



# Case management of kwashiorkor: an intervention project at seven nutrition rehabilitation centres in Malawi

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**Objectives:** (1) To improve case management of kwashiorkor at seven Nutritional Rehabilitation Centres (NRCs) through 2–4 weekly paediatric supervisory visits. (2) To evaluate the impact of the use of routine tube-feeding and a micronutrient supplement (Nutraset).

**Design:** An intervention project with descriptive clinical data in which Nutraset was introduced halfway through the project, and routine tube-feeding at one NRC was compared to no tube-feeding at a similar one.

**Setting:** NRCs located at two central hospitals, two district hospitals and three rural clinics in southern Malawi.

**Subjects:** 1625 consecutive kwashiorkor admissions from January–December 1995.

**Results:** The overall case-fatality rate was 24.2% (393/1625), varying by facility level (central 30.5%, district 25.8% and rural 7.5%), reflecting different severity of cases. From ELISA testing and a clinical protocol, we estimate that 21.7% (353/1625) of these kwashiorkor cases were HIV-infected, including 121 breastfed children. Routine tube-feeding was associated with better weight gain (8.24 g/kg/d) than no tube-feeding (4.51 g/kg/d) at central NRCs, but with no reduction in mortality (31.4% vs 30.3%). The introduction of Nutraset was associated with improved weight gain (6.06 vs 4.66 g/kg/d) and a lower mortality (20.8 vs 25.8%), but was confounded by seasonal factors.

**Conclusions:** From a clinical perspective, HIV infection has transformed kwashiorkor in this part of Africa. Routine tube-feeding was associated with improved body weight gain in the treatment of kwashiorkor. The benefit of paediatric supervision was limited by the infrequency of visits, by constraints of health worker motivation, by a lack of resources and by the severity of disease. Efforts need to focus—not just on case management protocols—but on how to actually improve clinical practice in this setting.

**Sponsorship:** Canada Fund, Malawi.

**Descriptors:** kwashiorkor, protein-energy malnutrition, zinc, potassium, Africa

## Introduction

Kwashiorkor is a form of severe protein-energy malnutrition in children characterized by oedema, irritability, anorexia, fatty infiltration of the liver, skin dyspigmentation, hair changes and reduced hepatic export proteins. The precise aetiology is still unclear, although many hypotheses have been advanced, such as protein deficiency, (Williams, 1935) methionine deficiency, (Roediger, 1995) pellagra, (Gillman and Gillman, 1951) dietary dysadaptation, (Gopalan, 1968) cyanogenic glucoside toxicity, for example, linamarin, in cassava, (Kamalu, 1993) aflatoxin poisoning, (Hendrickse, 1983) ADH-like effect of free ferritin, (Srikanthia, 1958) inappropriate endocrine responses, (Rao, 1974; Whitehead, 1981) and free radical damage (Golden, 1988). There are enormous regional disparities in the prevalence of kwashiorkor, and in regions where it is the predominant form of childhood malnutrition, it tends to be the final common pathway for nutritional insults such as food insecurity, a monotonous staple diet, chronic infec-

tions (TB or HIV), persistent diarrhoea and even cerebral palsy. As the most common form of severe malnutrition in Malawi, kwashiorkor (including marasmic-kwashiorkor) accounts for 75% of all admissions to Nutrition Rehabilitation Centres (NRCs) in the southern region. It has a high case-fatality rate at large hospital-based NRCs, which has changed little over recent decades despite an overall fall in under-five childhood mortality (Anonymous, 1995; Anonymous, 1994).

Recently, nutritionists and paediatricians have been accused of malpractice by Berg of the World Bank for failing to improve nutrition in the developing world despite considerable research advances in nutritional science (Berg, 1993). The proposed solution to this deplorable situation was the use of nutrition 'engineers', but it is still unclear how to address the problem and there is a lack of relevant operational research. This project was an attempt to record prospectively the results of case management of kwashiorkor at different levels of NRCs, and to try to improve the outcomes. The NRCs were typical of treatment centres for kwashiorkor in Malawi, so they were not transformed research units with a specialized level of practice. The project standardized treatment protocols for kwashiorkor at these NRCs, provided paediatric supervision through regular visits, supplied a micronutrient supplement (Nutraset),

and evaluated the results from both clinical impressions and data collection.

## Methods

The project was carried out in the southern region of Malawi at NRCs based at two central hospitals (Blantyre and Zomba), two district hospitals (Mwanza, Ntcheu) and three rural clinics (Mpemba, Namitambo and Chikwawa). The centres were selected on the basis of feasibility, willingness to participate, and to represent typical NRCs at each level in the region. These NRCs were not just feeding centres, but in-patient facilities for the treatment of sick children. All participating NRCs used the same standard treatment protocol, except for tube-feeding and a milk-free diet as explained below. Initial routine medications were co-trimoxazole and albendazole, with chloramphenicol for clinically-suspected sepsis. Micronutrient, mineral and vitamin supplements were not available initially (except for potassium at Mwanza and Blantyre), but the project provided these as Nutriset, which is a powder supplement for milk specifically designed for the treatment of severe malnutrition in the developing world (Briend and Golden, 1993). When added to high-energy milk, Nutriset contains supplemental potassium, calcium, magnesium, zinc, manganese, selenium, iodine, copper and multivitamins. It was started at NRCs in July (mid-project, when it arrived in Malawi from France), so we compared results before and after its use.

The milk-based diet was made from a premix of dried skim milk powder, vegetable oil and sugar supplied by the World Food Programme. The premix was made into a phase 1 milk for initiation of cure, which contained 278 kJ (66 kcal) and 1.0 g of protein per 100 mL. On recommended intakes, this meant a daily intake per kilogram of body weight of approximately 332 kJ (79 kcal) and 1.2 g of protein. Once the oedema, appetite and mental status had improved, children were advanced to a phase 2 diet, generally in the second week of treatment. This comprised four feeds of high energy milk, containing 477 kJ (114 kcal) and 4.1 g of protein per 100 mL; and two feeds of a local weaning porridge of maize, soy, sugar and oil, containing 469 kJ (112 kcal) and 3.3 g of protein per 100 mL. On recommended intakes of 150 mL/kg/d, this diet provided a daily intake of 712 kJ (170 kcal) and 5.8 g of protein per kilogram. Since routine tube-feeding (by intermittent rather than continuous feeding) was only done in Zomba, this represents the volumes given to the mothers rather than actual intakes. The protein and energy densities of these diets are similar to standard treatment protocols for the developing world (Waterlow, 1992; WHO, 1981). In addition, 226 children in Blantyre received a milk-free maize-based diet, the results of which have been reported elsewhere including the impact on intestinal permeability (Brewster *et al*, 1997). Oral rehydration solution and intravenous fluid were used cautiously to avoid excess sodium and fluid loads, which are poorly tolerated in the early phase of kwashiorkor treatment (Gordillo-Panagua and Frenk, 1990).

The other component of the project was regular paediatric visits to supervise the NRCs every 2–4 weeks. All children with nutritional oedema (kwashiorkor, including marasmic-kwashiorkor) admitted to project NRCs from mid-January to mid-December 1995 were included, but cases of oedema of non-nutritional origin, for example,

nephrosis or severe anaemia, and marasmus without oedema were excluded. Children with kwashiorkor and HIV infection were not excluded, since they are normally treated as part of the spectrum of kwashiorkor at NRCs. Efforts were made to include all kwashiorkor cases, including those absconding or dying soon after admission, on whom we had incomplete data. A questionnaire about household water supply, sanitation, hygiene practices, health and socio-economic status was administered to the parents or guardians of children in the project. The questionnaire had been field tested and modified before use. A numeric score for socio-economic status was developed from it based on parents education and employment, household attributes and possessions, water supply and sanitation characteristics, and previous child deaths. This score was distributed symmetrically in a bell-shape about a median of 20 with a range of 5–41.

Children in the project were weighed and measured on admission and at least twice weekly. Weights and recumbent lengths of subjects were measured by trained nurses using standard techniques on a Salter hanging scale and locally-made stadiometer. Although measurements were recorded to the nearest 0.1 kg and 0.1 cm, we found from repeated measurements on the same children that there was digit preference and a tolerance level closer to 0.5 cm for height. Since all children had recumbent length measured, because it is more reproducible in sick children, a correction factor of 1.5 cm was subtracted from the length measurements of children >24 months to approximate height for NCHS standard (Dibley *et al*, 1987). Although we measured length, we have still used the conventional terms 'weight for height' (WHZ) and 'height for age' (HAZ) z-scores. WHZ was calculated on the lowest weight recorded in hospital after oedema had resolved, but no correction was made for children who died with oedema. Wasting and stunting were defined conventionally as below 2 standard deviations for WHZ and HAZ, respectively, using NCHS standards. A reliable WHZ was only available for 1442 admissions (88.7%), due mainly to missing lengths, particularly from fatal and/or brief admissions. This was due to the effort made to record all kwashiorkor admissions to the NRCs and especially not to miss fatal cases with incomplete data.

The constraints of working in this environment meant that observations and measurements such as weight, length, oral intake, diarrhoea frequency and vital signs were not as accurate as in a research ward, so internal validity was sacrificed for external validity. Reliable microbiology and biochemistry tests were not available. Doctors were not available to look after malnutrition cases at district and rural NRCs, so other than the paediatric visits, they were cared for by a nurse with minimal support from a clinical officer or medical assistant. Clinical data were collected on admission and on the twice-weekly round by nurses at rural clinics, by clinical officers at hospitals and by the authors in Blantyre.

The ELISA test for HIV infection was only done in 354 children (21.8%) in the study, because only those with clinical indications (other than malnutrition) were tested and only after pre-counselling. The requirement for detailed informed consent in this setting made us reluctant to subject families to this process without clinical suspicion, and permission to test was frequently refused and sometimes resulted in the child being taken from hospital before discharge. However, we developed clinical guidelines for the diagnosis of probable HIV infection in severe

malnutrition, based on the scientific literature and local experience with ELISA testing in malnutrition. There were no significant differences in clinical variables between HIV cases diagnosed clinically and by ELISA test. The clinical protocol diagnosed another 164 untested children, which combined with the 189 positive ELISA tests (53.4%) was consistent with an HIV infection rate in project patients of 21.7% (353/1625).

Data were entered in Epi Info version 6 (World Health Organization/Centers for Disease Control, USA) on a portable computer, with anthropometric z-scores calculated by EpiNut within Epi Info. Variables which were not normally distributed, such as age and length of stays, were log transformed for analyses and are presented as geometric means and 95% confidence intervals (CI). Hyphenated values in parenthesis (for example 3.4–5.6) are CI unless otherwise specified. For normally distributed quantitative variables with homogeneity of variance (Bartlett's test), means were compared by ANOVA. Categorical variables were compared by Chi square (Yates corrected  $\chi^2$ ). Multiple linear and logistic regressions were analyzed using Epi Info Analysis and EGRET (Statistics & Epidemiology Research Corporation, Seattle, USA), respectively. There were missing values from many of the brief admissions due to early death or leaving before discharge, which were excluded from regression models. The *F*-test (in Table 4) measures the ratio of the variance explained by the independent variable to the residual mean square variance in the final model.

## Results

There were 1625 consecutive cases of kwashiorkor treated at the seven NRCs during the study period, including 901 (55.4%) at central hospitals, 351 (21.6%) at district hospitals and 373 (23.0%) at rural clinics. It was obvious both clinically and from the data in Tables 1 and 2 that the children treated at the three kinds of facilities differed in some important respects. On average, central hospital patients were younger, sicker, had a longer history of illness and were from families of higher socio-economic status than those from rural clinics. This is reflected in case-

fatality rates, which were 30.5% at central hospitals, 25.8% at district hospitals and 7.5% at rural clinics. The proportions of late deaths after 5 days treatments at NRCs (Table 3), as an indicator of the quality of case management, were 71% (rural), 52% (district) and 35% at central NRCs ( $\chi^2 P=0.006$ ). The proportion of patients diagnosed clinically as sepsis and treated with an antibiotic other than routine co-trimoxazole was much higher in central hospital patients (Table 3), reflecting both closer monitoring of patients and more severe illness. Central hospital patients also had earlier resolution of oedema, better weight gain, and shorter lengths of stay than those at district or rural NRCs (Table 3).

On multiple linear regression of admissions longer than 5 d, the risk factors for poor weight gain (controlling for length of stay, weight and season) were: slow oedema resolution, no tube-feeding, absence of wasting, use of a milk-free maize-based diet and HIV infection (Table 4). Out of the 1356 admissions of a least 5 d, 280 (20.6%) had no weight gain in hospital and another 65 (4.8%) had no repeat weight recorded. There were no differences in WHZ, HAZ, socio-economic status score, age or sepsis incidence between those with and without weight gain. However, the group without weight gain vs those who did gain weight had a longer mean duration of diarrhoea in hospital (4.1 vs 3.5 d, ANOVA  $P=0.01$ ), a shorter length of stay (13.9 vs 18.6 d,  $P=0.000001$ ), a higher rate of HIV infection (26.4% [91/345] vs 18.7% [189/1011],  $\chi$ ,  $P=0.003$ ) and a higher case-fatality (35.1% [121/345] vs 8.0% [81/1011],  $\chi$ ,  $P=0.000000001$ ).

The central hospital NRC in Zomba used routine nasogastric tube-feeding of all kwashiorkor admissions, but otherwise used the same case management protocol as other NRCs. Tube-feeding was not used elsewhere due to refusal by mothers, who associated it with death (since it was reserved for severely anorexic cases). It was important to evaluate this difference in feeding regimes, since it might be considered unethical as a randomized study design. Table 5 shows that although there was little difference in mortality, tube-fed cases had significantly (ANOVA  $P=0.000001$ ) greater weight gain in hospital than the Blantyre NRC (8.24 vs 4.51 g/kg/d). This improved

**Table 1** Baseline admission data of NRC patients by facility type

Parameter	Central Hospitals	District Hospitals	Rural Clinics	P-value*
Number of cases ( $n=1625$ )	901	351	373	
Male sex (%)	477 (52.9)	168 (48.0)	182 (48.8)	0.19**
Household members (CI)	4.9 (4.8–5.0)	5.0 (4.8–5.2)	4.9 (4.7–5.1)	0.53
Father died (%)	62 (7.3)	33 (10.4)	38 (10.7)	0.08**
Mother died (%)	61 (7.1)	21 (6.6)	24 (6.7)	0.93**
Chron. ill patient (%)	121 (13.7)	49 (14.9)	35 (9.7)	0.09**
Prev. child death (%)	334 (39.7)	145 (46.0)	166 (46.3)	0.04**
$\geq 2$ child deaths (%)	128 (15.2)	78 (24.8)	62 (17.3)	0.001**
Prev. malnutrition (%)	166 (18.5)	86 (25.4)	60 (16.9)	0.008**
Age (months) <sup>a</sup>	26.7 (25.8–27.6)	29.0 (27.3–30.7)	29.4 (27.9–31.1)	0.003
Socio-economic score <sup>a</sup>	17.5 (16.7–18.5)	13.6 (12.4–14.9)	15.2 (14.3–16.2)	0.00001
Hospital travel time in min (CI)	69 (66–73)	130 (116–146)	102 (43–113)	0.000001
Water collection-min/day (CI)	33 (31–36)	51 (46–57)	62 (57–67)	0.000001
Access to tapwater (%)	463 (55.5)	67 (21.2)	80 (22.5)	0.000001**
Days diarrhoea PTA (CI)	5.9 (5.4–6.4)	4.6 (4.0–5.3)	3.1 (2.7–3.6)	0.000001
Days oedema PTA (CI)	11.1 (10.4–11.8)	12.6 (11.4–14.0)	8.3 (7.5–9.1)	0.000001
Father's years schooling (CI)	6.5 (6.3–6.7)	3.9 (3.5–4.3)	4.6 (4.2–5.0)	0.000001
Mother's years schooling (CI)	4.0 (3.8–4.2)	2.1 (1.8–2.4)	2.4 (2.1–2.7)	0.000001

<sup>a</sup> geometric means (95% confidence intervals-CI); PTA=prior to admission.

\* P-values are ANOVA for quantitative measurements.

\*\* Correct Chi square for categorical measures.

**Table 2** Clinical findings on admission by facility

Clinical feature	Central Hospitals		District Hospitals		Rural Clinics		P-value*
No kwash. rash (%)	315	(35.4)	126	(38.0)	206	(56.7)	0.0000001
Severe kwash. rash (%)	266	(29.9)	119	(35.8)	69	(19.9)	0.000001
Hair changes (%)	641	(72.2)	263	(79.5)	272	(74.3)	0.04
Hepatomegaly (%)	226	(25.7)	36	(11.2)	47	(13.5)	0.0000001
Splenomegaly (%)	84	(9.6)	33	(10.2)	40	(11.5)	0.60
Oral thrush (%)	236	(26.8)	70	(21.7)	41	(11.8)	0.0000001
Irritability (%)	759	(87.0)	193	(60.5)	211	(60.7)	0.00000001
Cough (%)	497	(56.3)	141	(41.6)	163	(44.3)	0.0000007
Severe oedema (%)	328	(36.5)	89	(26.2)	61	(16.5)	0.000000001
Diarrhoea (%)	459	(51.1)	228	(66.3)	191	(51.5)	0.000004
Diarrhoea $\geq$ 3/day (%)	315	(38.8)	171	(55.0)	122	(35.7)	0.000000
Fever (%)	407	(46.1)	167	(49.3)	193	(52.4)	0.12
Wasting z-score ( $\pm$ s.e.m.)	-2.092	( $\pm$ 0.04)	-2.125	( $\pm$ 0.06)	-1.697	( $\pm$ 0.06)	0.000005**
Stunting z-score ( $\pm$ s.e.m.)	-3.577	( $\pm$ 0.05)	-3.415	( $\pm$ 0.08)	-3.276	( $\pm$ 0.08)	0.003**

\* P-values are Chi square for categorical measures.

\*\* ANOVA for quantitative measurements.

**Table 3** Clinical outcomes by facility

Outcomes	Central Hospitals		District Hospitals		Rural Clinics		P-value*
Number of deaths (%)	275	(30.5)	90	(25.8)	28	(7.5)	0.00000001**
0-5 days (%)	170	(61.8)	43	(47.8)	8	(28.6)	
6-10 days (%)	55	(20.0)	19	(21.1)	6	(21.4)	0.0004**
> 10 days (%)	50	(18.2)	28	(31.1)	14	(50.0)	
mean days <sup>a</sup> (CI)(%)	5.8	(5.2-6.4)	10.2	(7.6-12.8)	14.9	(9.1-20.7)	0.00001
Left NRC before discharge (%)	139	(15.4)	21	(6.0)	38	(10.1)	0.00001**
Transfer to other facility (%)	0		2	(0.6)	43	(11.5)	0.00000001**
Clinical sepsis (%)	420	(46.8)	83	(26.1)	76	(21.3)	0.00000001**
Days of diarrhoea at NRC <sup>a</sup> (CI)	2.6	(2.5-2.7)	2.6	(2.5-2.9)	2.0	(1.9-2.2)	0.0000001
Days for oedema to resolve (CI)	6.9	(6.5-7.2)	8.1	(7.5-8.8)	9.9	(9.2-10.6)	0.000000
% Weight loss of oedema (CI)	11.2	(10.5-11.9)	9.8	(8.7-10.9)	8.7	(7.7-9.7)	0.0008
HIV prevalence (%)	235	(26.1)	32	(14.2)	86	(17.2)	0.000008**
Gained weight in hospital (%)	553	(64.5)	230	(75.4)	252	(77.3)	0.000005**
Weight gain in g/kg/d <sup>a</sup> (CI)	11.2	(10.4-12.0)	7.1	(6.4-7.9)	6.4	(5.8-7.2)	0.0000001
Length of stay in days (CI)	11.2	(10.6-11.8)	20.2	(18.5-21.9)	19.0	(17.6-20.4)	0.0000001

<sup>a</sup> Geometric means (95% confidence intervals-CI).

\* P-values are ANOVA for quantitative measurements.

\*\* Chi square for categorical measures.

weight gain with tube-feeding was most evident during the wet season (8.5 vs 3.8 g/kg/d) but also occurred in the dry season (7.8 vs 5.5 g/kg/d,  $P < 0.006$ ) and remained significant when controlled for other confounders (Table 4).

Diarrhoea was present on admission in 54% (878/1625) of children, of whom 429 (48.9%) had a history of persistent diarrhoea (> 14 d). The mean duration of diarrhoea during hospitalization was only 2.5 d (2.4-2.6), which did not affect mortality (after 5 d) or weight gain on nutritional rehabilitation. However, prolonged diarrhoea in hospital was associated with greater initial weight loss, early death, HIV infection and wasting, when controlled for facility type, admission diarrhoea and length of stay.

Wasting was present in 52.1% (751/1442) of admissions after resolution of oedema. It was more common at central and district hospitals, in younger children and during the rainy season. Cases of marasmic-kwashiorkor had a higher mortality, greater weight gain, less oedema on admission and a longer length of stay (Table 4). Wasting was still present at discharge in 21.2% (191/899, excluding deaths, transfers and those who absconded). There was a 38.6% mortality rate in the 184 cases in whom WHZ could not be calculated due to missing values, often because of early death.

HIV infection (including clinically diagnosed cases) had a higher case-fatality rate at NRCs (37.4%, 132/353) than presumed negative cases (20.5%, 261/1272), for an odds ratio of 2.3 (1.8-3.0). HIV infection was also associated with significantly more wasting (-2.3 vs -1.9 z-scores, ANOVA  $P = 0.00006$ ) and stunting (-3.8 vs -3.4  $P = 0.0002$ ) and less weight gain in hospital (4.29 vs 5.18 g/kg/d,  $P = 0.009$ ) than non-HIV cases of kwashiorkor. On logistic regression, HIV infection was more common with death, stunting, younger age, clinical sepsis and chronic diarrhoea (Table 7). The strength of these associations is likely to be underestimated in this model, since 174 cases were excluded due to missing heights, including 54 HIV-infected deaths. Kwashiorkor was diagnosed in 121 breastfed children in this series with a mean age of 15.6 months (14.5-16.8). The ELISA test for HIV was positive in 38 breastfed children (14 infants) out of 55 tested and another 55 were diagnosed clinically as HIV infection, giving an odds ratio of 15.9 (10.0-15.7) for HIV infection in breastfed kwashiorkor cases.

The extent of seasonal variation in admissions is indicated in Table 6 in order to illustrate its importance in this data. The dry season months (July-December) had fewer admissions, a longer length of stay and a higher mortality;

**Table 4** Multiple regressions for weight gain, length of stay, diarrhoea duration and wasting

<i>Dependent Variable (increasing)</i>	<i>Independent variables (direction)</i>	<i>Partial F-test<sup>b</sup></i>	<i>% variance explained</i>
1. Weight gain (grams) ( <i>n</i> = 1357) <sup>a</sup> <i>F</i> = 85.6 <i>P</i> < 0.001	Length of stay (longer)	540.9	38.9
	<b>Time to get to lowest weight (less)</b>	211.8	
	<b>Tube-feeding</b>	41.6	
	Weight (greater)	31.1	
	<b>Wasting</b>	20.1	
	<b>Milk diet</b>	11.8	
	<b>Early weight loss of oedema (more)</b>	11.5	
	<b>HIV infection (negative)</b>	8.8	
	<b>Nutriset supplement</b>	7.5	
	Season (dry)	5.9	
	2. Length of stay ( <i>n</i> = 1368) <i>F</i> = 100.0 <i>P</i> < 0.001	Weight gain (less)	
<b>Diarrhoea in hospital (more)</b>		172.6	
Facility (rural-district-central)		80.1	
Survival (non-death)		60.5	
Age (younger)		19.0	
Socio-economic status (lower)		13.8	
<b>Previous malnutrition admission</b>		11.6	
<b>Sepsis</b>		7.3	
Diarrhoea on admission		83.6	
<b>Early weight loss of oedema (more)</b>		65.5	
3. Duration of diarrhoea in hospital ( <i>n</i> = 1324) ( <i>F</i> = 43.4) <i>P</i> < 0.001		Facility (central-district-rural)	24.5
	<b>Season (dry)</b>	17.3	
	<b>Death</b>	15.9	
	<b>Wasting</b>	14.9	
	Length of stay (longer)	13.5	
	Time to lowest weight (greater)	7.9	
	<b>HIV infection</b>	7.1	
	<b>Tube-feeding (none)</b>	4.5	
	Younger age	110.2	
	<b>Death</b>	66.5	
	Facility (central hospitals)	25.4	
4. Wasting (wt/ht z-score) ( <i>n</i> = 1352) <i>F</i> = 37.2 <i>P</i> 0.001	<b>More weight gain in hospital</b>	23.4	18.3
	<b>More wasting in hospital</b>	20.0	
	<b>Less severe oedema on admission</b>	18.7	
	Season (rainy)	17.8	
	<b>Longer length of stay</b>	11.8	

<sup>a</sup>excluding admissions < 5 days and those with missing values.<sup>b</sup>See methods for an explanation of the partial *F* test.The **bold** independent variables are the clinically important ones.

whereas diarrhoea and wasting were worse in the wet season (January–June). The introduction of Nutriset was associated with improved weight gain (6.06 vs 4.66 g/kg/d) and a lower mortality (20.8 [110/529] vs 25.8% [283/1096]), which remained significant despite controlling for confounders such as season (Tables 4 and 7).

## Discussion

### The Setting

Malawi is a landlocked country in eastern Central Africa with a population of 10.5 million which is growing at a rate of 3.7% annually (Kalipeni, 1993). This expanding population is exerting pressure on land and natural resources due to one of the highest population densities in Africa at 104 people/km of land, rising to over 250 in the southern region where this project was carried out. Malawi is one of the poorest countries in Africa with an estimated GNP per capita of US \$200 in 1993 before there was a precipitous fall in the value of currency (Anonymous, 1995). Early childhood mortality rates (per 1000) remain high at 134–142 for infants and 223–234 for children under-five years (Anonymous, 1994; Anonymous, 1995).

Recent community nutrition surveys in Malawi have reported a high community prevalence of stunting and

marked seasonal fluctuations in kwashiorkor prevalence. In a study of 1242 children aged 24–59 months, the prevalence of stunting was 69.3% for poor urban children and 83.2% for rural children (Quinn *et al*, 1995). The mean prevalence of kwashiorkor out of hospital was 18 per 1000, peaking at 18–23 months of age and during the rainy season from December to March (Courtright, Canner, 1995). There is considerable seasonal variation in wasting with a rise in prevalence from 1.5% in the postharvest dry season to 2.8% in the preharvest rainy season (Ashworth and Dowler, 1991). In terms of hospital data (Mbewe, 1993), severe malnutrition was the final diagnosis in 11% of all paediatric admissions in Blantyre in 1992–93, with a case fatality of 36.4% (378/1039).

Access to health services in Malawi is good, since 80% of households are within 8 km of a health unit. Full immunisation coverage is achieved (BCG, triple antigen, polio, measles) in 82% of children by 12–23 months (Anonymous, 1993). The Ministry of Health has 24 district or central hospitals, but health budgets are grossly inadequate. The low level of utilisation of curative health services is compounded by the poor quality of service, drug shortages and use of traditional healers. There is a severe shortage of trained health personnel in Malawi, with personnel to population ratios of 1:50 360 for doctors and 1:1 980 for registered nurses (Anonymous, 1995). The

**Table 5** Comparison of routine tube-feeding vs none at central hospitals

Feature n =	Blantyre NRC 748	Zomba NRC 153	P-value*
Nasogastric tube-feeding	nil	routine	
<i>Baseline:</i>			
Age (months) <sup>a</sup>	26.7 (25.8–27.7)	26.5 (24.2–29.1)	0.87
Socio-economic score <sup>a</sup>	22.2 (21.8–22.7)	19.8 (19.0–20.6)	<b>0.003</b>
Weight/height z-score	–2.06 (–1.97, –2.13)	–2.28 (–2.06, –2.50)	<b>0.04</b>
Height/age z-score	–3.56 (–3.45, –3.67)	–3.67 (–3.55, –3.79)	0.59
Diarrhoea on admission(%)	387 (51.9)	72 (47.1)	0.31**
Breastfed (%)	43 (5.9)	12 (7.8)	0.46**
Days of oedema PTA	15.3 (14.2–16.4)	21.4 (17.8–25.0)	<b>0.0002</b>
Days of diarrhoea PTA	12.3 (11.1–13.5)	10.4 (8.0–12.8)	0.19
<i>Results:</i>			
Death (%)	227 (30.3)	48 (31.4)	0.88**
Length of stay in hospital (days)	10.6 (10.1–11.2)	14.1 (12.2–16.0)	<b>0.005</b>
Days of diarrhoea in hospital	3.36 (11.1–13.5)	3.19 (2.7–3.7)	0.57
Days of oedema resolution	5.0 (4.6–5.5)	5.5 (4.8–6.2)	0.66
Day of lowest weight	5.8 (5.4–6.2)	6.0 (4.7–7.2)	0.73
Given antibiotic for clinical sepsis (%)	365 (48.8)	55 (36.7)	<b>0.009**</b>
Weight gain (g/kg/d) <sup>a</sup>	4.51 (4.09–4.93)	8.24 (6.63–9.86)	<b>0.000001</b>

<sup>a</sup> Geometric means (with 95% confidence intervals).

\* P-values are ANOVA for quantitative measurements.

\*\* Chi square for categorical measures.

PTA = prior to admission.

Statistically significant P-values are in **bold**.

**Table 6** Seasonal variations in admissions

Season	Jan–Mar (wet)	Apr–Jun	Jul–Sep (dry)	Oct–Dec
n =	<b>578</b>	519	311	218
Mortality (%)	168 (29.1)	115 (22.2)	46 ( <b>14.8</b> )	64 (29.4)
Diarrhoea on admission (%)	353 ( <b>61.5</b> )	223 (43.5)	167 (54.2)	135 (61.9)
Days diarrhoea in hospital <sup>a</sup>	3.1 ± 0.2	2.8 ± 0.2	<b>4.1</b> ± 0.2	3.5 ± 0.2
Length of stay <sup>a</sup>	13.3 ± 0.5	15.7 ± 0.5	<b>17.5</b> ± 0.7	14.1 ± 0.7
WHZ at lowest weight <sup>a</sup>	–2.21 ± 0.05	–2.00 ± 0.05	– <b>1.61</b> ± 0.07	–2.09 ± 0.08
WHZ on discharge <sup>a</sup>	–1.78 ± 0.05	–1.42 ± 0.06	– <b>0.80</b> ± 0.07	–1.35 ± 0.09
mean z-score increase/day	0.032	0.037	<b>0.046</b>	<b>0.052</b>
Wt gain (g/kg/d)	4.11 ± 0.27	4.85 ± 0.29	<b>5.49</b> ± 0.30	<b>5.57</b> ± 0.09
Days to lowest weight <sup>a</sup>	<b>5.6</b> ± 0.25	6.9 ± 0.36	6.7 ± 0.36	6.2 ± 0.40
Oedema resolution (days) <sup>a</sup>	8.4 ± 0.29	9.5 ± 0.30	9.0 ± 0.36	<b>7.0</b> ± 0.36

<sup>a</sup> ± s.e.m.

WHZ = weight for height z-score.

Notable differences are in **bold**.

**Table 7** Logistic regressions for death, sepsis and HIV infection

Dependent variable	Independent variables	Odds Ratio	95% CI	P-value
1. Death (n = 1373)	Clinical sepsis	3.2	2.4–4.4	< 0.001
	Diarrhoea on admission	2.5	1.8–3.4	< 0.001
	No Nutriset supplement	2.0	1.4–2.7	< 0.001
	Facility (central-district-rural)	1.9	1.5–2.3	< 0.001
	HIV infection	1.9	1.3–2.6	< 0.001
	Wasting (WHZ)	1.3	1.1–1.5	< 0.001
	2. Sepsis (n = 1365)	Death	3.9	2.6–5.0
Facility (central-district-rural)		2.0	1.7–2.5	< 0.001
Length of stays in days (longer)		1.03	1.01–1.04	< 0.001
Days diarrhoea in hospital (longer)		1.07	1.04–1.11	< 0.001
Fever on admission		1.6	1.3–2.1	< 0.001
Wasting (WHZ)		1.3	1.1–1.4	< 0.001
Season (dry)		1.4	1.1–1.9	< 0.001
HIV infection		1.5	1.1–2.0	0.007
3. HIV Infection (n = 1373)	Oedema, 0 to 3+ (more severe)	1.2	1.01–1.39	0.034
	Death	2.1	1.7–3.2	< 0.001
	Stunting (HAZ)	1.4	1.3–1.6	< 0.001
	Age in months (younger)	1.04	1.03–1.05	< 0.001
	Sepsis	1.6	1.2–2.1	0.002
	Days diarrhoea in hospital (longer)	1.04	1.0–1.1	0.027

WHZ = weight/height z-score.

HAZ = height/age z-score.

establishment of the University of Malawi College of Medicine in Blantyre should gradually reduce the doctor shortage and upgrade the level of clinical practice.

Finally, any discussion of child health in Malawi would be incomplete without mentioning HIV infection. According to recent data from the Johns Hopkins research project, (Taha *et al*, 1994; Miotti *et al*, 1992; Taha *et al*, 1995) the prevalence of HIV infection among pregnant women in Blantyre over the last three years has been stable at 30.2%. The relative risk of child mortality by 30 months for HIV-positive mothers compared to HIV-negative mothers is 5.0 (3.2–7.8) (Taha *et al*, 1995). Since the mother-to-infant transmission rate by PCR was 27.4% at birth in Blantyre, it is likely that about 10.6–12.5% of all births are infected *in utero*, intrapartum or postnatally through breastfeeding. It is hardly surprising, therefore, that HIV infection has transformed paediatric practice in Malawi, particularly in relation to malnutrition.

#### Clinical data

This paper presents descriptive clinical data on a large number of kwashiorkor patients studied prospectively in hospital in an attempt to apply nutritional knowledge to improve hospital outcomes. The statistical methods used to present the data are only intended to clarify possible associations of clinical significance. The variables selected are well-recognised clinical outcomes such as death, length of stay, duration of diarrhoea and anthropometric indices. Although Tables 4 and 7 present the data as regression models, they are presented as associations without implying causality. Indeed, the data need to be interpreted with caution because of the marked seasonal variations presented in Table 6. We have previously documented the importance of seasonal variation in paediatric admissions in a west African setting (Brewster and Greenwood, 1993).

The differences between the three levels of NRC facilities (central, district and rural) presented in Tables 1–3 indicate that central hospital patients tended to be sicker, have higher socio-economic status and give a longer history of illness than rural clinic patients. The anomaly of less travel time to central hospitals does not mean that central hospital patients lived in nearby urban areas, but rather that travel times from referring clinics to central hospitals involved greater distances but shorter travel times by road transport. The lower mortality at rural clinics reflects both less severe disease and transfer of sicker cases to larger NRCs. The rural NRCs tend to become feeding centres due to less pressure on beds, with longer stays of less severe kwashiorkor cases than at district or central NRCs. In addition to less severe disease, the lower rate of clinical sepsis at district and rural facilities may be related to under-diagnosis because of less clinical supervision. Ascertainment bias may also apply to differences in hepatosplenomegaly, since the authors could not see every case at district and rural NRCs.

The best predictors of weight gain in hospital on nutritional rehabilitation were prompt oedema loss, more severe wasting and treatment with nasogastric tube-feeding. Although tube-feeding improved weight gain, it is associated with an increased risk of aspiration pneumonia when nursing care is limited. This may have contributed to the high mortality in Zomba (31.4%), since we expected a lower mortality than in Blantyre. It is easy to see why more severe wasting was associated with better catch-up weight gain, but more severe oedema on admission was associated

with less wasting after the oedema had resolved (ANOVA  $P=0.003$ ) and less weight gain with treatment. This is due to early discharge of kwashiorkor cases without wasting (so called 'sugar babies'), who had more severe oedema. Thus, severe oedema was present on admission in 25.5% (179/729) of wasted children compared to 33.9% (78/230) for those above  $-1$  z-scores on WHZ ( $\chi^2$ ,  $P=0.007$ ).

HIV-infected cases of marasmic-kwashiorkor had a higher mortality, more stunting, less oedema, higher socio-economic status and lower weight gain than non-HIV cases. The better socio-economic status at central hospitals is partly related to the higher rate of HIV infection (26.1 vs 16.3%, Table 3), which is a more likely cause of malnutrition in better off families than in those living in dire poverty. Thus, the mean socio-economic score for HIV cases was 19.8 (19.0–20.6) compared to 18.6 (18.2–19.3) for non-HIV cases ( $\chi^2$ ,  $P=0.005$ ). However, the socio-economic score was a poor discriminator because of the uniformly low status of project families. Kwashiorkor is normally a disease of the weaning period and is most uncommon in breastfed children, so it is notable that we recorded it in 121 children (7.4%) in this project, including 44 infants. The association of breastfeeding with HIV infection was striking, illustrating that kwashiorkor is a final common pathway for many conditions, including HIV infection, in this setting.

A recent Conference on the treatment of childhood malnutrition in refugee camps recommended that if HIV testing was done at all, it is best delayed until after nutritional rehabilitation (Briend and Golden, 1993). This approach may be ethically correct for donor-funded feeding programmes, but it does not promote good clinical practice. Case management at NRCs must be based on accurate diagnoses, since malnutrition may result from many disease processes. Nutritional rehabilitation is expensive and should be targeted to those most likely to benefit. Malawi's child health care services can ill afford the luxury of hospitalizing all wasted HIV cases until death, nor is it in keeping with the desires of affected families.

The presence of oedema in kwashiorkor makes it difficult to compare our weight gain data to regions where marasmus predominates, since many kwashiorkor cases are not wasted, so cannot be expected to demonstrate catch-up growth. Moreover, the time for oedema loss and short length of stays also make comparisons of weight gain on a g/kg/day basis problematic. The 1076 children in this project who gained weight after a least five days in hospital had a mean gain of 7.0 g/kg/d (6.6–7.3). By comparison, an Oxfam study of relief feeding of 44 children (20 kwashiorkor) in Ethiopia reported only six deaths and a mean weight gain of 14.4 (11.2–17.6) g/kg/d for kwashiorkor with a mean length of stay of about 30 d (Mason *et al*, 1974). However, the Oxfam study calculated weight velocity from the time of minimum weight in kwashiorkor. The comparable figures for our patients would be 13.6 g/kg/d (12.3–14.8) for weight gain after the initial oedema loss and the mean length of stay of 18.6 d (17.8–19.3). Indeed, our weight gain would increase even further to 15.9 if only wasted cases were counted or to 28.0 g/kg/d for only tube-fed children. But it is important to bear in mind that we were orientated to clinical resolution of illness rather than to complete catch-up growth, particularly at central hospitals with their short mean lengths of stay. But a quarter of our discharged cases (345/1356) either had no weight gain in hospital or at least no documented weight gain due to missing values, and weight gain in this study was calcu-

lated on the basis of every hospital day including the days for oedema resolution.

#### *Nutriset supplements*

Evaluation of the micronutrient supplement (Nutriset) in this setting was complicated by methodological constraints. Although these supplements were not available before the project, we felt uncomfortable about using a placebo preparation in view of the known benefits of potassium and zinc. The introduction of the supplement during the project was also complicated by seasonal variation, although we tried to control for this on regression. But we wish to stress that this was an intervention project, so we wanted to observe the effect of introducing the Nutriset supplement in this setting. Anecdotally, there was a striking improvement in the anorexia and irritability of kwashiorkor cases with the introduction of Nutriset. We suspect that this was mainly related to zinc supplementation, since its introduction alone (40 mg/d) in Blantyre, just before Nutriset arrived, had a clinically obvious effect. Other studies in Malawi have shown zinc to be a limiting factor in the maize-based diets of children due to its high phytate content (Gibson, 1994; Ferguson *et al*, 1993; Ferguson *et al*, 1989).

There was a significant fall ( $\chi$ ,  $P=0.03$ ) in deaths after introducing the Nutriset with case-fatality rates of 25.8% (283/1096) before its use compared to 20.8% (110/529) after. This effect of Nutriset on mortality occurred despite controlling for seasonal factors on logistic regression (Table 7). We have documented a lowering of late mortality with higher potassium supplementation in a randomised trial (Manary and Brewster, 1997), but there is insufficient potassium in Nutriset for phase 1 treatment. The apparent effect of Nutriset on weight gain was particularly striking (ANOVA  $P=0.00003$ ) for Blantyre and Ntcheu with 3.73 g/kg/d (3.3–4.1) before *vs* 5.4 (4.8–6.0) after its introduction. The effect was less obvious at NRCs with routine tube-feeding (Zomba), good nursing care (Mwanza, because of expatriate nursing support) or erratic milk supply (Namitambo). This suggests that an important impact of the micronutrient supplement was on anorexia, which could be attributed to the known effect of zinc supplementation on appetite, but especially at centres with less supervised feeding where appetite determined intake. Although these results are confounded by seasonal variations, when controlled for month of admission, the admissions receiving Nutriset still had higher weight gain than those before Nutriset was introduced. Although we are still not confident that the effect of Nutriset could be separated from seasonal factors, we are convinced of the clinical benefit of Nutriset in kwashiorkor.

#### *Paediatric supervision of NRCs*

An important component of this project was paediatric visits and supervision of NRCs. As expected, it was very difficult to isolate this effect from the other factors affecting outcomes in our data. It would have been interesting to compare our results to control NRCs without supervision, but reliable data would be difficult to obtain without providing supervision. Nevertheless, by doing the project, we gained insights into the practical problems of treating kwashiorkor at the three levels of NRCs in Malawi, which we believe should be presented along with our data. We have to report that our clinical impressions of the impact of the project on case management and mortality was disappointing. This is not to deny that there were

undocumented benefits, such as fewer referrals to central hospitals and less isolation of district and rural health workers.

The reasons for these limited results, in our assessment, are: (1) too many constraints to improvements which the project could not address, (2) visits every 2–4 weeks were too infrequent to improve the level of care, (3) lack of skilled and motivated health workers, (4) milk powder and antibiotic shortages, and (5) the severity of kwashiorkor in this region. Our extensive international experience of treating malnutrition convinces us that kwashiorkor in this part of Africa is more severe than in other regions of the world, which is another important contributor to the poor outcomes. The difficulty of lowering mortality with improved case management of kwashiorkor is illustrated by a six week period of intensive nursing and medical care at the Blantyre NRC with extensive use of expensive antibiotics, which only reduced the mortality by modest proportions from 30.5–27.5% (11/40). It did, however, significantly improve mean weight gains to 6.7 g/kg/d (4.8–8.6) with the use of tube-feeding during initial management. This illustrates that more than just minor case management adjustments are needed to reduce the mortality of kwashiorkor cases at NRCs. Of course, prevention of kwashiorkor would be preferable, but interventions of proven effectiveness such as supplementary feeding are far too expensive.

In conclusion, we make the following recommendations to improve case management of kwashiorkor. A micronutrient supplement such as Nutriset should be provided to all NRCs along with the milk powder and vegetable oil. Additional potassium, however, is needed for phase 1 milk (initiation of cure) in order to provide 8 mmol/kg/d (Manary and Brewster, 1997). Routine tube-feeding of milk-based diets should be instituted for all children with wasting and anorexia. This requires good nursing care to prevent aspiration pneumonia, so should only be instituted at central or district level. In view of the limited health resources, it would be better to reduce the number of NRCs managing kwashiorkor, but provide adequate resources and supervision to those at central and district level. There are no easy solutions, but improved case management of kwashiorkor will not occur without better motivation and supervision of health workers. The level of supervision needed was greater than we could provide by visits in this project. The emphasis must shift from new protocol development to how to actually implement feasible protocols which improve outcomes at NRCs in the developing world. We must advance from protocols to actual practice.

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