1.05 (0.58–1.92)	0.87
Withdrew from the study	5 (2.5)	5 (2.7)	12 (6.2)								
Were hospitalized	10 (5.1)	6 (3.2)	7 (3.6)								
Continued to have severe acute malnutrition	9 (4.6)	8 (4.3)	16 (8.2)								

* CI denotes confidence interval.

groups (Table S3 in the Supplementary Appendix). Although the point estimates for nutritional recovery were higher and those for death were lower among children who received cefdinir than among those who received amoxicillin, these differences were not significant ($P = 0.22$ for recovery and $P = 0.53$ for death, for the comparison of amoxicillin and cefdinir by logistic regression). Recovery rates were higher and mortality rates were lower among children who received antibiotics than among those who received placebo, across a number of baseline characteristics (Fig. S2 in the Supplementary Appendix).

Secondary outcomes

Children with marasmic kwashiorkor recovered significantly more slowly than children with either kwashiorkor or marasmus (Table 3). Kaplan–Meier survival analysis for all children in the study showed that the time to recovery was shorter in the cefdinir group than in the amoxicillin group or the placebo group and was shorter in the amoxicillin group than in the placebo group (Fig. 1A). Similarly, children who received an antibiotic agent survived longer than those who received placebo (Fig. 1B).

Weight gain from enrollment until the second follow-up visit

Table 3. Secondary Outcomes, According to Intervention Group and Type of Severe Acute Malnutrition.*

Secondary Outcome	Amoxicillin	Cefdinir	Placebo	Total
Overall				
Time to recovery				
No. of children	820	839	783	
No. of days	30±19	29±19	30±19	29±19
Weight				
No. of children	883	897	873	
Gain (g/kg/day)†	3.4±4.0	3.9±6.3‡	3.1±4.1‡	3.5±4.9
Length				
No. of children	883	897	873	
Gain (mm/day)§	0.20±0.45	0.22±0.44	0.18±0.44	0.20±0.44
Mid-upper-arm circumference				
No. of children	878	888	866	
Gain (mm/day)§	0.27±0.42¶	0.28±0.42‖	0.22±0.41¶‖	0.26±0.42
Kwashiorkor				
Time to recovery				
No. of children	610	632	583	
No. of days	26±16	27±18	27±17	27±17
Weight				
No. of children	636	649	614	
Gain (g/kg/day)†	2.7±3.4	3.2±6.7**	2.5±3.4**	2.8±4.8
Length				
No. of children	636	649	614	
Gain (mm/day)§	0.21±0.48	0.24±0.47	0.20±0.48	0.22±0.48
Mid-upper-arm circumference				
No. of children	633	642	609	
Gain (mm/day)§	0.26±0.45††	0.26±0.42‡‡	0.21±0.42††‡‡	0.25±0.43
Marasmic kwashiorkor				
Time to recovery				
No. of children	54	51	55	
No. of days	44±21	39±17	40±18	41±19
Weight				
No. of children	65	67	76	
Gain (g/kg/day)†	4.1±3.4	4.9±4.3	3.6±5.1	4.2±4.4
Length				
No. of children	65	67	76	
Gain (mm/day)§	0.17±0.38	0.15±0.26	0.13±0.30	0.15±0.32
Mid-upper-arm circumference				
No. of children	63	66	75	
Gain (mm/day)§	0.22±0.33	0.34±0.42‡‡	0.19±0.37‡‡	0.25±0.38
Marasmus				
Time to recovery				
No. of children	156	156	145	
No. of days	37±23	35±21	38±23	37±22
Weight				
No. of children	182	181	183	
Gain (g/kg/day)†	5.6±5.3	6.0±4.7‡‡	4.9±5.0‡‡	5.5±5.1
Length				
No. of children	182	181	183	
Gain (mm/day)§	0.15±0.33	0.21±0.35	0.16±0.32	0.17±0.34
Mid-upper-arm circumference				
No. of children	182	180	182	
Gain (mm/day)§	0.32±0.37	0.34±0.41	0.28±0.38	0.31±0.39

* Plus–minus values are means ±SD. P>0.05 for all pairwise comparisons, except as noted.
† Weight gain was calculated from enrollment to the second follow-up visit (or to the first follow-up visit for children who had recovered by the time of the first follow-up visit or did not return for a second follow-up visit).
‡ P=0.002 for the comparison of placebo with cefdinir.
§ Gains in length and mid-upper-arm circumference were calculated from enrollment until the final study visit.
¶ P=0.01 for the comparison of placebo with amoxicillin.
‖ P=0.002 for the comparison of placebo with cefdinir.
** P=0.02 for the comparison of placebo with cefdinir.
†† P=0.04 for the comparison of placebo with amoxicillin.
‡‡ P=0.03 for the comparison of placebo with cefdinir.

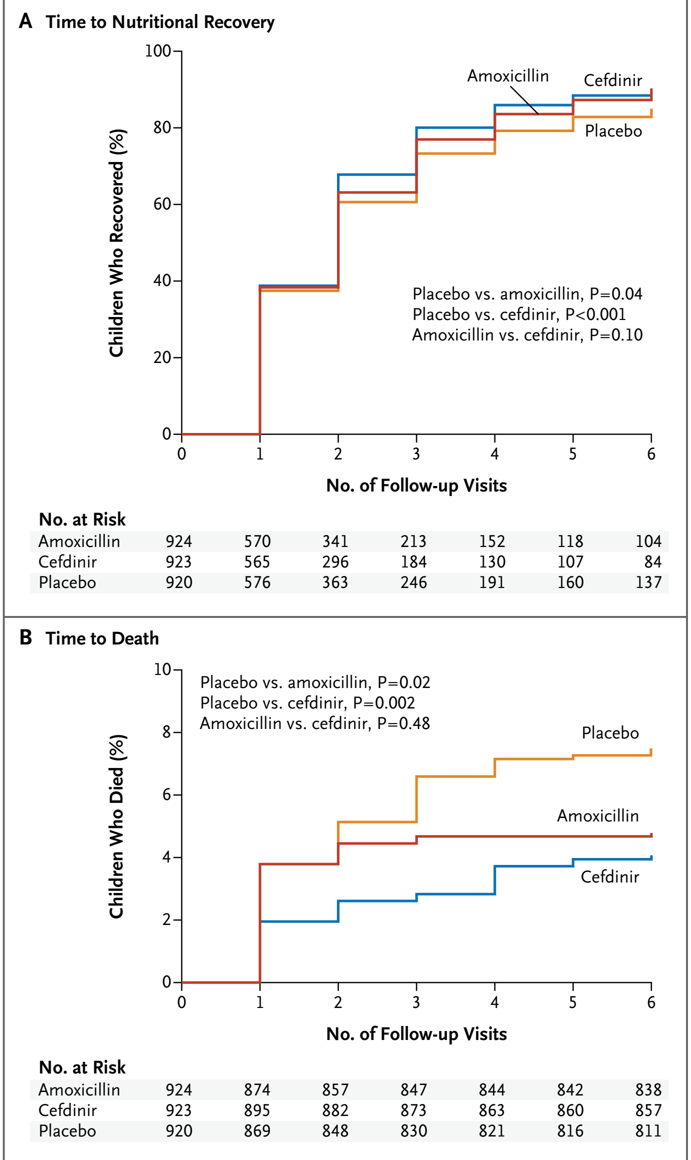

Figure 1. Kaplan–Meier Curves for Time to Nutritional Recovery and Time to Death.

Kaplan–Meier curves are shown for the number of study visits until nutritional recovery was achieved (Panel A) or until death occurred (Panel B). Recovery was defined as a weight-for-height z score of −2 or higher without bilateral pitting edema. Follow-up visits and the distribution of ready-to-use therapeutic food were scheduled for every 2 weeks, but some children were brought early or late for their follow-up visits. All P values were calculated by the log-rank test.

(or until the one follow-up visit for children with only one) was significantly higher among children who received cefdinir than among those who received placebo. Children who received either antibiotic agent also had greater increases in mid-upper-arm circumference than did those who received placebo.

Baseline characteristics related to recovery

As compared with children who did not recover, those who recovered were significantly older and were more likely to have their father alive and still in the home (Table S4 in the Supplementary Appendix). Among children with marasmus or marasmic kwashiorkor, those with the lowest mid-upper-arm circumference and the lowest weight-for-height z score at enrollment were most likely to have treatment failure or to die. Children with the lowest height-forage z score were least likely to recover. Although only 874 of 2765 children (31.6%) were tested for HIV, those who were known to be HIV-seropositive, especially if not receiving antiretroviral therapy, had the highest risks of treatment failure and death. Acute infectious symptoms and poor appetite both at enrollment and at the first follow-up visit (Table S5 in the Supplementary Appendix) were also associated with an increased risk of treatment failure.

A multiple logistic-regression model for baseline and intervention characteristics associated with nutritional recovery showed that younger age, marasmic kwashiorkor, greater stunting, HIV exposure or infection, and a cough before enrollment were associated with an increased risk of treatment failure (Table 4). These factors also proved to be significantly correlated with an increased risk of death; in addition, the caretaker's report of a good appetite at enrollment was significantly correlated with a reduced risk of death. As with the results of the univariate analysis, receipt of amoxicillin or cefdinir was strongly correlated with improved outcomes, although no significant difference between amoxicillin and cefdinir was observed. The interaction term between the type of severe acute malnutrition and the type of intervention proved not to be significant (P = 0.98 for nutritional recovery and P = 0.45 for death).

Discussion

Although improvements have been made in the treatment of severe acute malnutrition over the past decade, with the advent and widespread use of RUTF, more than 1 million children per year still die from this disease.[21] Given the

Table 4. Variables Associated with Nutritional Recovery or Death in the Multiple Logistic-Regression Models.

Variable	Nutritional Recovery		Death	
	Odds Ratio (95% CI)	P Value	Odds Ratio (95% CI)	P Value
Age, each 1-mo increase	1.007 (1.001–1.017)	0.02	0.989 (0.981–0.998)	0.01
Kwashiorkor vs. marasmic kwashiorkor	5.88 (4.15–8.33)	<0.001	0.25 (0.16–0.39)	<0.001
Marasmus vs. marasmic kwashiorkor	1.74 (1.22–2.47)	0.002	0.44 (0.28–0.71)	<0.001
Height-for-age z score, each 1.0-point increase	1.19 (1.09–1.31)	<0.001	0.78 (0.69–0.88)	<0.001
Mother or child HIV-seropositive	0.36 (0.27–0.47)	<0.001	2.01 (1.36–2.95)	<0.001
Cough during 2 wk before enrollment	0.76 (0.59–0.99)	0.04	1.52 (1.06–2.18)	0.02
Good appetite reported at enrollment*	—	—	0.51 (0.34–0.77)	0.001
Intervention group				
Amoxicillin vs. placebo	1.38 (1.02–1.86)	0.03	0.67 (0.44–1.00)	0.05
Cefdinir vs. placebo	1.69 (1.24–2.31)	0.001	0.57 (0.37–0.88)	0.01

* Data for good appetite at enrollment were not significantly associated with nutritional recovery and were not included in the regression model.

high incidence of severe acute malnutrition worldwide,[1] the number of children who die remains unacceptably high, despite the best current, proved treatment.[27] In this double-blind, randomized, placebo-controlled trial, we found that the routine addition of amoxicillin or cefdinir to the outpatient management of severe acute malnutrition was associated with marked improvements in recovery and mortality rates and significant improvements in weight and gain in the mid-upperarm circumference.

A 24.4% (95% CI, 4.1 to 40.4) reduction in the treatment-failure rate was observed when amoxicillin was added to routine therapy and a 38.9% (95% CI, 21.1 to 52.7) reduction was observed with cefdinir (Table 2). Moreover, a 35.6% (95% CI, 6.9 to 55.4) reduction in the mortality rate was observed with amoxicillin, and a 44.3% (95% CI, 18.0 to 62.2) reduction in the mortality rate was observed with cefdinir. Secondary outcomes (Table 3) were also generally consistent with these findings, with the shortest time to recovery and greatest gains in weight and mid-upper-arm circumference among children who received cefdinir and the longest time to recovery and smallest gains in weight and mid-upper-arm circumference among those who received placebo.

This study was conducted in rural sub-Saharan Africa in a stable subsistence farming population with a heavy burden of food insecurity and HIV infection and the acquired immunodeficiency syndrome, so these results may not necessarily be applicable in other populations, and thus they warrant validation in other contexts. However, no interaction between the type of severe acute malnutrition and the intervention group was observed, suggesting that this factor alone should not invalidate the generalizability of these findings. Although only a limited number of children had been tested for HIV, a high proportion of infected children had treatment failure or died (Table S4 in the Supplementary Appendix), providing further evidence for the need to provide integrated care for HIV infection and malnutrition in such children.[28,29]

During this study, we pursued an aggressive strategy to determine the clinical status of children lost to follow-up. Almost all the children whom we were able to find had in fact died or were so ill that they needed to be hospitalized. This accounts for the higher percentage of deaths in our study than in other studies in Malawi,[26,30,31] in which the children were likely to have been categorized simply as having withdrawn from the study.

The amoxicillin used in this study cost an average of $2.67 per child, and the cost of cefdinir was $7.85 but presumably would be lower if it were used on a large scale. For comparison, the cost of RUTF was approximately $50 for the course of therapy. Caretakers reported excellent adherence and did not report any difficulty in administering the medications. Among the children who received antibiotics, the rates of common side effects (most notably, diarrhea) were lower than they were among children who received placebo (Table S2 in the Supplementary Appendix). One might speculate that this may suggest a potential mechanism of effectiveness in the malnutrition armamentarium (i.e., decreasing the rates of bacterial pneumonia and dehydrating diarrhea in these immunocompromised children).

The children enrolled in this study had uncomplicated severe acute malnutrition, as do the vast majority of malnourished children who present for care,[21] in that they all showed a good appetite at enrollment and no clinical signs of sepsis. The small proportion of children who did not meet these criteria were transferred to inpatient treatment. Mucosal defenses (both respiratory and intestinal) are known to be compromised in resource-limited settings such as Malawi,[32] especially among malnourished children.[33,34] Studies of bacteremia in malnourished children[11] suggest that most severe invasive bacterial infections are due to translocation across these compromised mucosal surfaces. Thus, although these children did not specifically show signs of sepsis at the time of enrollment, antibiotics were effective in lowering the risk that these complications would develop during nutritional treatment. Although the increasing threat of antimicrobial resistance in the developing world[35-38] cannot be ignored and instances of highly resistant bacteria have been observed in malnourished children,[39] we believe that the routine use of antibiotics is worth serious consideration because of the observed benefits of nutritional recovery and a reduced risk of death in this specific high-risk population.

Our results suggest that children with uncomplicated severe acute malnutrition who qualify for outpatient therapy[4] remain at risk for severe bacterial infection and that the routine inclusion of antibiotics as part of their nutritional therapy is warranted. This prospective, randomized, double-blind, placebo-controlled study supplants our previous retrospective, uncontrolled study,[19] which showed no benefit of routine amoxicillin therapy. The results of the previous study were likely to have been confounded by the large differences in baseline characteristics between the children who received antibiotics and those who did not and may also have been confounded by other, unidentified factors in the implementation of the therapeutic feeding protocols between the two groups. Further studies are needed to evaluate long-term outcomes of routine antibiotic use in children with uncomplicated severe acute malnutrition and to determine whether a specific highrisk target population can be better defined.

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