ttachment 1.
FACE SHEET)

ETHICAL REVIEW COMMITTEE, ICDDR,B.

Date 16.06.97

DMONO

rincipal Investigator Dr. N.H. Alam

Trainee Investigator (if any)

pplication No. 97-012

Supporting Agency (if Non-ICDDR,B) WHO

itle of Study Efficacy of modified oral rehydration solution in severely malnourished children with watery diarrhoea

Project status:
(✓) New Study
( ) Continuation with change
( ) No change (do not fill out rest of form)

ircle the appropriate answer to each of the following (If Not Applicable write NA).

. Source of Population:
(a) Ill subjects (Yes) No
(b) Non-ill subjects Yes No
(c) Minors or persons under guardianship (Yes) No

. Does the study involve:
(a) Physical risks to the subjects Yes (No)
(b) Social Risks Yes (No)
(c) Psychological risks to subjects Yes (No)
(d) Discomfort to subjects (Yes) No
(e) Invasion of privacy Yes (No)
(f) Disclosure of information damaging to subject or others Yes (No)

. Does the study involve:
(a) Use of records, (hospital, medical, death, birth or other) (Yes) No
(b) Use of fetal tissue or abortus Yes (No)
(c) Use of organs or body fluids (Yes) No

Are subjects clearly informed about:
(a) Nature and purposes of study (Yes) No
(b) Procedures to be followed including alternatives used (Yes) No
(c) Physical risks (Yes) No
(d) Sensitive questions (Yes) No
(e) Benefits to be derived (Yes) No
(f) Right to refuse to participate or to withdraw from study (Yes) No
(g) Confidential handling of data (Yes) No
(h) Compensation &/or treatment where there are risks or privacy is involved in any particular procedure NA Yes No

5. Will signed consent form be required:
(a) From subjects Yes (No)
(b) From parent or guardian (if subjects are minors) (Yes) No

6. Will precautions be taken to protect anonymity of subjects (Yes) No

7. Check documents being submitted herewith to Committee:
___ Umbrella proposal - Initially submit an overview (all other requirements will be submitted with individual studies).
✓ Protocol (Required)
✓ Abstract Summary (Required)
✓ Statement given or read to subjects on nature of study, risks, types of questions to be asked, and right to refuse to participate or withdraw (Required)
___ Informed consent form for subjects
✓ Informed consent form for parent or guardian
✓ Procedure for maintaining confidentiality
___ Questionnaire or interview schedule *

* If the final instrument is not completed prior to review, the following information should be included in the abstract summary:
1. A description of the areas to be covered in the questionnaire or interview which could be considered either sensitive or which would constitute an invasion of privacy.
2. Examples of the type of specific questions to be asked in the sensitive areas.
3. An indication as to when the questionnaire will be presented to the Cttee. for review.

agree to obtain approval of the Ethical Review Committee for any changes volving the rights and welfare of subjects before making such change.

Principal Investigator

Trainee

RESEARCH PROPOSAL

SECTION-1 TITLE PAGE

Title: **Efficacy of modified oral rehydration solution in severely malnourished children with watery diarrhoea.**

Principal Investigator	:	Dr. N.H. Alam M.B.B.S., MD.
Co-Investigators	:	George Fuchs, M.D. Dr. Jena Hamadani M.B.B.S., D.C.H.
Consultant	:	Dr. O. Fontaine (WHO, Geneva, Switzerland)
Starting Date	:	As soon as possible
Ending Date	:	2 years from starting the protocol
Total Direct Cost (in US$)	:	98830
Funding Source	:	WHO

Date 16/6/97

Signature
Division Director
Clinical Sciences Division

SECTION II : RESEARCH PLAN

ABSTRACT SUMMARY

Controversy exists regarding the optimal electrolyte composition of oral rehydration solution especially for use in severely malnourished children. Children with protein energy malnutrition (PEM) have an excess of total body sodium and are depleted in potassium. This is due in part because children excrete less sodium and more potassium during an acute diarrhoeal illness. Hypokalemia in children with diarrhoea is not satisfactorily corrected by the standard WHO-ORS containing 20mmol/L of K^+. This study proposes to compare the effect of the following ORS formulations in a 3 cell randomised controlled trial : (a) WHO-ORS (Na^+90, K^+20, Cl^-80, Citrate 10, Glucose 111, Osmolality 311 mosmol/L) (b) A modified-ORS with lower sodium and higher potassium concentrations (Na^+45, K^+40,Cl^-76, Citrate 7, glucose 125, osmolality-293 momosmol/L) or (c) reduced osmolarity ORS ($Na60^+$, $K20^+$, CL^-57, Citrate 10, Glucose 111, osmolarity 258 mosmol/L) in correcting potassium deficit and in reducing the risk of developing overhydration in severely malnourished children with watery diarrhoea.

Major outcome variables of serum potassium and sodium changes and risk of development of overhydration will be compared between the treatment groups. We expect the results of this study to assist in better case management of severely malnourished children with watery diarrhoea.

PROJECT DESCRIPTION

HYPOTHESIS :

1. A modified oral rehydration solution with higher potassium concentrations will correct potassium deficits in severely malnourished children with diarrhoea better than the standard ORS.

2. High sodium ORS (e.g. standard ORS) has a risk of developing overhydration.

OBJECTIVE :

1. To determine the effect of a modified oral rehydration solution containing lower sodium and higher potassium concentrations in correcting sodium excess and potassium depletion in severely malnourished children with diarrhoea.

2. To determine the risk of developing fluid overload in patients treated with different ORS solutions (standard ORS, modified ORS & hypoosmolar ORS) by clinical evaluation and measuring total, intracellular, and extracellular body water.

BACKGROUND:

Malnutrition and diarrhoea are among the most common childhood illness responsible for high proportion of death in children[1-3]. Though oral rehydration therapy is well-established in the management of diarrhoeal dehydration, controversy remains regarding the optimal electrolyte composition[4]. The WHO ORS has met with some criticism for containing a relatively higher content of sodium and lower concentration of potassium than might be considered appropriate for use in children[5,6,7]. Cholera stool of children contains less Na^+ and more K^+ than adults and children are found to lose more K^+ in non-cholera diarrhoea than in cholera[8,9]. In addition management of malnourished children with diarrhoea need special care. Physiologically, malnourished children excrete less salts and water, and are unable to handle excessive salt and water load[10]. The malnourished child is sometimes found to be hyponatraemic, in fact all the sodium is being concentrated inside the cell (inefficient Na^+/K^+ pump)[11] and fluids containing large amounts of sodium (such as the standard ORS) may lead to further increase in intra cellular sodium, fluid overload and heart failure.Though the body composition of malnourished children has been studied in detail[12], there are no reports regarding the changes in body composition (total, intracellular and extracellular) during diarrhoea and different states of hydration. On the other hand children with PEM have depleted potassium stores[13]. Diarrhoea results in further depletion of the already diminished potassium stores of the malnourished children. Though the serum pottasium values do not always reflect the total body potassium[14], hypokalemia is an important finding in PEM and was found to correlate well with clinical presentations (neck-flop, abdominal distention, diminished bowel sound, weakness of limbs, lethargy etc.) in children with diarrhoea[15]. Moreover, hypokalemia in malnourished children with diarrhoea have higher risk of fatal outcome[16]. Although the efficacy

of standard ORS in correcting dehydration is unquestioned, its role in correcting potasium deficits was found to be insufficient in some children with diarrhoea[17]. There are reports of use of hypotonic ORS with different Na^+ contents[18,19], however trials with higher contents of K^+ in ORS are scarce. In a study comparing low and high sodium and potassium content in ORS it was found that higher K^+ containing ORS corrects K^+ deficits better than low K^+ containing ORS[7]. But in this trial a single solution having reduced sodium and increased K^+ content was not used. Moreover none of the studies were done in malnourished children. Presently, all children (severely malnourished or not) with diarrhoea are being rehydrated following the same treatment guidelines. From our experience, at ICDDR,B we found that while treating diarrhoeal children with hypokalemia pottasium supplementation is often required either orally or parenterally and many authors have expressed similar views[15,16,17]. But separate, regular potassium supplementation during diarrhoea is not feasible at community level or primary health care centres. Presently WHO experts in ORS formulation are also concerned about the use of the standard ORS therapy in severely malnourished children due to its high sodium and low pottasium content and suggests an alternative ORS with low sodium and high potassium concentration for use in these children[20] It is felt that an ORS containing lower sodium and higher pottasium concentration may be useful in correcting hypokalemia, and lowering the risks of excess sodium, in severely malnourished children with diarrhoea. Before recommending such a rehydration solution, its role needs to be evaluated by well designed controlled clinical trials.

STUDY DESIGN

Subjects / Patient Selection

Children attending the ICDDR,B, Dhaka Treatment Centre with a history of watery diarrhoea will be evaluated following the inclusion and exclusion criteria.

Inclusion Criteria :

1.	Age	:	6 mo - 36 mo
2.	Sex	:	Both
3.	H/O diarrhoea	:	History of watery stools (for at least last 72 hours)
4.	Nutritional status	:	W/H <70% of NCHS median with or without oedema.

Exclusion Criteria :

1. Bloody diarrhoea
2. Severe infection (severe pneumonia, clinical sepsis / septic shock , meningitis and other conditions requiring intensive care support).
3. Patients with severe dehydration.

Sample Size :

We expect to reduce the persistence of hypokalemia with the modified ORS treatment to 10% of patients in comparison to 33% of standard ORS therapy[7]. Considering 5% level of significance and 80% power, the sample size in each group will be 47. Assuming 20% drop out, the final sample size will be 57 in each group. Therefore, total sample size will be 171.

The incidence of hyponatraemia in the study group (modified-ORS group) is assumed to be 20% as compared with 2% in the control group (WHO-ORS). Considering 5% level of significance and 80% power, the sample size is calculated as 44. Considering 20% drop out, the final sample size in each group will be 53.

The incidence of over hydration in the WHO-ORS group is assumed to be 20% as compared with 2% in the modified-ORS group. Considering 5% level of significance and 80% power and 20% drop out the final sample size will be 53.

Enrollment of patients

Informed consent :

The patients admitted in the study, their parents or guardians will be fully informed about the trial and one of the investigators will obtain their freely given consent to participate in the study in writing.

Baseline information :

A baseline history and examination will be obtained in order to :

- determine the subjects' eligibility for inclusion in the study ;
- collect the relevant data prior to beginning the study.

The baseline history and examination will include :

- identification of the patients ;
- a description of the symptoms prior to admisssion and their duration ;
- detail of any treatment given for the illness before admission ;
- results of physical examination including the state of hydration .

Assessment of dehydration

This will be done according to the manual for management of severely malnourished children (Appendix-1).

Laboratory Tests :

After admission blood for Hct, total protein, albumin globulin ratio, and serum electrolytes will be sent before initiation of the assigned ORS. Serum electrolytes will be repeated after 24 and 48 hours after initiation of ORS therapy .Stool sample will be sent for microscopy (including cryptosporidium and giardia) and culture for shigella, salmonella, vibrio cholerae and ELISA for rotavirus will be done on admission and patient treated. Other relevant investigations like Total WBC count, Differential count, CXR or Blood C/S will be sent, if necessary.

Randomization :

The study will be done in a randomised 3-cell controlled clinical trial. Randomization of each cell will be stratified according to duration of diarrhoea (<7 days and >7 days). After enrollment and baseline information the patients will be randomized to receive one of the three oral rehydration solutions :

(1) WHO-ORS (Na^+90, K^+20, Cl^-80, Citrate 10, Glucose 111, Osmolality 311 mosmol/L).
(2) Modified-ORS (Na^+45, K^+40, Cl^-76, Citrate 7, Glucose 125, Osmolality 293 mosmol/L).
(3) Low osmolarity ORS (Na^+60, K^+20,Cl^-57, Citrate 10, Glucose 111, osmolality 258 mosmol/L).

A randomization list will be prepared by a person not directly related to the study by using a random number table of permuted block of variable length. The randomization list will contain a serial number. The investigators will be supplied with big packets (containing 20 small packets of ORS to be dissolved in half litre of water). The big packets will be numbered serially masking their identity. The patients' identity number will correspond to the packets serial number.

Case Management :

ORS

Initial rehydration - Patients will be assigned to study ORS according to randomization number. Patients will be rehydrated with ORS over 12 hours with the amount calculated according to the baseline dehydration status.

Maintenance phase - Treatment will continue with the assigned ORS with the minimum amount administered equal to replacement of ongoing losses (watery & loose stool and vomit). Patients will be allowed ORS until diarrhoea stops.

Intake of ORS, plain water, output of stool & urine, state of hydration and vital signs (pulse rate, heart rate, respiration rate and temperature) will be recorded every 6 hours by a nurse, as a part of routine diarrhoeal care. Body weight and dietary intake (g/kg/day) will also be recorded 6 hourly.

Standard management

The standard management will be followed according to the manual for management of severely malnourished children (Appendix-1)

Diet

All patients will be allowed breast milk *ad libitum*. Patients will also be given milk cereal mixture (Milk-Suji composition given in Appendix-2) providing a calorie of 75 Kcal/kg/day for partially breastfed infants and 110 Kcal/kg/day for non-breastfed babies. Food will be provided at 2 hourly intervals from 4 AM to 12 Midnight (11 feeds). Children who are anorectic and/or has repeated vomiting will be given nasogastric tube feeding.

Vitamins & Micronutrients

Multivitamins - A commercially prepared multivitamin and mineral mixture will be given to all children.

Study withdrawal

Reasons for withdrawal :

1. Any patient requiring unscheduled intravenous fluid therapy (due to worsening of dehydration or development of septic shock).
2. Development of complications including hypoglacaemia, severe pneumonia or clinical sepsis requiring I/V medication.

Management of withdrawal cases :

The withdrawal cases will be transferred to general ward or ICU and appropriate management provided according to routine hospital practice. Regular follow-up will be done and final outcome of the children will be recorded.

Data collected upto the time of withdrawal will be included for analysis.

Management after end of study :

Vital signs (pulse rate, heart rate respiratory rate and temperature) will be monitored for 3 consecutive days after the end of study and if stable, patients will be discharged with dietary advice or admitted in the nutrition rehabilitation unit, as required.

Definition:

End of study - The study end point will be considered when diarrhoea stops or 5 days of initiation of the ORS whichever comes first.

Cessation of diarrhoea - Diarrhoea will be considered to have stopped when the last watery stool is passed followed by soft or formed stool and/or no stool for 16 hours.

Hypokalaemia - Hypokalaemia is defined as serum potassium level <3.5 mmol/l .

Persistence of hypokalaemia - If the serum potassium level is <3.5 mmol/l on admission and it remains at that level even after 48 hours of therapy with ORS , it will be considered as persistence of hypokalaemia .

Overhydration -

As there is no standard criteria for defining overhydration, we have developed a working definition of overhydration for this protocol based on previous study reports and our clinical experience.Overhydration will be considered in a child who has more than a 5 % weight gain[22] (within48 hours) than expected after correction of dehydration and / or at least any two of : development of periorbital oedema ;

increased heart rate (>140/min); } In the absence of signs suggestive of pneumonia
increased respiration rate (>60 / min). } (fever, CXR abnormalities etc.)

Hypoglycaemia - will be defined as blood glucose ≤3 mmol/L
Hyponatremia - will be defined as serum sodium < 130 mmol/L
Severe pneumonia:

Patients aged 6 m - 12 m

- respiratory rate >50/minute with chest indrawing

Patients aged 13 m - 36 m

- respiratory rate >40 with chest indrawing (WHO guideline)

Organization of the trial :

Study site - The study will be done in the study ward of the Clinical Service Centre of ICDDR,B.

Study schedule - The study period will be 2 years from starting.

Recruiting and training of study personnel - First one month.

Data collection - 18 months

Data analysis and reporting - 5 month

BALANCE STUDIES (Sodium and potassium balance)

During the study of modified oral rehydration solution in severely malnourished children with acute diarrhoea, a subsample of male patients will undergo balance studies .

Selection of Patients

First 10 (ten) patients from each group will be selected for the balance studies.

Procedure (Balance study)

The procedure for the sodium and potassium balance study is adopted according to the method of Aperia et al[23]. At the start of ORS administration, a charcoal marker will be fed and urine collection will start and measurement of ORS and diet intake will commence. The stool collection will start with the appearance of charcoal marker in the stool. After 48 hours a 2nd marker will be given to the patient and urine collection will be completed and ORS & diet intake upto that point will be recorded. Stool collection will be stopped after the appearance of the 2nd marker in the stool. Stool and urine sodium, potassium and osmolality will be measured from the collected samples. Intake of sodium and potassium will be measured from the intake of ORS and diets. 5 ml of acetic acid will be given in the collecting stool buckets to prevent fermentation. All stool, urine and vomitus will be collected in similar way. These samples will be kept at-20©C. Aliquotes of stool samples from homogenized 48 hour collection will be taken and analysed for sodium and potassium.

MEASUREMENT OF TOTAL, INTRACELLULAR AND EXTRACELLULAR BODY WATER :

The total body fluid and extracellular and intracellular fluid will be measured by Bioelectrical impedance analyser (BIA) in a sub-sample of patients using a method we have recently validated (Hossain I et al, submitted). The measurements will be done at randomization, at 6 hours and 24 hours after starting ORS .

Selection of patients

Body fluids compartments will be measured in the first 10 (ten) patients from each group.

Procedure (BIA)

A multi-frequency analyser machine (Xitron Inc, San Diego, California) will be used to measure bioimpedance. The children will be positioned to lie quietly supine with arms slightly apart from the body; legs will be separated so that the thighs will not touch. After cleaning the skin with alcohol, one pair of electrodes will be placed on the back of the hand, the distal one over the distal end of the metacapal and the proximal one over an arbitrary midline between the radius and ulna at the wrist joint. Another pair will be placed at the distal end of the metatarsal and between medial and lateral malleoli at the ankle. During this procedure no metalic object (ornaments, stones) will be in contact with the skin.

During operation of the machine body weight, height and temperature will be measured and records will be entered into the machine. From the impedance values TBW, ECW and ICW (indirectly) will be estimated by using published equations[24].

OUTCOME VARIABLES :

Primary

(1) Serum potassium and sodium changes among the treatment groups.
(2) Risk of developing overhydration.

Secondary:

1. Calorie intake per day
2. Daily weight gain
3. Duration of hospitalization
4. Changes in extracellular and intracellular fluid and total body water.

DATA ANALYSIS:

All data generated from this study will be entered into a Personal Computer using StatPack Gold statistical package. Statistical analysis will be done with SPSS PC + statistical package. Continuous variables will be analysed using Anova, students *t*-test or non parametric tests according to the appropriateness and applicability. Dichotomous variables will be compared among the groups using Chi-squared test or Fisher's exact test. Statistical significance will be accepted at the level of 0.05.

SIGNIFICANCE OF EXPECTED FINDING

If the modified ORS is found to correct hypokalemia in malnourished children with diarrhoea, it will have a major public health significance as regard to better case management for malnourished children with diarrhoea.

BUDGET JUSTIFICATION

Personnel : Investigators request support calculated by % effort. Support for % effort of secreterial service is also requested.The research physician , nurses and research assistant will work at the study area at ICDDR, B hospital and will be provided with a salary supplement.

Patient hospitalization cost: The patients' hospitalization cost and other interdepartmental cost is calculated from the present rates at ICDDR, B .

Supplies : Furniture (tables & chairs) and file cabinet is requested for use by study personnel for desk work and record keeping .A computor is necessary for data management and analysis (All other computers at the clinical sciences division , ICDDR, B are fully engaged in other projects). Deep freezer will be required for storage of stool and urine samples which will be used later for balance studies.

Transportation: Support is requested for transport subsidy of the project staff and the study patients.

Title of the protocol: Efficacy of modified oral rehydration solution in severely malnourished children with watery diarrhoea

1, **BUDGET DETAILS (enter all amounts in whole US$)**				
1.1 Personnel				
Category of Personnel (list ALL participants, even if financial support is not required)	% of full time effort devoted to project	Year 1 US $	Year 2 US $	Total US $
Professional scientific staff (functional title and name - if available)				
1. Dr. N.H. Alam	30	4,800	5,150	9,950
2. Dr. Jena D. Hamadani	20	2,550	2,750	5,300
3. Dr G.J. Fuchs	10	nil	nil	nil
4. Study Physician	100	8,088	8,492	16,580
Technical staff (functional title and name - if available)				
1. Study Nurse - 4	100	6,000	6,000	12,000
2. Research Assistant - 1	100	3,600	4,000	7,600
3. Secretarial service	20	1,300	1,400	2,700
Other staff (functional title if available)				
Health Worker - 6	100	3,600	3,600	7,200
Sub-total		29,938	31,392	61,330
Supplies & Materials				
Office supplies		700	500	1,200
Hospital supplies		600	500	1,100
Others		500	500	1,000
Sub-total:		1,800	1,500	3,300
Other Contractuals				
Rent, communication & utilities		500	500	1,000
Printing & publication		500	500	1,000
Sub-total		1,000	1,000	2,000
Interdepartmental services				
Transportation cost		700	500	1,200
Xerox, mimeography		200	200	400
Library service		100	100	200
Medical Illustration		100	100	200
Laboratory tests: Blood - Hct, CBC, total protein, alb glob ratio, serum electrolytes, blood C/S		00	2,500	7,500
Stool microscopy & culture				0
Rotavirus			500	2,000
Patient hospitalization cost ($25x5x160)			200	700
Sub-total:		00	8,000	20,000
TOTAL		52,838	12,100	32,200
			45,992	98,830

16/6/97

Indirect cost is not covered. Apx 17% of Core cost is budgetted.

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Consent Form

Your child is suffering from acute watery diarrhoea and malnutrition. One of the major treatment of diarrhoea is rehydration and replacement of stool loss with rehydration solution suitable for your child.

ICDDR,B is undertaking a study in the Clinical Research Centre, Dhaka, to evaluate a modified Oral Rehydration Solution in severely malnourished children. It is expected that this solution is better than the standard (WHO-ORS) solution for malnourished children. We request you to allow your child to participate in this study.

If you agree, the following procedures will be followed:

1. Your child will be kept in this hospital for 5 days or till diarrhoea stops. During this period your child will be examined daily and will be provided routine medical care.

2. Your child will be fed any of the three Oral Rehydration Solutions namely Standard (WHO) ORS, a modified ORS and a low osmolarity ORS to replace his ongoing stool loss. The allocation of the ORS will be made as per randomization. He will also be given usual hospital diet for diarrhoea.

3. Stool sample will be obtained for Microscopy and culture at the time of admission and will be repeated if required.

4. Two milliliter of blood will be taken for Hct, Sp.qr, Total protein, AG ratio and serum electrolyte on admission. Serum electrolyte (1.5 ml) will be repeated 24 and 48 hours after admission.

   Other relevant investigations will be done if necessary.

5. Your child's total intracellular and extracellular body water will be measured by an electric device which does no harm to him/her.

6. The study involves no risk. We will maintain the confidentiality of the medical records.

7. At any stage of the study you may withdraw your child from the study, but his/her routine care by us will not be hampered.

8. If you agree to participate in this study please sign below.

Signature of the Investigator	Signature of Witness	Signature or thumb impression of the guardian

Draft # 5.4
November 1995

Management of the Child with Severe Malnutrition

A manual for physicians and other senior health workers

1. INTRODUCTION

This manual provides practical guidelines for the management of patients with severe malnutrition.[1] It seeks to promote the best available therapy so as to reduce the risk of death, shorten hospitalization, and facilitate rehabilitation and full recovery. Emphasis is given to the management of severely malnourished children; the management of malnourished adults is considered briefly.

Severe malnutrition is both a medical and a social disorder. That is, the medical problems of the child result from the social problems of the home in which the child lives. The disease is, thus, the end result of chronic nutritional and, frequently, emotional deprivation by caretakers who, because of poor understanding, poverty or family disintegration, are unable to provide the child the nutrition and care he or she requires. Successful management of the severely malnourished requires that both the medical and social problems be recognized and corrected. If the illness is viewed as being only a medical one, the child is likely to relapse when he or she returns home, and other children in the family will remain at risk of developing the same problem.

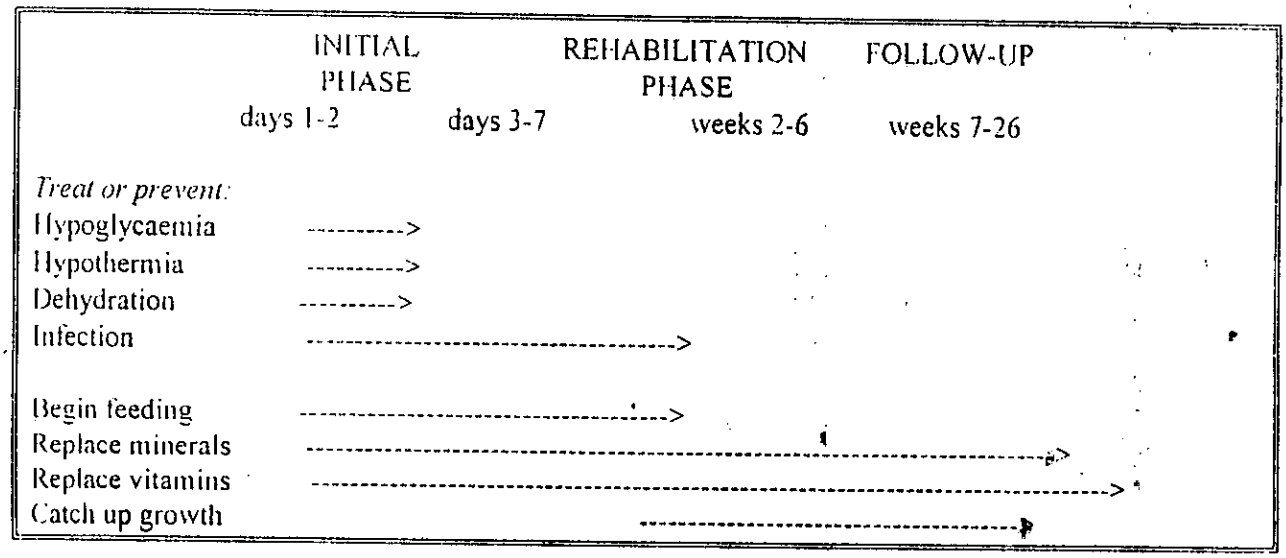
Management of the child with severe malnutrition is divided into three phases. These are:

(a) *Initial treatment:* life-threatening problems are identified and treated, specific deficiencies are corrected, metabolic abnormalities are reversed and feeding is begun;

(b) *Rehabilitation:* intensive feeding is given to recover most of the lost weight; emotional and physical stimulation is increased, the mother is trained to continue care at home, and preparations are made for discharge of the child; and

(c) *Follow-up:* after discharge the child and family are followed to prevent relapse and ensure continued physical, mental and emotional development.

A typical time-frame for the various steps in treatment and problems encountered is shown below:



[1] "Malnutrition" and "malnourished" are used as synonyms of "undernutrition" and "undernourished", respectively.

Play therapy	---------->
Prepare for discharge	---------->
Monitor growth	

Successful management of the severely malnourished child does not necessarily require sophisticated facilities and equipment, or highly qualified personnel. It does require, however, that each child be treated with tender, loving care and that each phase of treatment be carried out fully and carefully by appropriately trained and dedicated healthworkers. When this is done the risk of death can be substantially reduced and the opportunity for full recovery greatly improved.[2]

2. TREATMENT FACILITIES

Residential care is essential for initial treatment and for the beginning of rehabilitation of a child with severe malnutrition. The child should be admitted to hospital, preferably to a Special Nutrition Unit (SNU), which is an area in a general hospital that is dedicated to the initial management and rehabilitation of severe malnutrition. When the child has completed the initial phase of treatment, is without complications, and is eating satisfactorily and gaining weight (usually 2-3 weeks after admission), he or she can usually be managed at a non-residential Nutrition Rehabilitation Centre (NRC). An NRC is a "day hospital", primary health centre or similar facility that gives daytime care by staff trained in the rehabilitation of malnourished children. The child sleeps at home, is brought to the NRC each morning, and returns home each evening. Close co-operation between the hospital and NRC is necessary to ensure continuity of care for the child and facilitate returning the child quickly to hospital, should a serious problem develop. In urban areas, NRCs should, preferably, be established close to hospital facilities. Where there is no NRC, the hospital must continue to provide care until the child is ready for discharge. Important features of residential (hospital/SNU) and non-residential (NRC) treatment facilities are compared in Table 1.

3. EVALUATION OF THE MALNOURISHED CHILD

When first seen, the child must be examined, a history taken and a decision made on the treatment to be given. *Treatment should be started immediately* after the history, examination, weighing and measuring are completed. Details of the history and examination should be recorded later. Very sick children respond badly to frequent handling; they should not taken for X-rays; clinical specimens should be taken in the bed.

Table 1: Compared features of residential and non-residential care facilities

Feature	Residential care	Non-residential care

[2] A case fatality rate of >20% is unacceptable, 11-20% is poor, 5-10% is good, and <5% is excellant.

	(hospital/SNU)	(NRC)
Transport required	no	daily
Staff number and training	more staff, formally trained	fewer staff, informall trained
Diagnostic, consultant and support services	usually available	patient must be taken to hospital as an outpatient
Emergency care	day and night	not at night
Care available throughout 24h	yes	no
Patient can be fed throughout the night	yes	no
Inappropriate remedies given at home	no	often
Child is separated from the mother and home	yes or no	no
Procedures are adapted to special needs of malnourished child	unusual	yes
Staff develop special skill with malnourished children	unusual	yes
Staff turnover	rapid	slow
Risk of cross-infection	high	moderate
Mothers learn about hygiene, feeding, family planning and play therapy.	very unusual	yes
Intimidating for parents and patients	yes	much less
Cost	high	less costly

3.1. Nutritional status and admission criteria

Assessment of nutritional status according to weight, height[3] and oedema is summarized in Table 2 and illustrated in Figure 2. Also shown are the criteria for classifying severe malnutrition as "oedematous", "wasted" or "stunted". Normal values for weight-for-height or -length, are given in Appendix 1.

[3] In this manual length and height, as well as weight-for-length and weight-for-height, are used interchangeably. Children below 24 months, less than 85 cm tall, or too ill to stand should have their *length* measured lying down. Older and taller children who can stand should have their *height* measured.

Children whose weight-for-height is <70% of the median (-3SD) of NCHS reference values (termed "wasted"), or who have symmetrical oedema involving at least the feet (termed "oedematous malnutrition") are severely malnourished. They should be admitted to hospital where they can be observed treated and fed day and night.

Stunted children are usually considered to have a milder, chronic form of malnutrition. Their condition can rapidly worsen, however, with the onset of complications such as diarrhoea, respiratory infections or measles. Stunted children may be satisfactorily managed in the community, rather than in hospital. Management of children with severe stunting should follow guidelines for "preparation for discharge" (see Section 5.5).

3.2. History and examination

Points of special importance in the child's history and physical examination are listed in Table 3. It helps to use a printed proforma so that information is collected and recorded in a standard manner. A sample admission record form is in Appendix 2; it may be modified to suit local conditions.

TABLE 2: Classification of malnutrition

	Well-nourished	Mild malnutrition	Moderate malnutrition	Severe malnutrition (type)[4]
Symmetrical oedema	no	no	no	yes (*Oedematous malnutrition*)[5]
Weight-for-height	90 to 120%[6] (+2 to -1 Z)	80 to 89 % (-1 to -2 Z)	70 to 79 % (-2 to -3 Z)	< 70 % (-3 Z) (*Severe wasting*)

[4] The diagnoses are not mutually exclusive. A child can have severe wasting and oedematous malnutrition, or severe wasting and severe stunting, etc.

[5] This corresponds to the definitions of "kwashiorkor" and "marasmic kwashiorkor" in older classifications. However, to avoid confusion with the clinical syndrome of kwashiorkor, which includes other features, the term "oedematous malnutrition" is preferred.

[6] Percentage of the median NCHS standard and Z-score. For weight-for-age and weight-for-height, one Z-score unit is about 10% of the median, except in children less than 6 months of age. For height-for-age, one Z-score unit is about 5% of the median.

Height-for-age	95 to 110 % (+2 to -1 Z)	90 to 94 % (-1 to -2 Z)	85 to 89 % (-2 to -3 Z)	< 85 % (-3 z) (*Severe stunting*)

3.3 Laboratory tests

Where facilities permit, the tests given in Table 4 may help to *diagnose* specific problems. They are *not* needed, however, to guide or monitor *treatment*. The interpretation of test results is frequently altered by malnutrition. For this reason, laboratory tests may misguide inexperienced workers. *The most important guide to treatment is frequent careful assessment of the child.*

Table 3: Important points in the history and physical examination

History:

- Usual diet before recent illness
- Breast feeding history
- Food and fluids taken in past few days
- Recent sinking of eyes
- Duration, frequency and quality of vomiting or diarrhoea
- Time when urine was last passed
- Contact with measles or tuberculosis
- Any deaths of siblings
- Birth weight
- Milestones reached (sitting, standing, etc)
- Immunizations

Physical examination:

- Weight, and length or height
- Oedema
- Enlarged or tender liver, jaundice
- Abdominal distension, bowel sounds, abdominal "splash"
- Severe pallor
- Signs of circulatory collapse: cold hands and feet, weak radial pulse, diminished consciousness
- Temperature: hypothermia or fever

[7] This corresponds to "marasmus" (without oedema) in the Wellcome clinical classification, and to grade III malnutrition in the Gomez system, used for public health surveys. To avoid confusion between these definitions, the terms are not used in this manual. "Severe wasting" is the preferred term.

- Thirst
- Eyes: corneal lesions of vitamin A deficiency
- Ears, mouth, throat: evidence of infection
- Skin: infection or purpura
- Respiratory rate and type of respiration: pneumonia, heart failure
- Appearance of faeces

4. INITIAL TREATMENT

4.1 Principles of management

Table 4: Laboratory tests

Specimen or test	Result and significance
Tests that may be useful:	
Blood glucose	To *confirm* hypoglycaemia: glucose <3 mmol/l or <54 mg/dl
Blood smear	To detect malaria parasites
Haemoglobin or packed cell volume	Very severe anaemia is haemoglobin <40g/l or PCV <12%
Urine for pus cells; dip stick for infection; culture and sensitivity	Any bacteria on microscopy or more than 10 leucocytes per high power field means infection
Faeces	Observe for blood (dysentery). Microscopy for cysts or trophozoites of *Giardia*
Chest X-ray	Pneumonia causes less shadowing than in well nourished children. Vascular engorgement suggests heart failure. Bones may show rickets or rib fractures
Skin test for TB	Often negative in children with TB or previous BCG
Tests that have little value:	
Serum proteins	Not useful in management; they may guide prognosis
HIV test	Should *not* be done routinely; if done, result should be confidential
Electrolytes	Rarely helpful and may lead to inappropriate therapy

When first seen, the child with severe malnutrition is often a medical emergency. The child is "wasted", usually anorexic, often infected and appears seriously ill. Wherever possible, the child should be

referred to hospital. Successful initial management requires frequent, careful clinical evaluation and anticipation of common problems so they can be prevented, or recognized and treated at an early stage. The physiology of the malnourished child is seriously abnormal; how this affects management of the child is summarized in Appendix 3.

Recently admitted children should be kept in a special area where they can be *constantly monitored*. Because they are very susceptible to infection, this area should, if possible, be isolated from other patients. The child should not be kept near a window or in a draft, and windows should be closed at night. The child should be properly covered with clothes, including a hat, and blankets. Washing should be kept to a minimum and, if necessary, done during the day. When the child is washed he or she must be dried immediately and carefully. The room temperature should be kept at 25-30°C (77-86°F). This will seem uncomfortably warm for active, fully clothed staff, but is necessary for small, immobile children who easily become hypothermic.

Intravenous infusions should be avoided except when essential, as for severe dehydration or septic shock. Intramuscular injections should be given with care in the buttock, using a small gauge needle and the smallest possible volume.

Initial treatment begins with admission to hospital and lasts until the child's condition is stable and the child can eat, which is usually 2-7 days. If the initial phase takes longer than 10 days, the child is "failing to respond" and additional measures are required (see Section 7). The principal tasks during initial treatment, *in order of priority*, are to:

(1) *treat or prevent hypoglycaemia and hypothermia,*
(2) *treat or prevent dehydration and restore electrolyte balance,*
(3) *treat incipient or developed septic shock, if present,*
(4) *start to feed the child,*
(5) *treat infection*, and
(6) *identify and treat other problems, including vitamin deficiency, severe anaemia and heart failure.*

These tasks are described in detail below.

4.2 Hypoglycaemia

All severely malnourished children are at risk of developing hypoglycaemia (blood glucose <3mMol/l or <54 mg/dl), which is an important cause of death during the first two days of treatment. Hypoglycaemia may be caused by serious systemic infection or can occur when a malnourished child has not been fed for 4-6 hours, as often happens during travel to hospital. The best way to prevent hypoglycaemia is to give food at least every 2-3 hours day and night (see Section 4.5).

Signs of hypoglycaemia include low body temperature, lethargy, limpness and clouding of consciousness. Sweating and pallor do not usually occur in malnourished children. Often, the only sign before death is drowsiness.

If hypoglycaemia is suspected, treatment should be given immediately without laboratory confirmation; it can do no harm, even if the diagnosis is incorrect. If the patient is conscious or can be

roused and will drink, give 50 ml of 10% glucose or sucrose in water, or give F-75 diet by mouth (see Section 4.5), whichever is available most quickly. Stay with the child until he or she is fully alert.

If the child is losing consciousness, cannot be aroused or has convulsions, give 1 ml/kg body weight of sterile 50% glucose intravenously (IV), followed by a nasogastric (NG) infusion of 50 ml of 10% glucose or sucrose, to prevent a recurrence. If the dose of IV glucose cannot be given quickly, give the NG infusion first. When the child regains consciousness, immediately begin feeding F-75 diet or glucose in water (60g/l). Continue frequent oral (or NG) feeding with F-75 diet to prevent a recurrence.

Every malnourished child with suspected hypoglycaemia should also be treated with broad spectrum antimicrobials for serious systemic infection (see Section 4.6).

4.3 Hypothermia

Young infants, and those with marasmus, large areas of weeping skin or serious infection are highly susceptible to hypothermia. When rectal temperature is <35.5°C (<95.9°F) or under-arm temperature <35°C (<95°F) the patient should be warmed. The best way is to use an adult's body heat in the "kangaroo technique": the mother lies down supine, and the infant is placed on the mother's chest, against her skin, and covered with the mother's clothes and blankets. If the mother or another willing adult is not available, the child can be warmed by wrapping in blankets and placing a lamp[8] over (but not touching) the child's body. Hot water bottles are dangerous and should not be used.

Rectal temperature must be measured every 30 minutes during re-warming with a lamp, as the child may rapidly become *hyperthermic*. During rewarming, temperature under the arm is not a satisfactory guide to body temperature.

All hypothermic children must also be treated for hypoglycaemia (see Section 4.2) *and for serious systemic infection* (see Section 4.6).

4.4 Dehydration and septic shock

Dehydration and septic shock are difficult to differentiate in a child with severe malnutrition. Both show signs of hypovolaemia, and the effects progressively worsen if treatment is not given. Dehydration progresses from "some" to "severe", reflecting 5-10% and >10% weight loss, respectively; whereas septic shock progresses from "incipient" to "developed", as blood flow to vital organs decreases. Moreover, in many cases of septic shock there is a history of diarrhoea and some degree of dehydration, giving a mixed clinical picture.

4.4.1 Diagnosing dehydration and septic shock

Many signs normally used to assess dehydration are unreliable in a child with severe malnutrition, making it difficult or impossible reliably to detect dehydration or determine its severity. Moreover, many signs of dehydration are also seen in septic shock. This has two results, (1) dehydration tends to be over-

[8] An incandescent lamp, *not* a fluorescent lamp.

diagnosed and its severity over-estimated, and (2) it is often necessary to treat the child for *both* dehydration *and* septic shock.

(a) Signs of dehydration that are *not reliable* in a child with severe malnutrition include:

Mental state. The severely malnourished child is usually apathetic when left alone and irritable when handled. As dehydration worsens the child progressively loses awareness. Hypoglycaemia, hypothermia and septic shock also cause reduced consciousness.

Mouth, tongue and tears. The salivary and lacrimal glands are atrophied, so the child usually has a dry mouth and absent tears. Mouth breathing also causes a dry mouth.

Skin elasticity. The loss of supporting tissues and absence of subcutaneous fat make the skin thin and loose. It flattens very slowly when pinched, or may not flatten at all. Oedema, if present, may mask diminished elasticity of the skin.

(b) *Useful signs* of dehydration and/or septic shock include:

History of diarrhoea. A child with dehydration should have a history of watery diarrhoea. Small mucoid stools are commonly seen in severe malnutrition, but do not cause dehydration. *A child with signs of dehydration, but without watery diarrhoea, should be treated as having septic shock.*

Thirst. Drinking eagerly is a reliable sign of "some" dehydration. In infants this may be expressed as restlessness. Thirst is *not* a symptom of septic shock.

Hypothermia. When present, this is a sign of serious infection, including septic shock. Hypothermia is *not* a sign of dehydration.

Sunken eyes. These are a helpful sign of dehydration, but only when the mother says the sunken appearance is recent.

Weak or absent radial pulse. This is a sign of shock, either from dehydration or sepsis. As hypovolaemia develops, the pulse rate increases and the strength of each beat is weaker. If the pulse in the carotid, femoral and brachial artery are weak the child is near to death and must be treated urgently.

Cold hands and feet. This sign of diminished circulation is seen in both dehydration and septic shock. It should be assessed with the back of the hand.

Urine flow. Urine flow diminishes as dehydration or septic shock worsens. In severe dehydration or fully developed septic shock, no urine is formed.

The clinical features of dehydration and septic shock are compared in Table 5.

Table 5: Compared features of dehydration and septic shock in the severely malnourished child

	Some	Severe	Incipient	Developed

	some dehydration	severe dehydration	incipient septic shock	developed septic shock
Watery diarrhoea	yes	yes	yes or no[a]	yes or no[a]
Mental state	restless, irritable[b]	lethargy, coma	apathetic[a]	lethargy
Sunken eyes	yes[b,c]	yes[b,c]	no[a]	no[a]
Thirsty	drinks eagerly[b]	drinks poorly	no[a]	drinks poorly
Cool hands/feet	no[b]	yes	yes	yes
Weak or absent radial pulse	no[b]	yes	yes	yes
Urine flow	yes	no	yes	no
Hypoglycaemia	yes or no	yes or no	yes or no	yes or no
Hypothermia	no	no	yes or no[a]	yes or no[a]

[a] Signs that may be useful in diagnosing septic shock

[b] Signs that may be useful in diagnosing dehydration

[c] If confirmed as recent by the mother

(c) Other features of septic shock

With *incipient septic shock*, the child is usually limp, apathetic and profoundly anorexic, but is neither thirsty nor restless.

With *developed septic shock*, superficial veins, such as the external jugular and scalp veins, are dilated rather than constricted. The veins in the lungs may also become engorged, making the lungs stiffer than normal. For this reason the child may groan, grunt, have a shallow cough and appear to have difficulty breathing. As shock worsens the child develops kidney, liver, intestinal or cardiac failure. There may be "coffee ground" vomiting, blood in the stool, and abdominal distension with a "splash" and intestinal fluid levels on X-ray. When a child reaches this stage, survival is unlikely

4.4.2 Treatment of dehydration

Whenever possible, a dehydrated child with severe malnutrition should be rehydrated orally. *IV infusion easily causes overhydration and heart failure.* It should be used *only* when there are definite signs of shock.

(a) Oral rehydration solution for severely malnourished children

Full strength ORS solution should not be used. As total body potassium is low and total sodium is high, the rehydration solution should contain less sodium and more potassium than standard WHO ORS solution. Magnesium, zinc and copper should also be provided to correct deficiencies of these minerals. The composition of the recommended solution (named "ReSoMal") is given in Table 6.

Table 6: Composition of oral rehydration solution for severely malnourished children (ReSoMal)

Component	Concentration per litre
Glucose	125 mmol
Sodium	45 mmol
Potassium	40 mmol
Chloride	76 mmol
Citrate	7 mmol
Magnesium	6 mmol
Zinc	300 µmol
Copper	45 µmol
Osmolarity	300 mmol

ReSoMal is made by diluting one standard WHO ORS packet in *2 litres of water*, instead of 1 litre, and adding the following:

(1) 50 g of sucrose (25 g per litre) and
(2) 2 packets of "mineral mix"[9] *or*
40 ml (20 ml/litre) of concentrated mineral mix solution

(Appendix 4).

This process is summarized in Table 7.

Table 7: Preparation of ReSoMal

Ingredient	Amount
Standard WHO-ORS	one 1-litre packet
Mineral mix solution[a]	40 ml
Sucrose (cane sugar)	50 g
Water	2 litres

[a] or two packets of mineral mix salts

(b) Amount of ReSoMal to give

[9] Mineral mix packets contain the salts needed to prepare ReSoMal from diluted ORS. The same salts are also added to the child's food (see Section 4.5 and Appendix 4).

Between 70 and 100 ml of ReSoMal per kg body weight is usually enough to *restore normal hydration*. Give this amount over 12 hours, starting with about 10 ml/kg per hour for the first two hours, and then giving 5 ml/kg per hour. *This rate is slower than for children who are not severely malnourished.* Reassess the child *at least* every hour. The exact amount to give should be determined by how much the child will drink, the amount of on-going stool loss, and any signs of over-hydration, especially signs of heart failure. ReSoMal should be stopped if: (1) the respiratory rate increases, (2) the jugular veins become full, or (3) there is increasing abdominal distension.

Rehydration is completed when the child is no longer thirsty, urine is passed and any other signs of dehydration have disappeared. Fluids given to *maintain hydration* should be based on the amount of ongoing stool losses and the child's willingness to drink. As a guide, after each loose stool give a child less than two years old 50-100 ml (a quarter to half a large cup) of ReSoMal. Continue this treatment until diarrhoea stops.

(c) How to give ReSoMal

A child who can drink should be given 4-5 ml of ReSoMal every few minutes by spoon. However, malnourished children are weak and quickly become exhausted, so they may not continue to take enough fluid voluntarily. When this happens, give ReSoMal as a drip by NG tube at the same rate as orally. *An NG tube should be used from the start in all weak or exhausted children, and in those who vomit, have a rapid respiratory rate or painful stomatitis.*

(d) Intravenous rehydration

The *only indication for IV infusion* in a severely malnourished child is circulatory collapse caused by severe dehydration or septic shock. Use one of the following solutions (in order of preference):

(1) half-strength Darrow's solution with 5% dextrose,
(2) Ringer's lactate solution with 5% dextrose[10], or
(3) 0.45% (half-normal) saline with 5% dextrose[10].

Give 15 ml/kg IV each hour for two hours and monitor the child carefully for signs of overhydration. While the IV drip is being set up, also pass an NG tube and give ReSoMal through the tube (10 ml/kg per hour). After two hours, discontinue the IV infusion and continue rehydration orally or by NG tube as described above. At this time the child should have a strong radial pulse. If the radial pulse is still absent septic shock is likely and further treatment should follow guidelines for that condition (see Section 4.4.3).

(e) Feeding during rehydration

Breast-feeding should be offered every half hour without interruption. Begin to give the F-75 diet as soon as possible, orally or by NG tube, usually within 2-3 hours after starting rehydration (see amounts in Table 9). *If the child is alert and drinking, give the diet immediately, even before rehydration is completed.* Usually the diet and ReSoMal are given in alternate hours. If the child vomits, give the diet by NG tube. When the child stops passing watery stools, continue feeding, as described in Section 4.5.

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[10] If possible, add 20 mmol/l of sterile KCl.

4.4.3 Treatment of septic shock

Any severely malnourished child with signs suggesting incipient or developed septic shock should be treated for septic shock. This includes especially children with: (1) signs suggesting dehydration, but without a history of watery diarrhoea, (2) hypothermia or hypoglycaemia, and (3) oedema and signs suggesting dehydration.

Every child with septic shock should *immediately* be given broad spectrum antibiotics (see Section 4.6) and be kept warm to prevent or treat hypothermia (see Section 4.3). The child should not be handled any more than is essential for treatment. Nor should the child be washed or bathed; his or her bottom can be cleaned with a damp cloth. Iron should *not* be given. Other treatment is described below.

(a) Additional treatment of *incipient* septic shock

The child should be fed promptly, using the F-75 diet with added mineral mix. This will prevent hypoglycaemia. As these children are nearly always anorexic, *F-75 must be given by NG tube.* The amounts to be given and frequency of feeding are shown in Table 9.

(b) Additional treatment of *developed* septic shock

First, attempt to correct shock with an IV infusion using one of the fluids listed above. Give 15 ml/kg per hour. Observe the child carefully (every 5-10 minutes) for signs of overhydration and heart failure (see Section 4.9). As soon as the radial pulse becomes strong and consciousness returns, rehydration should be continued orally or by NG tube as described in Section 4.4.2 (d). If signs of heart failure develop or the child does not improve after two hours of IV therapy, give a blood transfusion (10 ml/kg slowly over at least 3 hours). If blood is not available, give plasma. If there are signs of liver failure (purpura, jaundice, enlarged tender liver) give a single dose of vitamin K_1, 1 mg intramuscularly.

During the blood transfusion nothing else should be given orally or IV. There is a substantial risk that the transfusion will cause heart failure. If there is any sign of heart failure (distended jugular veins, increasing respiratory rate or respiratory distress), give a diuretic and slow the rate of transfusion (see Section 4.9). Steroids, adrenaline or nikethamide are of no value and should *never* be used.

After the transfusion, begin to give F-75 diet by NG tube (see Table 9). If a child develops increasing abdominal distension or has repeated vomiting, give the diet more slowly. If the problem does not resolve, stop the NG feeding and give one of the IV fluids listed above at a rate of 2-4 ml/kg per hour. Also give 2 ml of 50% magnesium sulphate solution intramuscularly (see Section 4.5.3).

4.5 Dietary treatment

Children who do not require other *emergency* treatment, especially for hypothermia, dehydration or septic shock, should *immediately be given a formula diet.* Mothers should *continue to breast-feed* regardless of other foods and treatments.

4.5.1 The basic formula diets

Almost every severely malnourished child has infection, liver and intestinal dysfunction, and electrolyte imbalance when first admitted to hospital. Because of these, the child does not tolerate the usual amounts of dietary protein, fat and sodium. It is important, therefore, initially to give the child a diet that is low in these ingredients, and high in carbohydrate. The daily requirements of the severely malnourished child are given in Appendix 5.

Two formula diets are used for severely malnourished children. The first, *F-75 (75 kcal/100 ml)*, is used during the initial phase of treatment. The second, *F-100 (100 kcal/100 ml)*, is used during the rehabilitation phase, after the appetite has returned. These formulas can be purchased as a powder[11] that is simply mixed with water, or they can easily be made in a hospital kitchen from the basic ingredients: cereal flour, dried skim milk, sugar, oil, mineral mix and vitamin mix (Table 8). The recipe for the *vitamin mix* is in Appendix 4.

The mineral mix supplies potassium, magnesium and other essential minerals: it *must be added to the diet*. The potassium deficit, present in all malnourished children, adversely affects cardiac function and gastric emptying. Magnesium is essential for potassium to enter cells and be retained. Preparation of concentrated mineral mix solution is described in Appendix 4.

Table 8: Composition of liquid diets

F-75 diet

Ingredient	Amount[12]
Dried skim milk	25 g
Cane sugar	60 g
Oil	20 g
Rice flour or other cereal flour	60 g
Mineral mix	20 ml
Vitamin mix	see Appendix 5
Water	to make 1000 ml

F-100 diet

Ingredient	Amount

[11] Nutriset, Malaunay, France

[12] Mix milk powder, sugar, oil and flour in 700 ml water. Boil for 5-7 minutes. Cool, dissolve mineral mix and vitamins, and add water to make 1000 ml.

Dried Skim Milk	80 g
Cane sugar	50 g
Oil	60 g
Mineral mix	20 ml[a]
Vitamin mix	see Appendix 5
Water	to make 1000 ml

[a] or one packet of mineral mix salts per litre

4.5.2 Feeding on admission

To avoid overloading the intestine, liver and kidney, it is critical that food be given *frequently and in small amounts*. Children too weak to eat should be fed by continuous NG drip (do *not* use IV feeding). Children who can eat should be given the diet in hourly, two-hourly or three-hourly portions, day and night. If vomiting occurs, give smaller feeds more frequently.

The F-75 diet is advised for all children during the initial phase of treatment. The child should be given *at least 80, but not more than 100, kcal/kg per day*. If less than 80 kcal/kg per day are given, the child will continue to break down his or her own tissues and will deteriorate. If more than 100 kcal/kg per day are given, the child may develop a serious metabolic imbalance. The volumes of F-75 needed for 1-, 2- and 3-hourly feeds for children of various weights are given in Table 9.

Table 9: Amount of diet to give at each feed to achieve 100 kcal/kg per day

Weight of child (kg)	Volume of *F-75* for each feed (ml)			Volume of *F-100* for each feed (ml)		
	every hour (24 feeds)	every 2 h (12 feeds)	every 3 h (8 feeds)	every 2 h (12 feeds)	every 3 h (8 feeds)	every 4 h (6 feeds)
2.0	11	21	32	16	24	32
2.5	13	27	40	20	30	40
3.0	16	32	48	24	36	48
3.5	19	37	56	28	42	56
4.0	21	43	64	32	48	64
4.5	24	48	72	36	54	72
5.0	27	53	80	40	60	80
5.5	29	59	88	44	66	88
6.0	32	64	96	48	72	96
6.5	35	69	104	52	78	104
7.0	37	75	112	56	84	112
7.5	40	80	120	60	90	120
8.0	43	85	128	64	96	128
8.5	45	91	136	68	102	136
9.0	48	96	144	72	108	144
9.5	51	101	152	76	114	152
10.0	53	107	160	80	120	160

Example 1: If a 7.0 kg child is given F-75 every hour, each feed should be 37 ml.
Example 2: If a 4.5 kg child is given F-100 every 3 hours, each feed should be 54 ml.

Nearly all malnourished children have poor appetites when first admitted to hospital. Patience and loving care are needed to gently coax the child to complete each feed. Feed the child from a cup and spoon: *feeding bottles should never used*, even in very young infants. While being fed, the child should always be held securely in a sitting position on the attendant's or mother's lap. Children should never be left alone in bed to feed themselves, because they usually do not eat well.

4.5.3 Naso-gastric feeding

Despite coaxing and patience, many children will not take sufficient diet by mouth during the first few days of treatment. Common reasons include very poor appetite, weakness and painful stomatitis. Such children should be fed by NG tube. However, *NG feeding should end as soon as possible. At each feed, the child should first be offered the diet orally*, even though a tube is in place. After the child has taken as much as he or she wants, the remainder is given by tube. When the child is taking three quarters of the day's diet orally, or takes two consecutive feeds fully by mouth, the tube should be removed. If over the next 24 hours

the child fails to take 80 kcal/kg, the tube can be re-inserted. If the child develops abdominal distension during NG feeding, give 2 ml of a 50% solution of magnesium sulphate intramuscularly.

4.5.4 Feeding after appetite improves

The child's appetite is a barometer of progress: if it improves, the child is being successfully treated. The initial phase of treatment ends when the child becomes hungry. This indicates that infections are coming under control, the liver is able to metabolise the diet, and other metabolic abnormalities are much improved. The child is now ready to begin the rehabilitation phase. This usually occurs after 2 to 7 days. Some children with particularly complicated problems may take longer: whereas others are hungry from the start and can immediately be fed following guidelines for rehabilitation (see Section 5.2). It should be emphasized that ***it is the child's appetite and general condition that determine the phase of treatment*** **and not the length of time since admission.**

As soon as the child is taking 100 kcal/kg per day of F-75 orally, the diet should be changed to F-100, but intake should remain at 100 kcal/kg per day until steady weight gain is established (see Section 5.2). The amounts of diet to give are shown in Table 9. *All children receiving F-100 diet should be offered additional water between feeds.*

4.5.5 Milk intolerance

Clinically significant milk intolerance is unusual in severely malnourished children. Intolerance should be diagnosed *only* if copious watery diarrhoea occurs promptly after milk feeds are begun, the diarrhoea clearly improves when milk intake is reduced or stopped, and it recurs when the child is given milk a second time. In addition, faecal pH is <5 and there are increased faecal reducing substances. In such cases, milk should be partially or totally replaced by another liquid food (see Section 7.3.2.a). Before the child is discharged, milk feeding should be attempted again to determine whether the intolerance has resolved.

4.5.6 Recording food intake

The type of feed given, the amounts offered and taken, and the time of day must be charted accurately after each feed. If the child vomits, the amount lost should be estimated in relation to the size of the feed, for example, a whole feed, half a feed, and so on, and deducted from the total intake. Once a day the caloric intake for the past 24 hours should be determined and compared with the child's weight. If this shows the child has taken less than 80 kcal/kg, more should be given. If more than 100 kcal/kg have been given, the amount for each feed should be reduced. A typical feeding chart is shown in Figure 3.

4.6 Infections

4.6.1 Bacterial infections

Nearly all severely malnourished children have bacterial infections when first admitted to hospital. Many have several infections caused by different organisms. Infection of the lower respiratory tract is especially common. Although signs of infection should be carefully sought when the child is evaluated,

they are often subtle or absent. Unlike well nourished children with infection, who react with fever and inflammation, malnourished children with serious infections may only become apathetic or drowsy.

Early treatment of bacterial infections with effective antimicrobials improves the nutritional response to feeding, prevents shock and reduces mortality. Because infections are so common and also difficult to detect, *all children with severe malnutrition should routinely receive broad-spectrum antimicrobial treatment when first admitted for care*. Each institution should have a policy on which antimicrobials to use. These are divided into *first-line* treatment, given routinely to all severely malnourished children, and *second-line* treatment, used when a child is not improving or a specific infection is diagnosed. Although local conditions of bacterial resistance patterns, antimicrobial availability and cost will determine the policy, a suggested scheme is given below.

(a) First line treatment

(1) For children *without* suspected infection:
Cotrimoxazole, oral

(2) For children *with* septic shock, oedematous malnutrition, hypothermia, hypoglycaemia or suspected serious infection:
Penicillin, 2 days IM, then oral, *and*
Gentamicin, IM

(b) Second line treatment

(1) For children not improving with penicillin and gentamicin, or with suspected meningitis, *add*:
Chloramphenicol, oral, *or*
Cefotaxime, IM

(2) For children with dysentery, *add*:
Nalidixic, oral

See Appendix 6 for antimicrobial dosage. Length of treatment depends upon the response of the child and his or her nutritional state. Usually, antimicrobials are continued at least 5 days, *and* until the child regains appetite and starts to gain weight. When there is steady weight gain for 3 days they should be stopped.

If specific infections are detected for which another treatment is needed, for example candidiasis, malaria or intestinal helminthiasis, it should also be given (see Section 7.3). Tuberculosis is common, but anti-tuberculous drugs should be given *only* when tuberculosis is diagnosed.

4.6.2 Measles and other viral infections

Measles vaccine should be given to every malnourished child when admitted to hospital. This protects the hospitalized child from infection, and the associated high mortality, that might otherwise be introduced by a newly admitted child who is incubating measles. A second dose of vaccine should be given before discharge.

There is no specific treatment for measles, disseminated herpes or other systemic viral infections. However, most children with these infections develop secondary systemic bacterial infections and septic

shock, which must be treated as described in Section 4.4.3. Symptomatic treatment of measles includes antipyretics for temperatures over 39.5°C (103° F) and moistened air for cough.

4.7 Vitamin A and other vitamin deficiencies

Severely malnourished children are at a high risk of developing blindness due to vitamin A deficiency. For this reason ***vitamin A should be given routinely to all malnourished children on admission.***

Start treatment immediately, giving large doses of vitamin A on the first two days. Before discharge give a third dose. Intramuscular treatment is preferred at the beginning in children with severe anorexia, oedematous malnutrition or septic shock; oral treatment is satisfactory for others. Water miscible retinyl palmitate should be used, if possible. The treatment schedule is given in Table 10.

Great care must be taken during examination of the eyes, as they easily rupture in children with vitamin A deficiency. The eyes should be examined gently for signs of xerophthalmia, corneal wrinkling, dullness, xerosis and ulceration, and keratomalacia. If there is ocular inflammation or ulceration, protect the eyes with saline soaked pads. Tetracycline eye drops (1%) should be instilled 4 times a day until all signs of inflammation or ulceration resolve. Atropine eye drops should also be applied and the eye should be bandaged, as scratching with a finger can cause rupture of an ulcerated cornea. More details on the management of vitamin A deficiency are given elsewhere.[13]

Table 10: Treatment of clinical vitamin A deficiency for children 12 months or older[14]

	Retinyl palmitate	Retinyl acetate	International units[15]
Days 1 *and* 2	55 mg IM or 110 mg oral	33 mg IM or 66 mg oral	100,000 IU IM or 200,000 IU oral
Discharge	110 mg oral	66 mg oral	200,000 IU oral

[13] *Vitamin A deficiency and its consequences. A field guide to detection and control.* Third edition, 1995. WHO, Geneva

[14] Children 6-11 months should be given one half the dose shown and those less than 6 months one quarter of the dose.

[15] The International Unit (IU) of vitamin A was discontinued in 1954, but its use persists, particularly in the labelling of capsules and injectable preparations.

All malnourished children should receive 5 mg *folic acid* orally on admission. Many children are also deficient in riboflavin, ascorbic acid, pyridoxine, thiamine and the fat soluble vitamins D, E and K. All diets should be fortified with these vitamins by adding the vitamin mix (Appendix 4).

4.8 Very severe anaemia

If the haemoglobin concentration is less than 40 g/l (4g/100ml) or packed cell volume (haematocrit) less than 12%, the child has *very severe anaemia*, which can cause heart failure. Children with very severe anaemia need a blood transfusion. Give 10 ml packed red cells, or whole blood, per kg body weight *slowly* over 3 hours. If there are signs of heart failure (see below), blood should be withdrawn (2.5 ml/kg) before the transfusion is started and at hourly intervals during the transfusion so that the total volume removed equals the volume transfused. Where testing for HIV and hepatitis B is not possible, transfusion should be given *only* when haemoglobin falls below 30 g/l (or below 10% haematocrit), or when there are signs of life-threatening heart failure. Do *not* give iron during initial treatment, as it can have toxic effects and can reduce resistance to infection.

4.9 Congestive heart failure

This is usually a complication of over-hydration (especially when an IV infusion or standard ORS solution is given), very severe anaemia, blood or plasma transfusion, or giving a diet with a high sodium content. The first sign of heart failure is an increasing respiratory rate (>40/min up to 2 years; >30/min above 2 years); treatment should be started when this occurs. Later signs are respiratory distress, rapid pulse, venous engorgement, cold hands and feet, and cyanosis of the finger tips and under the tongue. Heart failure must be differentiated from respiratory infection and septic shock. It is useful to recall that these usually occur within 48 hours of admission, whereas heart failure usually occurs somewhat later.

When heart failure is *caused by fluid overload* the following measures[16] should be taken:

(a) Stop *all* oral intake and IV fluids; the treatment of heart failure takes precedence over feeding the child. No fluid should be given until the heart failure is improved, even if this takes 24 or 48 hours.

(b) Give a diuretic intravenously.[17] The most appropriate choice is furosemide (1 mg/kg).

(c) Do not give digitalis unless the diagnosis of heart failure is unequivocal (jugular venous pressure is elevated) *and* the plasma potassium level is known to be normal. In that case, 5 microgram/kg body weight of digoxin may be given intravenously as a single dose, or orally, if the IV preparation is not available.

4.10 Dermatosis of kwashiorkor

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[16] There is no reported experience in malnourished children with ACE inhibitors or other drugs used to treat heart failure.

[17] Diuretics should *never* be used to reduce oedema.

This is characterized by hypo- or hyperpigmentation, shedding of skin in scales or sheets, and ulceration of the skin of the perineum, groin, limbs, behind the ears and armpits. There may be widespread weeping skin lesions which easily become infected. Spontaneous resolution occurs as nutrition improves. Atrophy of the skin in the perineum leads to severe napkin dermatitis, especially if the child has diarrhoea. The perineum should be left exposed to dry without napkins; if the perineum becomes colonised with *candida*, it should be treated with nystatin ointment or cream and the child should be given oral nystatin (see Section 7.3.2.ed. In other affected areas, applying zinc and castor oil ointment, petroleum jelly or paraffin gauze dressings helps to relieve pain and prevent infection. The zinc supplement contained in the mineral mix is particularly important in these children, as they are usually severely deficient.

Bathe the affected areas in 1% potassium permanganate solution for 10-15 minutes daily. This dries the lesions, helps to prevent loss of serum, and inhibits infection. Povidone ointment (10%; Betadine) can also be used. It should be used sparingly, however, if the lesions are extensive, as there is significant systemic absorption

All children with this problem should receive systemic antibiotics (see Section 4.6).

5. REHABILITATION

A child enters the rehabilitation phase when a good appetite returns. No child who is being tube fed is yet in the rehabilitation phase.

5.1 Principles of management

The principal tasks during the rehabilitation phase are to:

(1) *encourage the child to eat as much as possible,*
(2) *stimulate emotional and physical development,* and
(3) *prepare the mother to continue to care for her child after discharge.*

The child should remain in hospital for the first portion of the rehabilitation phase. When a child fulfils *all* the criteria in Table 11 the child can be transferred to an NRC. This is often 2-3 weeks after admission to hospital.

Table 11: Criteria for transfer to a Nutrition Rehabilitation Centre

- Eating well
- Mental state has improved: smiles, responds to stimuli, interested in surroundings
- Sits, crawls, stands, or walks (depending on age)
- Normal temperature

Appendix 2

Composition of Milk-Cereal Diet (Milk-Suji)

Ingredients/litre	Milk Suji
Full cream milk powder	40 g
Rice powder	40 g
Sugar	25 g
Oil (Soya)	25 g
Magnesium chloride	0.5 g
Calcium	2 g
Energy (kcal/100 ml)	67
Protein (g/100 ml=l)	1.4

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Message No.:

Page 1 of 1 pages Date: 28 April 1997

From: Dr Olivier Fontaine, CHD/HQ

To: Dr N. Dewan, ICDDR, Bangladesh

Fax No.: 8802 883 116

Your ref:
Our ref:

Originator:

Subject: **EFFICACY OF MODIFIED ORAL REHYDRATION SOLUTION IN SEVERELY MALNOURISHED CHILDREN WITH WATERY DIARRHOEA**

Dear Dr Dewan,

I refer to your research proposal entitled "Efficacy of modified oral rehydration solution in severely malnourished children with acute diarrhoea" which has now been reviewed by our external advisers.

Our external advisers believed that the topic of your proposal was in an important area and agreed to provide US$53,200 for the first year of the project, subject to your agreement and answers to the following suggestions and comments:

1. The power of the study to detect differences between treatment groups in the incidence of hyponatremia and over-hydration should be provided. In addition, primary outcome variables include changes in extracellular fluid and total body water, which are proposed to be measured in a subsample. The power of the study to detect differences in these changes should be clearly stated.

2. Body weights should be measured every 6 hours for the first 24 hours and every 24 hours thereafter.

3. The definitions of hypoglycemia, hyponatremia and severe pneumonia should be provided.

4 The blinding of the study should be described in more detail.

5. Finally, in the data analysis section of the proposal, the authors are mentioning that "In addition, multivariate analysis will be done...". This statement is not clear and most probably reflects inadequate understanding of multivariate analysis. This should be clarified and described in more details.

We would appreciate your sending us your answers to these comments and suggestions in a letter (fax). Upon receipt of this, and provided the required ethical and administrative clearances within WHO are obtained, a Technical Services Agreement for US$53,200 should reach you in the near future for your signature.

With best wishes.

Dr O. Fontaine

Answer to question of WHO Reviewer's on the protocol entitled "Efficacy of modified oral rehydration solution in severely malnourished children with watery diarrhoea"

Ans. to Question No. 1

The incidence of hyponatraemia in the study group (modified-ORS group) is assumed to be 20% as compared with 2% in the control group (WHO-ORS). Considering 5% level of significance and 80% power, the sample size is calculated as 44. Considering 20% drop out, the final sample size in each group will be 53.

The incidence of over hydration in the WHO-ORS group is assumed to be 20% as compared with 2% in the modified-ORS group. Considering 5% level of significance and 80% power and 20% drop out the final sample size will be 53.

The documentation of the changes in extracellular fluid and total body water by BIA method is largely exploratory. So, we consider these to be secondary outcome variables.

Ans. to Question No. 2

We agree to measure body weights of every 6 hours for the first 24 hours and every 24 hours there after.

Ans. to Question No. 3

The definition of the conditions you mentioned are as follows :

a. Hypoglycaemia will be defined as blood glucose ≤ 3 mmol/L
b. Hyponatremia will be defined as serum sodium < 130 mmol/L
c. Severe pneumonia

Patients aged 6 m - 12 m

- respiratory rate > 50/minute with chest indrawing

Patients aged 13 m - 36 m

- respiratory rate > 40 with chest indrawing (WHO guideline)

Ans. to Question No. 4

The randomization technique and assignment of the ORS are described in the text. Since the three oral rehydration solution will be clear fluid, and the randomization technique should take care of the blinding of the study.

Ans. to Question No. 5

The statement "In addition, multivariate analysis has been deleted from the text."

All of the above corrections and informations have been incorporated in the protocol.