Letters

RESEARCH LETTER

Extended Follow-up From a Randomized Clinical Trial of Routine Amoxicillin in the Treatment of Uncomplicated Severe Acute Malnutrition in Niger

Evidence to support current guidelines recommending routine antibiotic use in the outpatient management of uncomplicated severe acute malnutrition (SAM) is limited and based largely on data from historical inpatient settings. The evidence from 2 clinical trials on the effect of routine antibiotic use on nutritional recovery differs. In Malawi, where HIV and kwashiorkor prevalence are high, routine antibiotics increased nutritional recovery and decreased mortality. In Niger, where HIV and kwashiorkor prevalence are low, we found no benefit of routine amoxicillin on nutritional recovery or mortality, although children receiving amoxicillin had a reduced risk of transfer to inpatient care.

Both reports only considered short-term risks and benefits during nutritional treatment (mean [SD] time to recovery, 29 [19] days in Malawi and 29 [13] days in Niger), although immunodeficiencies and risk of relapse or morbidity associated with SAM may persist beyond nutritional recovery. To broaden the available evidence, we present a more extensive follow-up during and after nutritional treatment. Briefly, children aged 6 to 59 months who presented with uncomplicated severe acute malnutrition (SAM) in Madarounfa, Niger, between October 2012 and November 2013 were randomly assigned 1:1 to receive amoxicillin (80 mg/kg/d) or a placebo for 7 days. All children received standard care for uncomplicated SAM for a minimum of 3 weeks and a maximum of 8 weeks. Children were followed up weekly for anthropometric, clinical, and vital status during treatment and (as per trial protocol) at 4, 8, and 12 weeks after admission. The Comité Consultatif National d’Ethique, Niger, and the Comité de Protection des Personnes, Île-de-France, France, provided ethical approval. An independent data safety monitoring board reviewed study progress and safety events, and all participants provided written informed consent.

We used the weighted Kaplan-Meier method and Cox proportional hazard models to assess the effect of routine amoxicillin vs placebo on sustained nutritional recovery, transfer to inpatient care, and death from admission to 12 weeks. Inverse probability weights were used to account for censoring at the time of death or transfer to inpatient care. The intervention outcomes on total anthropometric gains among children who had recovered from admission to 12 weeks were assessed using $t$ tests (of weight) and linear regression adjusted for baseline measurements (of mid-upper arm circumference and height). Anthropometric gains over time were estimated by intervention group using hierarchical generalized linear models with a cubic spline.

Data analysis took place from December 2017 to June 2018. Analyses were performed using R, version 3.3 (R Foundation for Statistical Computing). Two-sided $P$ values were considered significant at less than .05.

Results | All 2399 children (mean [SD] age, 16.7 [8.6] months; 1196 female children [49.9%]) of the primary analysis were eligible for inclusion in this extended analysis. Analysis found no association of routine amoxicillin administration with the risk of nutritional recovery, transfer to inpatient care or death, total weight, mid-upper arm circumference, or height gain from admission to 12 weeks (Table). The nutritional and anthropometric benefits of amoxicillin reported previously may have been limited to the first 2 to 4 weeks after admission to the nutritional program and not maintained thereafter, including a decreased risk of transfer to inpatient care (cumulative incidence 0–<2 weeks postdismission: amoxicillin group, 8%; placebo group, 9%; 2–12 weeks postadmission: amoxicillin group, 36%; placebo group, 27%) and improved mean (SD) weight gain (during treatment: amoxicillin group, 6.47 [2.65] g/kg/day; placebo group, 5.85 [2.85] g/kg/day; after program discharge: amoxicillin group, 1.01 [1.12] g/kg/day; placebo group, 1.06 [1.14] g/kg/day) (Figure).

| Clinical Outcome                  | No. of Events per Person-Year | Hazard Ratio or Mean Difference (95% CI) | $P$ Value |
|----------------------------------|-------------------------------|------------------------------------------|-----------|
| Sustained nutritional recovery    | Amoxicillin: 3.2; Placebo: 3.20 | 0.95 (0.86-1.05)*                      | .36       |
| Transfer to inpatient care       | Amoxicillin: 1.72; Placebo: 2.05 | 0.97 (0.84-1.13)*                      | .70       |
| Death                            | Amoxicillin: 0.10; Placebo: 0.08 | 1.11 (0.58-2.13)*                      | .75       |
| Anthropometric gains, mean (SD)  |                                |                                          |           |
| Weight, g/kg/d                   | Amoxicillin: 2.82 (1.05); Placebo: 2.75 (1.02) | 0.07 (~0.04 to 0.18)*                      | .21       |
| Mid-upper arm circumference, mm/d| Amoxicillin: 0.18 (0.08); Placebo: 0.17 (0.07) | 0.00 (0.00-0.01)*                      | .22       |
| Height, mm/d                     | Amoxicillin: 0.19 (0.13); Placebo: 0.19 (0.13) | 0.01 (~0.01 to 0.02)*                      | .41       |

* Hazard ratios and 95% CIs for amoxicillin relative to placebo are based on the univariate weighted Cox proportional hazard model.

The mean difference and 95% CIs of anthropometric gains were calculated from unweighted linear regression among children who remained recovered at their final study visit.
Discussion | Results from this clinical trial with extended follow-up from admission to 12 weeks suggest no longer-term benefit of routine antibiotic use in the treatment of uncomplicated SAM. Current guidelines rightly acknowledge that it would be inappropriate to withhold an intervention that may substantially reduce mortality in a high-risk population,6 and in settings where it can save lives, routine antibiotic use should remain part of clinical protocols for uncomplicated SAM. This use, however, should be weighed against the risk of the emergence of antibiotic resistance, implications for program costs and coverage, and likely short-lived individual benefits. Guidance that allows treatment protocols to be adapted and simplified in specific contexts while maintaining individual effectiveness, protecting public health safety, and assuring access to care should be prioritized.

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Breastfeeding is the most efficient way to prevent child mortality and is particularly important in early life, as about 20% of all malaria deaths occur in infants younger than 5 years of age.1 This highlights the need for successful prevention of malaria infection, especially in early life. Breastfeeding reduces malaria risk in infants who are breastfed.6 Therefore, we propose what is to our knowledge an original hypothesis: the presence of malaria antigen in breast milk, such as allergens or viral antigens, could elicit strong immune responses in offspring who are breastfed.5 Mouse and human data have shown that the presence of foreign antigens in breast milk, such as allergens or viral antigens, could elicit strong immune responses in offspring who are breastfed.6 Thus, we investigated whether Plasmodium falciparum histidine-rich protein 2 (pHRP-2) and lactate dehydrogenase (pLDH) are detectable in the breast milk of mothers from Uganda, a country endemic for malaria.1

Methods | This study included mothers who were lactating and visited our malaria clinic at St Anne Health Center III, Katakwi District, northeastern Uganda, during the high or low malaria-transmission seasons. Five-milliliter samples of breast milk and fingerprick blood samples were collected after the mothers provided informed consent. Ethical approval for the study was provided by the Uganda National Council for Science and Technology.

Results | A total of 123 mothers who were lactating visited the malaria clinic during the low malaria-transmission season; an additional 201 visited during the high transmission season. The overall mean [SD] age, body mass index (calculated as weight in kilograms divided by height in meters squared), and lactation duration of the mothers analyzed in this study were 26.2 [6.8] years, 23.6 [2.8], and 12.3 [5.5] months, respectively. None of the mothers had clinical malaria. When malaria transmission was low and high, 14 of 123 women (11.4%) and 74 of 201 women (36.8%), respectively, harbored asymptomatic malaria (P < .001). Among the 88 breast milk samples from mothers with asymptomatic malaria, 7 had detectable pHRP-2 (7.9%) with a median (interquartile range) level of 45.0 (2.0-180.2) pg/mL, and 10 had detectable pLDH (11.3%) with median (interquartile range) values of 6.6 (5.6-9.9) arbitrary units/mL (Figure 1). Overall, 14 breast milk samples (15.9%) were positive for either pLDH or pHRP-2, and 3 (3.4%) were positive for both pLDH and pHRP-2. Forty-four milk samples from mothers without malaria were used as control samples, and none of these showed detectable pHRP-2 or pLDH antigens (Figure 1).

To address whether the detection of malaria antigens in breast milk depended on the density of P. falciparum were used immediately to detect asymptomatic malaria by an ultrasensitive P falciparum HRP-2-based rapid diagnostic test (uRDt) (Alere Malaria Ag Pf [Standard Diagnostics Inc]). The presence of malaria antigens in breast milk samples was investigated by P falciparum-specific pHRP-2 and pLDH enzyme-linked immunosorbent assays (Quantimal CELISA [Cellabs]), with protocol adaptation (detection levels were 1.2 pg/mL and 4.8 units/mL, respectively).

Data analyses were performed with Prism version 6 (GraphPad Software). We used 2-sided Fisher exact tests to address differences between groups, and P values less than .05 were considered significant. Data collection and analysis occurred from March 2018 to December 2018.

Results | A total of 123 mothers who were lactating visited the malaria clinic during the low malaria-transmission season; an additional 201 visited during the high transmission season. The overall mean [SD] age, body mass index (calculated as weight in kilograms divided by height in meters squared), and lactation duration of the mothers analyzed in this study were 26.2 [6.8] years, 23.6 [2.8], and 12.3 [5.5] months, respectively. None of the mothers had clinical malaria. When malaria transmission was low and high, 14 of 123 women (11.4%) and 74 of 201 women (36.8%), respectively, harbored asymptomatic malaria (P < .001). Among the 88 breast milk samples from mothers with asymptomatic malaria, 7 had detectable pHRP-2 (7.9%) with a median (interquartile range) level of 45.0 (2.0-180.2) pg/mL, and 10 had detectable pLDH (11.3%) with median (interquartile range) values of 6.6 (5.6-9.9) arbitrary units/mL (Figure 1). Overall, 14 breast milk samples (15.9%) were positive for either pLDH or pHRP-2, and 3 (3.4%) were positive for both pLDH and pHRP-2. Forty-four milk samples from mothers without malaria were used as control samples, and none of these showed detectable pHRP-2 or pLDH antigens (Figure 1).

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