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Extending Supplementary Feeding for Children Under Five with Moderate Acute Malnutrition Leads to Lower Relapse Rates

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Abstract

Objectives—Children with moderate acute malnutrition (MAM) have a high rate of relapse and death in the year following recovery. In this pilot study, we evaluate the long-term benefits of an extended course of nutritional therapy for children with MAM.

Methods—Rural Malawian children 6-59 months old with MAM, defined as a weight-for-height Z-score (WHZ) between -2 and -3, were provided supplementary feeding for a fixed duration of 12 weeks. The children were then followed for 12 months to assess long-term nutritional status, and compared to children initially treated only until they first reached WHZ > -2.

Results—Compared to children treated until they reached WHZ > -2, children treated for 12 weeks were more likely to remain well-nourished (71% vs. 63%, $P = 0.0015$) and maintain more normal anthropometric indices during 12 months of follow-up; there was also a trend towards lower rates of severe acute malnutrition (7% vs. 10%, $P = 0.067$) and death (2% vs. 4%, $P = 0.082$). Regression modeling showed that mid-upper arm circumference and WHZ at the end of supplementary feeding were the most important factors in predicting which children remained well-nourished ($P < 0.001$ for each).

Conclusions—The duration of supplementary feeding for children with MAM may not be as important as their anthropometry in terms of remaining well-nourished after initial recovery. The currently accepted recovery criteria of WHZ of -2 may be insufficient for ensuring long-term nutritional health; consideration should be given to setting higher recovery criteria.

Keywords

moderate acute malnutrition; wasting; children; Malawi; ready-to-use supplementary food; long-term outcomes; anthropometry; mid-upper-arm circumference; weight-for-height Z-score

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Introduction

About 5% of children under five years old worldwide suffer from moderate acute malnutrition (MAM), defined as having a weight-for-height Z score (WHZ) between -2 and -3 (1). Compared to well-nourished children, the mortality rate for children with MAM is 3-fold higher (2), and survivors suffer deficits in cognitive development (3, 4). Supplementary feeding programs remain the standard of care for treating children with MAM as outpatients in rural settings (5) with the hope of reducing the rate of these adverse outcomes (6).

Unfortunately, recent evidence suggests that children successfully treated for MAM continue to be at an increased risk for malnutrition and death 12 months after initial recovery (7). Improved treatment protocols are thus needed to reduce the long-term risk of adverse outcomes, while continuing to achieve anthropometric recovery at an affordable cost. Operational practice varies when treating children with MAM, with some programs treating until children reach a fixed anthropometric target (most often to $WHZ > -2$), while others treat children for a fixed duration of time (8). As yet, there have been no direct comparisons to inform which protocol is more effective (9), and the optimal exit criteria from targeted supplementation programs remains a high-priority research topic (10). Similarly, the recent trend towards using a fixed mid-upper arm circumference (MUAC) level of 12.5 cm as diagnosis and discharge criteria (9, 10) has not been explicitly compared with a fixed duration of treatment.

This pilot study tested the hypothesis that clinical outcomes 12 months after recovery from MAM would be better in children treated for a fixed duration of 12 weeks, rather than being treated only until they reach the recovery goal of $WHZ > -2$. By comparing these two treatment protocols, we also explored whether any information about anthropometric predictors of adverse outcomes during the follow-up period can be gleaned in order to inform optimal graduation criteria in operational practice for MAM supplementary feeding programs (9, 11, 12).

Methods

This was a quasi-experimental concurrently controlled prospective study comparing the 12-month clinical outcomes of children successfully treated for MAM with supplementary feeding for 12 weeks without respect to anthropometry, to those children fed to the anthropometric goal of $WHZ > -2$. The study was conducted among children who recovered from MAM after participating in a randomized controlled clinical trial comparing 3 supplementary foods at 18 different sites in southern Malawi in 2009-11. Recovery from MAM was defined as achieving $WHZ > -2$; upon recovery supplementary feeding was stopped for children at 14 of these 18 sites ("treat-to-goal group"). Children at 4 randomly selected study sites were provided with the additional intervention of extended supplementary feeding to complete 12 total weeks of total therapy ("treat-to-time group").

The study was approved by the University of Malawi College of Medicine Research and Ethics Committee and the Washington University in St. Louis Human Research Protection Office.

Participants

All children aged 6-59 months who recovered from MAM as part of a randomized controlled trial comparing the clinical efficacy of Corn-Soy Blend Plus-Plus (now called Supercereal Plus), soy ready to use supplementary food (soy RUSF), and soy/whey ready-to-use supplementary food (soy/whey RUSF) in the treatment MAM were recruited for this study (13, 14). Children who did not recover during the initial MAM treatment study were offered treatment for SAM and were excluded from this study. Children with chronic debilitating illnesses other than tuberculosis and HIV were also excluded.

Study Procedures

After providing verbal and written consent, caregivers provided demographic information, and completed the validated Household Food Insecurity Access Scale (HFIAS) (15).

Trained nutrition researchers and senior pediatric research nurses assessed each child for acute malnutrition using standard methodologies for anthropometric measurements: weight was measured using an electronic scale to the nearest 5g; length was measured in triplicate to the nearest 0.2 cm using a rigid length board; MUAC was measured with a standard insertion tape to the nearest 0.2 cm; and each child was evaluated for the bilateral pitting edema diagnostic of kwashiorkor (16).

Anthropometry and the HFIAS were repeated at scheduled follow-up visits 3, 6, and 12 months after enrollment. Caregivers and village health workers were also encouraged to refer children back to the clinics any time there was concern for nutritional deterioration. At each visit, caregivers were also asked about the child's appetite, infectious symptoms, health center visits, and medication use during the preceding 2 weeks.

Caregivers of children who relapsed to MAM at any visit were given focused nutritional counseling and supplemental soy RUSF rations and treated to recovery through biweekly clinic visits. Those diagnosed with SAM were treated with ready-to-use therapeutic food (RUTF) as outpatients or transferred to inpatient care as appropriate (16). If a child missed a scheduled follow-up visit, community health workers sought them out in their villages and encouraged them to return to the clinic as soon as possible.

Outcomes

The primary outcomes for this study were survival and nutritional status during the 12 months after the treatment intervention completed. Each child was classified as having a) remained well-nourished, defined as $WHZ > -2$ or $MUAC \geq 12.5$ cm at every follow-up visit for 12 months; b) relapsed to MAM, defined as $-3 < WHZ \leq -2$ and $MUAC < 12.5$ cm at any point during the follow-up period; c) developed severe acute malnutrition (SAM), defined as $WHZ \leq -3$ (marasmus) and/or bipedal edema (kwashiorkor) at any point during the follow-up period; d) died; or e) defaulted, defined as not completing the full 12 months of follow-up.

The criteria of *both* $MUAC < 12.5$ cm and $WHZ < -2$ to define relapses into MAM was used, whereas in operational clinical practice generally *either* criteria are employed (16). These more strict criteria were intentionally chosen to help identify a true decrease in the

child's nutritional health, since the use of WHZ criteria alone is often complicated by short-term linear growth (7). Linear growth is commonly seen as a child recovers, which often makes it difficult to achieve recovery by WHZ criteria if real-time length measurements are used for the calculation; thus recovery goals from MAM are defined on the basis of the initial length at the time of diagnosis (17). A child may grow in stature and body mass, both signs of recovery, yet appear to relapse when they return for follow-up visits because updated calculations of their WHZ using their new increased length makes them appear to have a low WHZ. The inclusion of MUAC as an additional and necessary relapse criterion is thus meant to avoid this conundrum.

Adverse outcomes during the follow-up period included the development of MAM or SAM, loss to follow-up (defaulting), or death. The *first* adverse outcome identified during the follow-up period was used to determine the final classification.

Data Analyses

Anthropometric Z-scores were calculated using Anthro or AnthroPlus (WHO, Geneva), based on the 2006 WHO Child Growth Standards (18). Comparisons of outcomes between the treat-to-time and treat-to-goal groups were made using either Fisher's exact test or the Chi-square test with Yates' correction for dichotomous variables and Student's t-test for continuous variables. *P* values less than 0.05 were considered statistically significant. The intention-to-treat approach was employed for all analyses.

To determine risk factors for poor outcomes while controlling for baseline differences in the enrollment characteristics of children in the two groups, logistic regression models for remaining well-nourished and death during the follow-up period were created. The regression models were created using a stepwise backward method where the criteria for inclusion of a term in the final model was $P < 0.10$. Covariates initially included in the models were intervention group (treat-to-time vs. treat-to-goal), age, gender, whether the child's mother was alive, whether the child's father was alive, whether the mother was the primary caretaker of the child, whether the father was present in the home, mother's HIV status, child's HIV status, number of children in the household under 5 years, the month in which treatment was initiated, the child's initial MUAC, WHZ, HAZ, HFIAS score, and the caretaker's report of appetite at enrollment. Covariates with coefficients with a 95% CI that did not include 1 were considered significant. Food insecure months were defined as January through April, as the annual harvest in southern Malawi generally occurs in April-May.

To assess the influence of a range of MUAC and WHZ measurements at the time of graduation from MAM therapy on the rate of remaining well-nourished throughout the follow-up period, receiver-operating characteristic (ROC) curves were created. The number of additional children needed to treat to a range of higher MUAC and WHZ recovery thresholds to keep one additional child well-nourished throughout the follow-up period was also calculated.

Results

Between November 2009 and January 2011, 382 children with MAM were enrolled in the treat-to-time group (Figure 1), while 1967 children were enrolled in the treat-to-goal group (7). Characteristics of these two groups of children at the time they each had reached WHZ > -2 were clinically generally similar (Table 1), except that the children in the treat-to-time group were more likely to be female, to still be breastfeeding, and were significantly less stunted. The children in the treat-to-goal group had a higher MUAC and also had a higher rate of maternal HIV.

During the extended feeding time between when children in the treat-to-time group achieved nutritional recovery (WHZ > -2) and the end of the 12 week time span, 8 (2%) of these 382 children developed kwashiorkor and 4 (1%) developed marasmus, despite continued supplementary feeding (Figure 1). These 12 children thus did not complete their 12 weeks of MAM therapy, but instead were transferred into a treatment protocol for SAM, receiving 175 kcal/kg/d of RUTF, until they recovered (WHZ > -2 without edema) (19, 20). These children proved to be a particularly high-risk group during the 12-month follow-up period, with only 5 of the 12 (42%) remaining well-nourished during that time.

The remaining 370 children in the treat-to-time group showed evidence of continued growth during the extended 12-week feeding period, increasing their average WHZ from -1.61 ± 0.47 to -1.14 ± 0.67 and their average MUAC from 12.4 ± 0.7 cm to 13.0 ± 0.8 cm ($P < 0.0001$ for both comparisons). No decrease in stunting was seen, with 282 (76%) having HAZ < -2 and 143 (39%) still severely stunted with HAZ < -3 , with an overall average HAZ of -2.75 ± 1.19 .

Of the 382 children enrolled in the treat-to-time group, 337 (88.2%) remained well-nourished during the first 3 months of follow-up, 301 (78.8%) remained well-nourished throughout the first 6 months of follow-up, and 272 (71.2%) remained well-nourished throughout the 12 month follow-up period (Figure 1 and Table 2). These rates were all significantly higher than the rates among children in the treat-to-goal group (7), an improvement of 9.3% (95% confidence interval [CI], 5.0% to 13.7%, $P < 0.0001$) at 3 months, 10.0% (95% CI, 5.0% to 15.0%, $P < 0.0001$) at 6 months, and 8.7% (95% CI, 3.4% to 13.9%, $P = 0.0015$) at 12 months. These 272 children in the treat-to-time group who remained well-nourished throughout the study had significantly higher WHZ and HAZ at the end of the follow-up period, compared to the 1230 children in the treat-to-goal group who remained well-nourished (Table 2).

By 3 months, 6.5% (95% CI, 2.5% to 10.5%, $P = 0.002$) less children in the treat-to-time group had relapsed to MAM or SAM than in the treat-to-goal group; by 6 months, 5.0% (95% CI, 0.35% to 9.6%, $P = 0.04$) less had relapsed; and by 12 months, 3.6% (95% CI, -1.2% to 8.4%, $P = 0.16$) less had relapsed. A non-significant trend towards increased survival was also seen in the treat-to-time group: the relative risk for mortality in the treat-to-time group at 3 months was 0.18 (95% CI, 0.025 to 1.35, $P = 0.07$) at 3 months, 0.19 (95% CI, 0.48 to 0.79, $P = 0.008$) at 6 months, and 0.49 (95% CI, 0.23 to 1.05, $P = 0.08$) at 12 months.

Two logistic regression models were developed to identify baseline characteristics that were associated with children in both cohorts who either remained well-nourished or had died during 12 months of follow-up (Table 3). Children in both the treat-to-goal and treat-to-time groups were all included together in these models. Due to the relatively small number of deaths, the model for risk of death showed poor predictive power. Although the treat-to-time group had a significantly higher rate of remaining well-nourished than did the treat-to-goal group in univariate analysis (Table 2), the treatment protocol used proved not to be a significant predictor of remaining well-nourished in these multivariate models. Instead, the characteristics with the strongest statistical association with remaining well-nourished were greater WHZ and MUAC at the onset of the follow-up period, and the characteristics with the strongest association with death were HIV infection and low MUAC.

MUAC at the end of initial MAM therapy proved to be slightly better than WHZ in predicting which children would remain well-nourished over the subsequent 12 months (Supplementary Figures 1-3). Children who finished their initial MAM treatment with MUAC measurements of at least 12.9 cm or with WHZ of at least -1.75 were significantly more likely to remain well-nourished over the course of the follow-up period (Supplementary Table 1); these odds improved in a dose-response manner as their anthropometry increased. If the WHZ recovery threshold were increased from -2 to -1.5, nearly 16 children would need to be treated to keep one additional child well-nourished; if the threshold were increased to -1, then the additional number needed to treat would be nearly 7 relative to the WHZ of -2 threshold.

Discussion

Children treated for MAM for 12 weeks were more likely to remain well-nourished in the subsequent 12 months than children treated simply to WHZ > -2. We also observed a trend towards lower rates of SAM and death among children in the treat-to-time group. Those that did remain well-nourished had higher WHZ and HAZ parameters at the end of those 12 months. This likely reflects the better anthropometric indices at the start of the 12-month follow-up period, and suggests that these indices achieved at the end of 12 weeks of MAM therapy can be sustained during the subsequent 12 months.

It may seem that treating children with MAM for a fixed duration of time was more effective in reducing relapse over the subsequent 12 months, but logistic regression modeling actually identified greater MUAC and WHZ as the most important variables that predicted which children would remain well-nourished; whether they were in the treat-to-time or treat-to-goal group proved *not* to be a significant factor. This suggests that optimized anthropometric criteria are more important than a pre-determined extended duration of feeding.

Given that so many children did not remain well-nourished using the standard recovery threshold, we explored whether higher MUAC and/or WHZ thresholds could be used to determine a more optimal time to end therapy for MAM. This would inevitably involve a trade-off in cost as this will extend the duration of feeding for many additional children, but may be a necessary measure in vulnerable populations (11). Continuing to feed a child who

may no longer be strictly wasted, but nevertheless maintains a WHZ and/or MUAC on the cusp of MAM, could provide a safety net against subsequent acute infectious illnesses and food insecurity in this vulnerable population (11, 21). Increasing the WHZ recovery threshold to -1.5 would greatly increase the specificity of predicting which children remained well-nourished to 67% but would require treating 16 children to this level rather than to the WHZ of -2 level to keep one additional child well-nourished. Similarly, increasing the recovery criteria to WHZ of -1.0 would be nearly 94% specific and would require treating only 7 additional children to keep one additional child well-nourished, compared to treating only to WHZ of -2. Presumably, similar significant benefits in mortality rates would also be realized by an approach that involved treating to a higher WHZ threshold, but the present study was limited in its sample size to make an accurate estimate of this benefit. This higher WHZ of -1.5 as a recovery threshold has been recommended in the past (22) but more recent international recommendations (23), research studies (5, 24), and operational programs (11, 13) have generally used WHZ of -2 as the recovery threshold, even though there is no clear consensus on this issue (8-10). Our results suggest that a return to this higher WHZ of -1.5 may help reduce the rate of long-term nutritional relapse. Additionally, our data here suggest that MUAC of 12.5 cm may not be sufficient to prevent relapse in the subsequent year after recovery, which may be a particularly relevant finding given that more supplementary feeding programs are operationally relying more frequently on MUAC as entry and graduation criteria. In particular, a larger MUAC at the completion of supplementary feeding was significantly predictive of lower mortality rates (while WHZ was not), adding to the growing body of evidence that MUAC is a better predictor of mortality among malnourished children (25, 26).

The results of this study may not be applicable to areas outside of rural sub-Saharan Africa, in areas with lower rates of falciparum malaria and HIV-1 (27), or where the incidence of acute malnutrition does not follow a similar seasonal pattern. Additionally, the initial treatment for MAM was conducted in the context of a randomized clinical trial that provided specialized fortified foods with intensive nutritional counseling (13); outcomes would likely be worse in a programmatic setting with fewer resources.

Future interventions should attempt to reduce the relapse rate by studying and restoring physiologic and immunologic competence (28), in addition to anthropometry, as these may indeed be the key prognostic variables. Potential interventions could include provision of bed nets, antimalarial prophylaxis, micronutrient supplementation, deworming, closer integration with immunization programs and with HIV testing and treatment programs, and regular follow-up with nursing staff to help educate and advise caregivers about proper feeding techniques for their growing child.

The study results should be considered preliminary as children were not specifically randomized to different recovery thresholds, but instead treated to either a pre-specified goal weight (WHZ of -2) or for a pre-specified treatment duration (12 weeks). However, this design did generate a range of anthropometry at graduation and allowed us a unique opportunity to conduct these analyses. A randomized prospective study testing the durability of optimizing MAM treatment in keeping children well-nourished for a prolonged period

after treatment ends is warranted. Given the enormous burden that acute malnutrition plays in global child mortality, this study adds to the larger context of recent work demonstrating that there is still much that can be done (1) to optimize the care of acutely malnourished children to improve both their short-term (29) and long-term (7, 30) outcomes.

In conclusion, we show that in this 12 month observational study following 12 weeks of supplementary feeding for MAM, 71% of children who recovered from MAM remained well-nourished, while less than 2% died. This is the first report of a direct comparison of long-term outcomes for children treated to a target WHZ compared to children treated for a fixed duration of time. Higher anthropometry at the end of MAM therapy appears to be the most important predictor of long-term nutritional status, regardless of the duration of therapy provided, and thus more stringent recovery criteria such as WHZ of -1.5 and/or MUAC of 13 cm should be considered for moderately malnourished children to decrease the rate of relapse.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Flow of patients in the treat-to-time group.

Table 1

Characteristics of study children with moderate acute malnutrition (MAM) upon successful completion of initial MAM therapy.^a

	Treat-to-Time Group (n=382)	Treat-to-Goal Group ^b (n=1967)	P Value
Female	257 (67)	1205 (61)	0.03
Age, <i>mo</i>	19.8 ± 11.0	20.7 ± 11.1	0.12
MUAC, ^c <i>cm</i>	12.4 ± 0.7	12.6 ± 0.9	0.04
WHZ ^d	-1.61 ± 0.47	-1.63 ± 0.47	0.52
HAZ ^e	-2.67 ± 1.24	-2.95 ± 1.25	<0.0001
HAZ -2	276 (72)	1546 (78)	0.007
HAZ -3	135 (35)	928 (47)	<0.0001
Twin	14 (4)	116 (6)	0.04
Primary caretaker is mother	368 (96)	1879 (96)	0.25
Mother is alive	380 (99)	1935 (98)	0.04
Father is alive	372 (97)	1922 (98)	0.34
Still breastfeeding	263 (69)	1259 (64)	0.03
Mother known to be HIV-infected	22 (6)	195 (10)	0.004
Number of children under 5 in the home	1.7 ± 0.7	1.6 ± 0.7	0.009
HFIAS ^f score	6.5 ± 4.6	6.2 ± 5.3	0.38
Duration of feeding needed to reach WHZ > -2			
2 weeks	232 (61)	1242 (63)	0.11
4 weeks	75 (20)	440 (22)	
6 weeks	36 (9)	159 (8)	
8 weeks	23 (6)	78 (4)	
10 weeks	11 (3)	31 (2)	
12 weeks	5 (1)	17 (1)	

^aData expressed as mean ± standard deviation or number (%).

^bData for treat-to-goal group from Chang, et al (7).

^cMUAC = Mid-Upper Arm Circumference.

^dWHZ = Weight-for-Height Z-score.

^eHAZ = Height-for-Age Z-score.

^fHFIAS = Household Food Insecurity Access Scale.

Table 2

Outcomes of children that were successfully treated for moderate malnutrition 12 months later.^a

	Treat-to-Time Group (n=382)	Treat-to-Goal Group ^b (n=1967)	P Value
Remained well-nourished, ^c n (%)	272 (71)	1230 (63)	0.0015
MUAC, ^d cm	14.0 ± 0.9	14.0 ± 0.9	0.17
WHZ ^d	-0.54 ± 0.89	-0.82 ± 0.84	0.02
HAZ ^d	-2.70 ± 1.04	-2.87 ± 1.13	< 0.0001
Relapsed to MAM, ^e n (%)	63 (17)	334 (17)	0.87
Developed SAM, ^f n (%)	25 (6.5)	190 (9.7)	0.067
Died, n (%)	7 (1.8)	74 (3.8)	0.082
Defaulted, n (%)	15 (3.9)	139 (7.1)	0.031

^aThe first adverse outcome recorded determined final classification.

^bData for treat-to-goal group from Chang, et al (7).

^cDefined as WHZ > -2 or MUAC < 12.5 cm throughout the follow-up period.

^dAnthropometric measurements at the final follow-up visit among those children who remained well-nourished.

^eDefined as -3 < WHZ < -2 and MUAC < 12.5 cm at any time during the follow-up period.

^fDefined as WHZ < -3 or bipedal edema at any time during the follow-up period.

Table 3

Variables associated with remaining well-nourished or death during the follow-up period in logistic regression models.^a

	Model 1: Risk of Remaining Well-Nourished^b	
Variable	Odds Ratio (95% CI)	P Value
Age, <i>each 1-mo increase</i>	1.04 (1.03-1.05)	< 0.001
Female gender	1.76 (1.41-2.20)	< 0.001
Child without HIV infection	1.74 (1.05-2.88)	0.032
Initial treatment in food insecure season (Jan-Apr)	0.76 (0.63-0.92)	0.004
MUAC, <i>each 1-cm increase</i>	1.30 (1.14-1.50)	< 0.001
WHZ, <i>each 1-Z increase</i>	2.83 (2.26-3.53)	< 0.001
HAZ, <i>each 1-Z increase</i>	1.21 (1.11-1.32)	< 0.001
	Model 2: Risk of Death^c	
Variable	Odds Ratio (95% CI)	P Value
Female gender	1.56 (0.99-2.45)	0.056
Child without HIV infection	0.32 (0.15-0.69)	0.003
Number of children in house, <i>each 1 child increase</i>	0.70 (0.48-1.02)	0.060
MUAC, <i>each 1-cm increase</i>	0.68 (0.53-0.88)	0.003

^a Binary logistic regression models constructed with a stepwise backward method, retaining only those factors with $P < 0.10$.

^b Model $R^2 = 0.131$ by Cox and Snell; $R^2 = 0.181$ by Nagelkerke; Hosmer and Lemeshow chi-square = 324.

^c Model $R^2 = 0.011$ by Cox and Snell; $R^2 = 0.044$ by Nagelkerke; Hosmer and Lemeshow chi-square = 8.3.