Title

A critical evaluation of the appetite test for children with severe acute malnutrition

Short title

The appetite test in severe acute malnutrition

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Abstract

Objectives

The appetite test is used to risk-stratify for children with severe acute malnutrition (SAM) in in-patient or out-patient care. The test is recommended in guidelines despite lack of evidence. We evaluated its ability to identify children at risk of a poor treatment outcome.

Methods

We conducted an observational study of children diagnosed with SAM at three health facilities in Ethiopia. The appetite test was done independently of the routine staff, and the result did not affect decisions about hospitalisation and clinical care. Data was analysed using mixed linear and logistic regression models.

Results

The appetite was tested in 298 (89%) of the 334 children enrolled; 56 (19%) passed. Children failing the appetite test had a 6·6% higher weight gain per day (95% CI 2·6, 10·8) adjusted for type of treatment, oedema, duration of follow up, and age than children passing the test. We found medical complications in 179 (54%) children. Medical complications were associated with blood markers of metabolic disturbance. Children with medical complications tended to have lower weight gain than those without complications (3·5%, 95%CI -0·25, 7·0). Neither the appetite test nor medical complications were correlated with bacteraemia or treatment failure.

Conclusions

Our findings question the use of the appetite test to identify children who need in-patient care. An assessment of medical complications alone could be a useful risk indicator but needs to be evaluated in other settings.

Keywords

Severe acute malnutrition; appetite; community management; risk assessment; therapeutic foods

Background

Severe acute malnutrition (SAM) is a condition with high mortality mostly affecting children in low- and middle-income countries (1). It is recommended that children with SAM and either poor appetite or medical complications should be hospitalized, while children with good appetite and no medical complications can be treated as out-patients with ready-to-use therapeutic foods (RUTF) (2, 3). Originally, appetite was assessed roughly to help decide if a child could be treated with RUTF (4). Later appetite assessment was standardized and included in the guidelines for treating children with SAM to identify children that could be treated as out-patients (5-7). A failed "appetite test" is now used as a proxy for sepsis or major metabolic abnormality, defined as *"liver dysfunction, electrolyte imbalance, and cell membrane damage or damaged biochemical pathways"* (5) and therefore risk of poorer treatment response and need for hospitalization.

Limited information is available on appetite in malnourished children and the rationale behind the test is a proposed link between infection and food intake, and the fact that severe infections cause anorexia (8-10). The authoritative emphasis placed on the appetite test in international and national guidelines is not based on scientific evidence (3, 5). The World Health Organization (WHO) acknowledges this and recommends that validating the appetite test should be a research priority (3). A recent review of methods for appetite assessment did not find any studies that have clinically validated the appetite test (11). The test is complex and time-consuming and a cut-off for appetite to reliably identify children in need of hospitalization has not been established.

We here present the first clinical study to evaluate the ability of the appetite test to identify children with SAM in need of hospitalization. Our objective was to evaluate the usefulness of the test for identifying SAM children with sepsis or major metabolic abnormality, and to determine if the appetite test can identify children with poorer treatment outcomes and need for hospital admission. The secondary objective was to evaluate alternative versions of the appetite test and other prognostic markers for complications including a simple algorithm for medical complications.

Methods

Study design and participants

The study was conducted in three health facilities in Ethiopia. Jimma University Specialized Teaching Hospital (JUSTH) treated children that were referred from lower level health facilities or came directly to the hospital. Serbo Health Centre (SHC) covered a neighbouring rural area and received patients directly or referred from community health workers. The Missionaries of Charity Clinic (MiCC) in Jimma town received patients directly from the town and surrounding rural area. In JUSTH and MiCC all children with SAM were admitted, regardless of severity of the disease. ~~Patients~~ Children with SAM were enrolled at JUSTH from June 2016 and we expanded to SHC in February 2017 and to MiCC in June 2017, because of a lower caseload than expected. We reached the target sample size of 330 children in May 2018. The enrolled children were treated according to the national protocol (12), based on recommendations of the WHO (3), using F-75 (Aspen nutritionals, Pharmacare, South Africa), F-100 (Nutriset, Malaunay, Frace), or RUTF (Plumpy'Nut™, Nutriset, Hilina Enriched Foods, Addis Ababa, Ethiopia) and empiric antibiotic treatment with amoxicillin (50-100 mg/kg/d) with the addition of gentamicin (5 mg/kg/d) for in-patients. Most children were treated for a few days with F-75 and F-100 before changing to RUTF, irrespective of their signs and symptoms. It was not routine clinical practice to use the appetite test in the study sites; in JUTSH and MiCC all children with SAM were admitted for in-patient care, irrespective of severity, and in SHC the decision to admit was based on the presence or absence of medical complications.

The study was a prospective observational study, to evaluate if a standardised appetite test, conducted at the time of enrolment, could be used to grade disease severity and predict clinical outcome. The children were initially investigated by the clinical staff, who managed the patients independently of the research staff. Before any treatment was started, the research staff informed the parents about the study and asked for written consent to let their children participate. The research staff then performed the appetite test, drew a venous blood sample and collected demographic and clinical data using standardized case report forms. Disease severity at enrolment was assessed clinically and based on blood tests. Clinical outcome was monitored at weekly follow-up visits and from hospital medical records. Children were categorized as having "treatment failure" if they

died, were transferred to a higher-level health facility or were undergoing treatment or still had SAM with no further follow-up data available after 4 weeks of treatment.

We enrolled all children from 6 months to 15 years with SAM. Inclusion criteria were one or more of the following; weight-for-height<70% of the median of the National Center for Health Statistics (NCHS) reference curve, mid-upper arm circumference (MUAC) <115mm, or bilateral oedema. The appetite test was not performed if a child had overt signs of critical illness such as unconsciousness, convulsions, need of oxygen, active bleeding, or required admission to the intensive care unit for other reasons as decided by the clinical staff.

Appetite test

We used the weight-based test, where the children pass the test if they eat a pre-specified amount of RUTF relative to their weight (5), as the primary predictor (Table 1). We also evaluated other definitions of reduced appetite including the weight-independent test where the children pass the test if they eat at least one third of the RUTF sachet (6, 7) and a "new appetite test" that was passed if more than one-tenth of the sachet had been eaten.

Table 1: Intake cut-offs for weight-based appetite test

Child weight:	**Test was passed if the child ate this amount, or more:**
less than 4 kg	1/8 of the sachet
more or equal than 4 kg, but less than 7 kg	1/4 of the sachet
more or equal than 7 kg, but less than 10 kg	1/3 of the sachet
more or equal than 10 kg, but less than 15 kg	1/2 of the sachet
more or equal than 15 kg, but less than 30 kg	3/4 of the sachet
more or equal than 30 kg	1/1 of the sachet

The RUTF sachet was weighed to the nearest gram (Sartorius TE412 in JUSTH and EatSmart ESKS in MiCC and SHC) before the caregiver encouraged the child to eat the content. The child was offered water throughout

the test. After 30 minutes, the test was stopped, and the sachet was weighed again. The research nurse did not determine whether the test was passed or not, but only recorded the amount eaten. In addition to the formal appetite test, the research nurse subjectively categorized the child's appetite as either "refused" to eat, "poor", or "good". The results were not made available to the clinical staff.

Clinical parameters

We weighed the children daily during admission and at all follow up visits (Tanita BD-815 MA Infant weighing scale, Japan and Seca weighing scale, Germany). At admission we also measured length or height and MUAC (Seca height and length boards, Germany and MUAC tapes, UNICEF, Denmark). We tested for medical complications at admission, defined as one or more of the following; axillary temperature <35°C or >39°C, grade three oedema (pitting oedema of entire body), repeated (≥3 times) vomiting during the appetite test, admission to intensive care, history of convulsions, palmar paleness, fast breathing, or chest in-drawing (13, 14).

Laboratory methods

One EDTA plasma tube (Vacuette, Becton Dickinson (BD), Austria) and, if the child was not admitted to intensive care, one Serum Sep Clot tube (Vacuette, BD, Austria) were obtained. Furthermore, blood cultures were performed using aerobic and anaerobic blood culture vials (BACTEC Peds Plus and BACTEC Lytic/10 Anaerobic, BD, USA) as previously described (15).

Blood cultures were incubated in an automatic blood culture system (BACTEC FX40, BD, USA) and positive cultures were subcultured on agar plates. The results of the initial identification and susceptibility testing in the local microbiology laboratory were reported to the clinical staff without delay. Isolates were frozen at -80°C, shipped to Denmark, and identified using Matrix-Assisted Laser Desorption Ionization–time of flight (MALDI-TOF) mass spectrometry. We defined organisms known to cause bacteraemia in children as "likely pathogens".

The complete blood count was analysed on an automated haematology analyser (KX-21 N, Sysmex Corporation, Bellport, USA) and samples were tested for malaria using rapid diagnostic tests, (First Response Malaria Ag (pLDH/HRP2), Premier Medical Corporation, Daman, India). After centrifugation of the primary tubes, plasma and serum were aliquoted in cryovials and frozen at -80°C. The samples were sent to the Denmark, and analysed at the Department of Clinical Biochemistry, Rigshospitalet, for aminotransaminases (ALT), albumin, bilirubin, creatinine, calcium (Ca), C-reactive protein (CRP), magnesium (Mg), phosphate (PO4), sodium (Na), and potassium (K) (Cobas, Roche Diagnostics, USA). The serum samples were screened for HIV at the Department of Clinical Immunology, Rigshospitalet using Vitros anti-HIV1+2 Enzyme Immunoassay (Ortho Clinical Diagnostics, Pencoed Bridgend, UK), and initial screen reactive samples were submitted to confirmatory testing (INNO-LIA HIV I/II Score, Fujirebio Europe, Gent, Belgium). Datasets and samples were de-identified by assigning unique study id numbers, before shipping samples to Denmark.

Statistical analysis

We used bacteraemia as the outcome in our sample size calculation, since we expected this would be the rarest outcome. We assumed that the bacteraemia proportion would be at least 15% in cases failing the appetite test and 5% in cases passing the test(16) and that we would not get appetite test results from 20 cases. With a 95% CI and 80% power we calculated a minimum sample size of 330 children. Age was categorized as 6-11, 12-23, 24-59, and >59 months in the statistical analysis. We entered and validated data with EpiData 3·1 (EpiData, Odense, Denmark) and used SAS Enterprise Guide, Version 7·11 of the SAS System for Windows (SAS Institute Inc., Cary, NC, USA) for data analysis. A p value lower than 0·05 was considered significant and 95% CIs were used throughout the analyses. Weight-for-height/length z-score (WHZ) was based on WHO standards (17). We used Chi-square test to compare differences in proportions and a general linear model for continuous variables. We used a mixed linear model for continuous outcomes and a mixed logistic regression model for binary outcomes, both with random effects for site to adjust for any potential differences between the sites. Weight was log transformed to ensure normal distribution. Weight gain was calculated at each measurement as relative weight gain per day (g/kg/day) compared with the first oedema-free weight. We used a mixed model linear regression analysis to assess the effect of various variables (e.g. the result of the appetite

test) on weight gain (presented as percent difference between the two groups), adjusted for potential confounders (e.g. oedema and age), and added random effects for site and a Gaussian covariance structure for repeated measurements.

Results

Of 343 children screened, 334 (97%) had SAM and were enrolled, 228 (68%) at JUSTH, 78 (24%) at MiCC, and 28 (8%) at SHC (Figure 1). Of the 334 enrolled children, 298 (89%) had their appetite tested. One child had blood samples taken but died before admission data was collected. Data on mortality was available for 283 (85%) of the study participants of whom 17 (6%) died and another 57 (20%) had ~~likely~~ treatment failure. We had sufficient data on weight and treatments from 95 (28%) children for evaluating the effect of the appetite test on weight gain. We had sufficient data from 112 children for evaluating the effect of medical complications on weight gain. No children had HIV, one had malaria and 11 (4%) had bacteraemia with a likely pathogen.

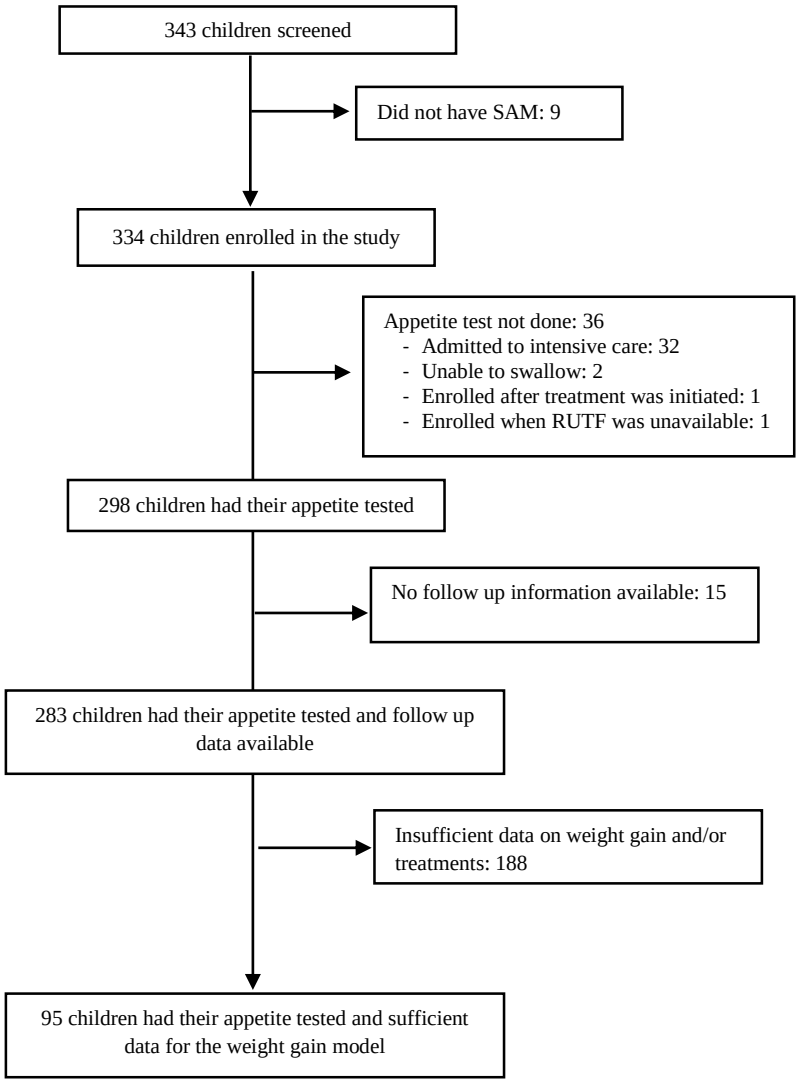

Figure 1: Flow diagram

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Table 2: Baseline characteristics of enrolled children with severe acute malnutrition

	n[a]	Value
Female sex, % (n)	333	48% (160)
Age, months[b]	333	33·0 (14·0; 60·0)
> 59, % (n)	333	27% (90)
Mid-upper arm circumference[c]	332	117 (19)
among children without oedema	118	106 (16)
Weight-for-length/height z-score (6-59 months)[b,d]	261	-2·7 (-3·8, -1·2)
among children without oedema	88	-3·7 (-4·8, -3·1)
Length/height for age z-score (6-59 months)[b,d]	262	-3·3 (-4·4, -2·2)
BMI for age (5-14 years)[d]	29	-4·0 (1·9) [3]
Bilateral oedema	333	63% (215)
Medical complications	333	54% (179)
Referred from another health institution	293	54% (159)
Treatment for malnutrition during the last week	282	9% (24)
Treatment with antibiotics during the last week	310	16% (50)

[a] Number of children for whom data was available

[b] Median (25^{th}; 75^{th} percentiles)

[c] Mean (standard deviation)

[d] WHO z-scores

Appetite test

Of the 298 children (89%) who had their appetite tested, 56 (19%) passed the weight-based test. Of the 36 cases that did not have their appetite tested, 34 (94%) had a clinical condition that precluded testing. Among these 34 children, 2 (6%) were unable to swallow due to developmental disorders and 32 (94%) were admitted to intensive care due to critical illness (Figure 1). The appetite test result was not correlated with age, admission weight, first oedema-free weight, bilateral oedema, WHZ, or MUAC (Table 3). Results were similar in the subgroup of children with sufficient data to be included in the weight gain model, including the result of the appetite test (19% passed both overall and in the subgroup). Children failing the appetite test received gentamicin more often than children that passed the test (p=0·04). The adjusted weight gain per day was 6·6% higher in children failing compared with children passing the appetite test (6·6, 95% CI 2·6, 10·8, p=0·002) with adjustments made for type of treatment (i.e. whether gentamicin, F-75, F-100 and RUTF were given),

oedema, duration of follow up, and age. Adjustment for number of days on F-75, F-100, and RUTF did not affect the estimate, i.e. we still found a higher weight gain in those failing the test (p=0·004). Lastly, only adjusting for oedema, duration of follow up, and age had limited effect on the result (5·5, 0·06, 9·9, p=0.03). Replacing the first oedema-free-weight with the lowest weight observed after oedema had receded in the model gave similar results.

Table 3: Comparison of children passing or failing the appetite test[a]

	Passed appetite test (n=56)	**Failed appetite test (n=242)**	**p**
Age, months[b]	36 (14, 66)	30 (14, 60)	0·64
Admission weight, kg[b]	8·9 (6·5, 13·0)	8·6 (6·7, 11·5)	0·89
First oedema-free weight, kg[b]	8·3 (5·7, 13·3)	8·3 (6·0, 11·1)	0·73
Bilateral oedema, n (%)	31 (55)	165 (68)	0·07
WHZ[b]	-2·6 (-3·5, -1·6)	-2·5 (-3·7, -1·0)	0·23
MUAC, mm, mean (sd)	115 (20)	119 (18)	0·19
Diarrhoea, n (%)	25 (45%)	130 (54%)	0·25

[a] Tested in a mixed model linear regression with random effects for site and variables log-transformed, except WHZ and MUAC. Data available for 298 children.

[b] Median (25^{th}; 75^{th} percentiles)

Table 4: Difference in weight gain per day between proposed risk indicators

Test	**Variable**	**Criteria**	**Percent difference in weight gain per day (95 % CI)**	**p**
Standard appetite test	Failed - passed	Differentiated by weight, see table 1	6·6 (2·6, 10·8)	0.002
Weight independent appetite test	Failed - passed	The test was passed if a child ate at least 1/3 of the sachet regardless of the child's weight	5·7 (-20·3, 40·2)	0·7
New appetite test	Failed - passed	The test was passed if a child ate at least 1/10 of the sachet regardless of the child's weight	5·5 (1·5, 9·7)	0·007
Nurses' evaluation of child's appetite	Refuse or poor - good	Nurses' subjective evaluation, passed if good	7·5 (3·1, 12·1)	0·0009

Medical complications	With - without	Defined as presence of at least one of the following; temperature <35°C or >39°C, grade 3 oedema, vomiting everything during appetite test, admission to intensive care, history of convulsions, palmar paleness, fast breathing, or chest indrawing	-3·5 (-7·0, 0·25)	0.07

Tested in a mixed model linear regression with random effects for site and adjusted for F75, F100, RUTF, gentamicin, oedema, age, and duration of follow up. Weight gain was calculated by subtracting first oedema free weight from the follow up weights divided by first oedema free weight and measured as gain per day (g/kg/day). Difference between the two groups is presented as percent difference. Weight gain per day was the interaction term between the appetite test result and the effect on weight gain of the number of days of treatment after the first oedema-free weight

Overall case fatality was 6·0% (n=17), but 31% of the children that died had not had their appetite tested, mostly because the child was not in a condition to collaborate. For children completing the test there was a case fatality of 4·9% among children failing the appetite test and 4·3% among children passing it (OR 1·31, 95% CI 0·05, 33·29, p=0·87, adjusted for type of treatment given, oedema and age). Treatment failure, caregiver assessment of their child's illness after three months, and bacteraemia were not correlated with the result of the appetite test. Children that failed the appetite test had lower serum calcium than children that passed (p=0·009), whereas all other measured markers of metabolic disturbances did not differ between the two groups (Table 5).

Table 5: Correlation of laboratory tests with the appetite test result[a]

	n (passed/failed)	Passed appetite test	Failed appetite test	p
Infection-related				
Bacteraemia, n (%)	231 (39/192)	0 (0)	8 (4)	0·19
CRP, mg/L[b]	242 (45/197)	4 (1, 14)	12 (3, 37)	0·09
Platelets, $10^3/\mu l$[b]	263 (47/216)	356 (172, 497)	304 (190, 452)	0·48
Haematology				
Hb, g/dl[c]	263 (47/216)	10·0 (2·4)	10·1 (2·2)	0·76
WBC, $10^3/\mu l$[b]	263 (47/216)	9·0 (6·8, 12·9)	10·2 (7·9, 13·7)	0·17
Biochemistry				
ALAT, U/L[b]	231 (43/188)	29 (14, 39)	25 (15, 39)	0·94

Albumin, g/L[b]	242 (45/197)	24 (17, 30)	17 (11, 26)	0·056
Bilirubin, µmol/L[c]	242 (45/197)	2 (4)	3 (5)	0·29
Creatinine, µmol/L[c]	242 (45/197)	25 (9)	26 (9)	0·42
Calcium, mmol/L[c]	222 (41/181)	2·08 (0·28)	1·94 (0·27)	0·009
Potassium, mmol/L[c]	196 (35/161)	4·3 (0·8)	4·1 (1·1)	0·47
Magnesium,mmol/L[c]	222 (41/181)	0·86 (0·11)	0·82 (0·14)	0·33
Sodium, mmol/L[c]	222 (41/181)	137 (3)	136 (6)	0·17
Phosphate, mmol/L[c]	237 (45/192)	1·33 (0·35)	1·22 (0·32)	0·09

[a] Tested in a mixed model linear regression with random effects for site

[b] Median (25th; 75th percentiles), variables log-transformed

[c] Mean (standard deviation)

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226 **Medical complications**

227 One or more medical complications were present in 179 (54%) of the patients. We found that children without
228 medical complications had a higher weight gain, adjusted for type of treatment given, oedema, duration of
229 follow up, and age, than children with complications, but the difference was not statistically significant (3·5%
230 difference, 95% CI -0·25, 7·0, p=0.07). Medical complications at admission were not correlated with mortality.
231 The first oedema-free weight, age, prevalence of bilateral oedema, MUAC, and WHZ did not differ between
232 the two groups with and without complications, and this was also the case among the children for which we
233 had sufficient data for the weight gain model. Treatment failure and the caregivers' assessment of their child's
234 illness after three months were not correlated with medical complications. However, medical complications
235 were correlated with several of the laboratory investigations (Table 6).

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Table 6: Correlation of laboratory tests with medical complications[a,b]

	n (without/with medical complications)	**No medical complications**	**Medical complications**	**p**
Infection-related				
Bacteraemia, n (%)	258 (119/139)	3 (2·5)	8 (5·8)	0·21
CRP, mg/L[c]	268 (123/145)	7 (2, 29)	15 (4, 51)	0·08

Platelets, 10^3/µl[d]	296 (134/162)	314 (195, 460)	296 (173, 455)	0·25
Haematology				
Hb, g/dl[d]	296 (134/162)	10·5 (2·2)	9·6 (2·4)	0·001
WBC, 10^3/µl[c]	296 (134/162)	9·9 (7·8, 13·7)	10·5 (7·8, 13·6)	0·96
Biochemistry				
ALAT, U/L[c]	256 (117/139)	22 (13, 34)	29 (18, 49)	0·007
Albumin, g/L[c]	268 (123/145)	24 (15, 31)	14 (9, 21)	<0·0001
Bilirubin, µmol/L[d]	268 (123/145)	2 (3)	4 (7)	0·002
Creatinine, µmol/L[d]	268 (123/145)	26 (10)	26 (10)	0·98
Calcium, mmol/L[d]	223 (117/106)	2·05 (0·29)	1·87 (0·25)	<0·0001
Potassium, mmol/L[d]	196 (104/92)	4·1 (1·1)	4·1 (1·0)	0·92
Magnesium,mmol/L[d]	223 (117/106)	0·85 (0·13)	0·80 (0·14)	0·01
Sodium, mmol/L[d]	223 (117/106)	137 (4)	136 (6)	0·32
Phosphate, mmol/L[d]	262 (121/141)	1·31 (0·33)	1·18 (0·31)	0·002

[a] Defined as one of the following; temperature < 35°C or >39°C, grade 3 oedema, vomiting everything during appetite test, admission to intensive care, history of convulsions, palmar paleness, fast breathing, or chest indrawing

[b] Tested in a mixed model linear regression with random effects for site

[c] Median (25^{th}; 75^{th} percentiles), variables log-transformed

[d] Mean (standard deviation)

Alternative methods of assessing the appetite

We also evaluated alternative appetite tests and for the "new appetite test" we got similar results as for the weight-based appetite test, with a higher weight gain among those failing compared with those passing the tests (Table 4). We adjusted for type of treatment given, oedema, duration of follow up, and age. We did not find any association between weight gain and the results of the weight-independent test. Passing the weight-independent appetite test was correlated with higher serum phosphate (p=0·05). We finally evaluated the discriminatory ability of appetite as assessed subjectively by the study nurses. There was no difference between the group the nurses categorized as "refused" to eat and a combined group of those with "poor" or "good" appetite, but children that either "refused" or had a "poor" appetite had a higher weight gain than children with a "good" appetite (Table 4).

Discussion

The main finding of our study is the somewhat counterintuitive observation that children that passed the appetite test had a slower weight gain during follow up than children that failed the test. Furthermore, a failed appetite test was not associated with clinical severity or metabolic abnormalities. Alternative methods for evaluating the appetite, including tests recommended by international organizations (3, 7), gave similar results. The appetite test is currently recommended in national and international guidelines and in nutrition programs in most parts of sub-Saharan Africa and south Asia to determine whether children with SAM need hospitalization. The underlying assumption behind the use of the appetite test is that children with poor appetite will be more ill and gain weight at a slower rate if treated at home, and that they should therefore be treated as in-patients. To our knowledge, this is the first study to assess the clinical and predictive utility of the appetite test. We interpret our findings as evidence against its continued use and its continued inclusion in treatment guidelines.

Although we did not formally blind the clinical staff, the study design effectively prevented that results of the appetite test could influence treatment decision. Furthermore, adjustment for duration and type of treatment did not alter the significance of our results. We stopped the appetite test after 30 minutes, even though continuing up to 60 minutes has been suggested (5), but we found it unfeasible to recommend an examination that would be even more time-consuming for busy low-level health workers.

A limitation in our study, especially for the weight gain analysis, is the low number of children for which we had complete data. While we had follow-up information from 85% of the children, we only had data on both treatment and follow-up weight from 28%. We cannot rule out selection bias but the proportions and characteristics of children that failed and passed the appetite test did not change significantly after removing cases with incomplete follow-up data from the analysis. It is therefore unlikely that the strength and significance of our findings can be explained by selection bias.

Comparing weight gain measured as gram per kg body weight will be unreliable if one of the groups being compared had heavier children on average, since the relative weight gain is smaller in children with a higher initial weight. However, we did not find any difference in first oedema-free weight between children failing and passing the test.

In a large-scale nutrition program in which children were given a RUTF sachet while the caregiver was interviewed, not eating any of the content during a 10-minute period was correlated with mortality (18). We could not confirm this association, as there was no difference between the groups of children whose appetite had been subjectively classified by the nurse as "refused", and children who were assessed as having "poor" or "good" appetite. A recent study from a referral hospital with a high HIV-prevalence suggested an association between lack of appetite and mortality, but only in the univariate analysis, and the investigators did not specify how they tested the appetite(19).

The appetite test was not correlated with bacteraemia; however, our study may have had insufficient power as the prevalence of bacteraemia was lower than expected. The low positivity rate could be due to prior treatment with antibiotics and small sampling volumes for the blood cultures. We did a post hoc power calculation showing that we would be able to detect a difference in prevalence between 0·5% and 9% based on the 244 cases that were included in the analysis. A low prevalence of bacteraemia was also reported in a recent multicentre study(20). The low prevalence of bacteraemia as opposed to the high positive rate of the appetite test (81%) would in any case render the appetite test very unspecific as a proxy marker for bacteraemia.

Hypophosphatemia was more common in those failing the weight independent appetite test, but it has been argued that phosphate levels are a more relevant predictor for outcome when measured after initiation of treatment (21). Although the appetite test was correlated with reduced calcium levels this could be confounded by the fact that we did not test the appetite in children with convulsions or lethargy. We also did not find any association between mortality and calcium levels.

As an alternative to the appetite test the Integrated Management of Childhood Illnesses (IMCI) guidelines(14) recommend using a list of medical complications as part of an algorithm to identify children with SAM in need of hospitalization. To our knowledge, this IMCI algorithm has never been evaluated, although studies have assessed the prognostic value of some of the clinical signs and symptoms included in it (21). This set of medical complications tended to indicate a lower weight gain during follow-up and to be associated with abnormal biochemistry results at admission.

Conclusion

In conclusion, our findings question the continued use of the appetite test to identify children with SAM for in-patient treatment. A best-case interpretation of our findings is that the appetite test is unreliable; a stricter interpretation is that the appetite test is directly misleading. Our findings should ideally be confirmed in other settings, particularly in community programs and sites from Asia. Further work will be needed to develop new clinical decision tools. Although not pre-defined as primary outcomes in this study, our findings indicate that a combination of signs and symptoms – broadly defined as "medical complications" – could be further evaluated as markers to identify children at risk of poorer treatment response.

List of abbreviations

CI – Confidence interval

F-75 – Formula F-75, 75 kcal/100/ ml

F-100 – Formula F-100, 100 kcal/100 ml

HIV – Human immunodeficiency virus

IMCI – Integrated management of childhood illness

JUSTH – Jimma University specialised treatment hospital

MiCC – Missionary of charity clinic

MUAC – Mid-upper arm circumference

NCHS – National centre for health statistics

OR – Odds ratio

RUTF – Ready-to-use therapeutic foods

SAM – Severe acute malnutrition

SHC – Serbo health centre

WHO – World Health Organisation

WHZ – Weight-for-length/height z-score

Declarations

Ethical approval and consent to participate

The study was approved by Jimma University Institutional Review Board (Reference HRPGC/239/2015) and the Ethiopian National Research Ethics Review Committee (Reference 310/285/2017) and received consultative approval by the Danish National Committee on Health Research Ethics (Reference 1800407). After obtaining written informed consent from caregivers the children were considered eligible.

Availability of data and material

The datasets generated and analysed during the current study are not publicly available due regulations by the Danish Data Protection Agency.

Competing interests

The authors declare that they have no competing interests

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Author contributions

MZ, HF, AB, JK and TG conceptualized the study. The study was designed by MZ, AA, ØJ, HF, AB, JK and TG. MZ, AA, ØJ, GT, BE and TG led the data collection and all authors contributed to the data analysis and interpretation of data. MZ prepared the first draft of the paper and all authors contributed to the revisions, discussion of results and to the completion of the final manuscript.

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