Attachment 1.

Date 13/9/88

ETHICAL REVIEW COMMITTEE, ICDDR,B.

Principal Investigator Dr. R.N. Mazumder

Trainee Investigator (if any) _____

Application No. 88-025

Supporting Agency (if Non-ICDDR,B) _____

Title of Study HIGH CALORIE FEEDING OF UNDERNOURISHED CHILDREN WITH SHIGELLOSIS

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

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

1. Source of Population:
   (a) Ill subjects (Yes) No
   (b) Non-ill subjects Yes (No)
   (c) Minors or persons under guardianship (Yes) No
2. 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)
3. 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)
4. 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 (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.

(PTO)

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

mendra N. Mazumder
Principal Investigator

SEP 29 1988

Trainee

SECTION 1 - RESEARCH PROTOCOL

1.	TITLE	: HIGH CALORIE FEEDING OF UNDERNOURISHED CHILDREN WITH SHIGELLOSIS
2.	PRINCIPAL INVESTIGATOR	: DR.RAMENDRA N.MAZUMDER
3.	CO-INVESTIGATOR	: DR.IQBAL KABIR
4.	CO-INVESTIGATOR	: DR.HASSAN ASHRAF
5.	CONSULTANT (Project Coordinator)	: DR.DILIP MAHALANABIS
8.	STARTING DATE	: August 1988
9.	COMPLETION DATE	: Eighteen (18) months from the date of starting
10.	TOTAL DIRECT COST	: $ 66000
11.	SCIENTIFIC PROGRAM	: This protocol has been approved by the Clinical Sciences Division.

Signature of the Associate Director, CSD

Date: 13/9/88.

ABSTRACT

Shigellosis is a major cause of morbidity in developing countries like Bangladesh. It leads to malnutrition, marasmus, kwashiorkor, growth faultering,prone to recurrent infection which increases the mortality of affected population. So nutritional intervention at the start of the infection/disease process may alter the outcome reducing morbidity and mortality.

Patients selected for study will be 1-4 years of age who will attend the outpatient department of Clinical Research Center with a history of less than 5 days of bloody mucoid diarrhoea, and who have >20 WBC/hpf on microscopic examination of stool. Patients with complicating illness will be excluded from the study. On admission, and prior to treatment and nutritional intervention all patients will have two stool cultures , one urine culture , and one blood culture taken , a chest X-ray performed , and a complete blood count, blood chemistries including total protein, serum albumin , and retinol binding protein will be determined . Patients will be hospitalized for a total of ten(10) days . Stool culture , blood count and chemistries including total protein , serum albumin, retinol binding protein will be repeated on day 5 and day 10. Blood cultures and other tests will be repeated if indicated.

Outcome will be judged by clinical and nutritional improvement, Clinical cure will be judged by duration and frequency of motions , resolution of tenesmus and abdominal cramps and fever, Nutritional improvement will be judged by weight gain , total protein, albumin, RBP assessment.

SECTION II - RESEARCH PLAN

A. INTRODUCTION

1. Objective:

To determine if intensive high calorie feeding of undernourished children with shigellosis with a calorie dense diet can improve their clinical and nutritional outcome. During their severe anorexic phase of illness (usually 48-72 hours of admission) the patients will receive nasogastric feeding if required.

2. Background:

Of the 15 million deaths occurring each year in children under five years in the developing world approximately 4 million are associated with diarrhoea. Based on studies by ICDDR,B, Dhaka and extrapolating them to world wide figures it has been estimated that approximately 0.7 to 0.8 million deaths occur in children under 5 from dysentery each year. These estimates are based almost entirely on data obtained from Bangladesh. Comparable data are not available from other parts of the world. A fatality rate of 1.2% has been reported for endemic shigellosis in the Matlab, Bangladesh treatment facility (Black et al 1980). At the Dhaka Treatment Centre of ICDDR,B mortality rate in patients with shigellosis were 3.5% for those under 1 year of age and 0.3% for all other ages including adults (Stoll et al 1982). However mortality rates as high as 6% have been reported during epidemics of shigella dysenteriae type 1 (Rogerie et al 1986, Huppertz et al 1986). The primary negative effect on the health of children who do not die from dysentery is a worsening of their nutritional status (Black et al 1984). Basic supportive therapy

for Shigella dysentery includes use of ORS and early feeding which is similar for all diarrhoeal illness. Clinical dehydration, however, is not frequently seen with dysentery when it occurs it indicates an increased severity of disease. Antibiotics are the cornerstone of treatment for shigellosis. Eradication of these large bowel invasive organisms shortens the clinical illness substantially.

Shigella infections occur most frequently in children in developing countries in the age group 1 to 4 years (Stoll et al, 1982; Boyce et al, 1987 unpublished). Under the age of one year, Shigella causes disease only about 1/2 to 1/3 as frequently but, when it occurs, the disease is more likely to be severe (Duncan et al, 1981; Martin et al, 1983; Struelens et al, 1985).

Primary negative effect on the health of children who do not die from dysentery, is the worsening of their nutritional status (Black et al, 1984). Also, from a number of studies (Duncan et al, 1981; Martin et al, 1983; Struelens et al, 1985; Clemens et al, 1986), certain risk factors have been recognised which are malnutrition (<70% weight for age), absence of breastfeeding, age less than 1 year, moderate-severe dehydration, and lack of fever or hypothermia. Malnutrition being both a risk factor for mortality from shigellosis and an important adverse consequence of the disease, nutrition management of children with Shigella disease assumes importance. During the acute phase of the disease, anorexia is an important constraint to liberal feeding of children with shigellosis, particularly those who have severe

clinical disease. A recent controlled trial in Peru (Brown et al, 1988 Unpublished) showed that energy intake at a level of 100 mcal/kg/24 hours from the first day of treatment of children with acute diarrhoea had a significantly better nutritional outcome on day 8 and day 14 of treatment compared to the group treated with restricted food intake during the first 48 hours of treatment. Shigellosis being predominantly a large bowel disease small bowel function is likely to be retained to a large extent; therefore dietary intervention in the acute phase of the disease may be very effective.

3. Rationale:

- Shigellosis is a major public health problem in developing countries.
- Shigellosis leads to adverse nutritional consequences; undernutrition is also a risk factor for severe shigellosis.
- Undernourished children are particularly velnutrable to adverse nutrition consequences due to shigellosis.
- Restoring/maintaining nutrition during acute phase and after is an attractive strategy for prevention of malnutrition and maintenance of nutrition.
- Evaluation of feeding at high calorie intake will need to be carefully evaluated to develop appropriate recommendations on feeding children with shigellosis.

2. EXPERIMENTAL DESIGN AND METHODOLOGY

SPECIFIC AIMS

1. Does intensive high calorie feeding during acute shigellosis in undernourished children 1 year to 4 years lead to better clinical outcome?

2. Does intensive high calorie feeding during acute shigellosis in undernourished children aged 1year to 4 years lead to better nutritional outcome?

C. METHODS OF PROCEDURE

1. Inclusion criteria

- Patients aged 1 year to 4 years of both sexes with a history of bloody mucoid diarrhoea of less than 5 days duration and who have more than 20 pus cells per high power field on stool microscopy,and with weight for age less than 80% of NCHS median weight will be included.

2. Exclusion criteria

- Patients with additional and obvious systemic illness (e.g. pneumonia,meningitis,etc.)will be excluded.

- Patients with complications requiring parenteral , maintenance of fluid and nutrition e.g.paralytic ileus and toxic megacolon, severe hypoglycemic/hyponatremic complications, suspected intravascular coagulation and/ or haemolytic uremic syndrome.

- Patients with kwashiorkor

3. Response variables

- Body weight changes during treatment;
- Frequency of bowel motions for each day of treatment;
- Duration of abdominal pain/tenderness by eight hourly; evaluation (as evident by pain on abdominal palpation)
- Clinical "cure" rate on day 4 and day 5; "cure" being defined by absence of liquid stools and number of bowel motions equal to or less than 4 in previous 24 hours;
- Weight and mid arm circumference on day 10;
- Food intake;

4. Sample size estimate

Patients in the control group who are offered standard treatment are expected to loose weight by atleast 10% by day 5.In a recent clinical trial of nalidexic acid in children with shigellosis at ICDDR'B the mean weight and standard deviation of a group (mean age 39 months) were 10.37 kg and 1.17.We expect that the study group receiving a high calorie intake during the 5 days of treatment will at least regain or retain their admission weight by day 5.

The sample size should be large enough to detect weight difference of this magnitude or more at a significance level of 0.05 and 80% power. The calculated sample size is therefore 22 in each group .Assuming a 15% dropout,the total sample size should be 52.

5. Baseline examination

A baseline history and examination will be obtained to determine the subject's eligibility for inclusion in the initial trial and to collect relevant data prior to beginning the study that allow,a)comparison of the study groups after randomisation and b) description of the study population to determine whether the results obatined can be compared with those from other trials. The baseline history and examination will include identification of patients,a description of symptoms prior to admission and their duration ,any treatment given for the illness, a description of feeding status prior to admission and prior to illness, a description of the stool prior to admission, results of physical examination including state of hydration, fever, body weight and other nutritional anthropometry and results of stool microscopy.The above information will be recorded on predesigned and pretested forms.

6. Informed consent:

If the patient is found to be eligible for inclusion into the study an informed consent will be obtained (Bangla consent form attached). The consent form indicates in simple words, easily understood by a nonprofessional person the purpose of the trial, the benefits and any side effects of the intervention in the study group, the fact that diet treatment will be randomly allocated, the length of stay in the hospital, examinations to be performed i.e.stool sample blood samples and nasogastric feeding if required and a clear indication that the patient is free to withdraw from the study at any time and will then receive the

standard treatment used in this hospital for his/her disease. The consent will be administered by PI and then will be witnessed by another staff member. From third day of hospitalisation patients may receive compensation for the wage loss at an appropriate rate.

7. Allocation of treatment groups

The subjects will be randomly allocated to treatment groups using methods that avoid bias. A randomisation code will be prepared using random permuted blocks with a variable block length. The randomisation list will contain more subjects than the estimated sample size to allow for patients that leave the study prematurely. After the randomisation code has been prepared, individual patients assignments clearly typed (on a piece of paper), corresponding to the master randomisation list, will be placed in a series of sealed envelopes serially numbered to correspond to trial numbers. After each patient is selected for study, next envelope in order of trial number (i.e. in numerical sequence) is opened to determine the treatment assignment; thus the investigator will not know the order of randomisation and is unable to predict what the next assignment will be. Master randomisation list and sealed envelopes will be prepared by a responsible and appropriately trained person who is not otherwise associated with the study and will be kept safely in two independent places. The randomisation list will not be accessible to persons in charge of recruiting patients or responsible for observing and recording outcome variables.

d. Case Management

Baseline data will be obtained which will include history, physical examination, stool and rectal swab for culture, stool microscopy, admission blood samples, weight, height/length, mid-arm circumference, triceps and subscapular skinfold thickness. Patients will be treated with ORS if he/she has signs of dehydration. Administration of nalidexic acid by mouth will commence soon after obtaining stool and rectal swab for culture.Control group will be offered food from 4 hours of admission appropriate for age (defined below) and then offered according to ward routine. The intention is not to deviate from the existing practices which is dependent on resources available and conforms with standard patient care. For breastfed babies mothers will be encouraged to breast feed ad lib. Intake of food (other than breast milk) will be measured. The study group will receive a two hourly feeding with a calorie dense diet (defined below) to achieve a rate of $\geq$ 200 kcal/kg/24 hour. Intake will be measured by weighing. At 8 hours of starting feeding, rate of food intake will be evaluated and if the rate is less than 40 kcal/kg/8 hrs then a nasogastric tube will be introduced and 2 hourly feeding continued and measured. The diet will largely be based on milk/cereal/oil/sugar mixture. All patients will receive Nalidixic Acid as standard antibiotic treatment, which will be changed only if the organism is found to be resistant to it.

9. Withdrawals from the study:

If a patient leaves the hospital before the end of the study, data upto the point of leaving will be considered in the analysis. If a patient develops complications which prevents the planned treatment to continue, the patient will be withdrawn from the study e.g. HUS (who may require transfer to another hospital), paralytic ileus, septicemia, pneumonia, meningitis, severe hypoglycemia/hyponatremia, a patient requiring exclusive parenteral fluid /nutrition management for any reason , data upto the time of withdrawal

will be considered in the analysis.

10. Diet:

a) Control group. Hospital diet appropriate for age will be offered on a 3-4 hourly schedule. Intake will be measured by weight.

b) Study group. A special diet composed of rice powder, milk, soya oil , sugar and rice,lentil and meat and will be used. The diet will be pretested in a representative sample of patients in two age groups 1 to 2 years and over

2 years.

11. Organization of the trial:

Patients will be selected from those attending outpatient and admitted to Research Ward II if they fulfill admission criteria. The PI with the assistance of two co-investigators will take care of the patients. Eight hourly evaluation will be recorded on a predesigned form. Patients will

be admitted from among those seen in the morning upto 11 am to enable a convenient 8 hourly schedule and facilitate recording of relevant events. Diet will be prepared in metabolic kitchen both for controls and study patients. A full time senior research assistant will be assigned to supervise diet. A pilot phase will be conduced to standardize procedures.

12. Summary of procedures:

a. Preparation and composition of diets to be used in the study.

++ Proposed high energy diet: for example a patient weighing 10.0 kg(10.0 * 200 =2000 kcal/kg/day).

Breakfast at 7 A.M.	Protein/gm	Fat/gm	Energy/kcal
Bread - 60 gm/2 slices	4.45	1.2	160
Egg (boiled) -50gm/one	6.15	6.1	80
+ Milk sujee - 200ml	7.0	14.2	300
*			
At 10 A.M.			
Milk sujee - 200ml	8.75	18.0	375
*			
At lunch			
Boiled rice - 125gm	2.65	----	150
Cooked dhal 60gm	1.5	6.6	60
**			
At 3 P.M.			
Milk sujee - 250ml	8.75	18.0	375
*			
At 6 P.M.			
Boiled rice - 125gm	2.65	----	375
Cooked dhal - 60gm	1.50	6.6	60
*			
At 9 P.M.			
Milk sujee - 200ml	7.0	14.2	300
*			
	50.4	84.9	2235
Protein Energy Ratio	10%	38%	

++ Similar charts will be prepared for patients weighing 5.5 kg,7 kg,9 kg,10 kg,12 kg,15 kg.

+Composition of milk sujee:

Full cream milk powder	--120 gm	600 kcal
Rice-powder	-- 50 gm	175kcal
Sugar	--- 90 gm	360kcal
Soy oil	-- 40 gm	360kcal
Water upto	-- 1000 ml	
		1495kcal

* Option to offer milk sujee if needed to assure planned energy intake.
**Option to add fish/meat.

++ Proposed normal diet:for example a patient weighing 10.0 kg(10.0*100 =1000 kcal/kg/day.

Breakfast at 7 A.M.	Protein/gm	Fat/gm	Energy/kcal
Bread - 30 gm/2 slices	2.22	0.6	80
Egg (boiled) -50gm/one	6.15	6.1	80
+++Milk sujee - 200ml	2.5	4.7	100
***			
At 10 A.M.			
Milk sujee - 150ml	3.75	7.05	150
At lunch			
Boiled rice - 100gm	2.1	---	120
Cooked dhal - 50gm	1.25	6.0	50
At 3 P.M.			
Milk sujee - 150ml	3.75	7.05	150
At 6 P.M.			
Boiled rice - 100gm	2.1	---	120
Cooked dhal - 50gm	1.25	6.0	50
At 9 P.M.			
Milk sujee - 100ml	2.5	4.7	100
	27.57	42.2	1000
Protein Energy Ratio	11%	38%	

+++Composition of Milk-sujee

Full cream milk powder	---80 gm	400 kcal
Rice-powder	---50 gm	175 kcal
Sugar	-50 gm	200 kcal
Soya oil	---25 gm	225 kcal
Water upto	1000 ml	1000 kcal

*** If patient demands more food 1/2 strength Milk sujee will be offered to meet the demand i.e by increasing the frequency.

Following is the summary of investigations and measurements to be done during the study period.

Admission and 8 hourly:

1. History and physical examination,

   - Weight
   - Pulse
   - Temperature
   - Rspirations
   - State of dehydration

Anthoprometry: Ht, Wt, MAC, Skinfold thickness - day1,day3, day 5,day 10(triceps,subscapular).

2. 8 hourly:

- Stool frequency and approximate volume (using diapers).
- Urine frequency and approximate volume (using PUC).
- Vomitus
- Calorie intake (by dietecian and /P.I)

After 24 hours:

- Body weight

Laboratory investigations

Admission:

Stool - Microscopic examination.

Culture for Shigella, salmonella, and Vibrios,

Campylobactor.

Elisa for for rotavirus.

Rectal swab for shigella.

Sensitivity for shigella.

Urine - analysis

Blood - Hb%, HCT, TC, DC, PC glucose (R)

- Culture
- Serum Electrolytes, Serum creatinine, Serum Total protein.
- Plasma Sp. Gr., Serum Albumin, Retinol binding protein(RBP).

CXR - APV and/or PAV

Day -5 and Day - 10

Stool - Microscopic examination

- C/S for Shigella

Blood - Hb%, HCT, TC,DC, PC, Glucose (R)

- Serum electrolyte, Serum Creatinin, Serum Total Protein, Plasma Sp. gr., Plasma Albumin, RBP.

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SECTION III - BUDGET

1. Personnel services

Name	Position	% of effort	US $
1. Dr.R.N.Mazumder	Principal Investigator	50%X18m	7863.0
2. Medical Officer		100%X18m	15606.0
3. Research Officer		50%X18m	4435.0
4. Dietecian		40%X18m	5221.0
5. Data entry technician		50%X18m	2919.0
6. Aya's (2)		100%*18m(2)	1800.0
		Total $	41776.0

2. Supplies and materials

Stationary goods	$ 500.0
Diapers	$ 600.0

3. Transportation of the patients at end of the study	$ 1000.0
4. Patient hospitalization 52 X $25 X 10days X.25	$ 13000.0
5. X-ray 52X1X.25X$2	$ 200.0
6. Drug cost	$ 500.0

7. Laboratory tests

Clinical pathology and microbiology

Stool microscopy	$ 312.0
Stool culture	$ 418.0
Rectal swab for all plates	$ 418.0
Blood for complete blood count	$ 468.0
Urine analysis	$ 104.0
	$ 1720.0

Biochemical tests

Blood electrolytes and Sp.gr.	$ 624.0
Blood glucose(Dextrxtix)	$ 000.0
Retinol binding protein	$ 2652.0
Serum Albumin	$ 416.0
	$ 3692.0

8. Xeroxing and memiography	$ 500.0
9. Medical illustration	$ 250.0
10. Computer service	$ 1000.0

BUDGET SUMMARY

Local staff salaries and benifits	$ 41776.0
Travel	$ 1000.0
Supplies and materials	$ 1200.0
Transport	$ 1000.0
Interdepartmental service cost	$ 20000.0
Xerxing	$ 500.0
Medical illustration	$ 250.0
Computer service	$ 1000.0
Total US $:	$ 66000.0

Budget has been reviewed by Budget office. This budget is ok.

S. Mon
13.9.88

CONSENT FORM

Your child is suffering from blood dysentery. It has been shown in different studies that, due to profuse loss of blood, mucus and high fever, children can develop malnutrition, oedema and weight loss. The children are also susceptible to recurrent infection. Most of the patients develop anorexia so they are unable to maintain their calorie. To counteract this problem we are investigating whether a diet with high calorie content is helpful to improve the nutritional status during acute stage of disease. If you agree to participate into the study, your child will have to stay in the hospital for 10 days. During this time your child will be treated with appropriate antibiotics. Beside this your child will be fed with either regular hospital diet or a study diet containing high calorie (1.5 kcal/g). Stool, urine and 3 ml of blood will be taken for investigation on admission and 2 ml of blood on day 5 and day 10. If your child refuse to take food by mouth, a nasogastric tube will be introduce to ensure adequate calorie intake.

You may withdraw your child from the study anytime and proper care will not be altered by that. If you agree please sign or give a thumb impression.

Signature of Investigator Signature/L.T.I. of guardian

Witness:---------- Date: -------