62

Date 1 7 81

ETHICAL REVIEW COMMITTEE, ICDDR,B.

...pal Investigator Dr. Shafiqul Alam Trainee Investigator (if any) _____

...ation No. 81-044 (Rev. 8/80-29) Sarker. Supporting Agency (if Non-ICDDR,B) _____

...of Study Protein losing entero-pathy in Post Measles Diarrhoea.

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

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

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

...oes 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)

...s the study involve:
(g) Use of records, (hospital, medical, death, birth or other) Yes (No)
(h) Use of fetal tissue or abortus Yes (No)
(i) Use of organs or body fluids (Yes) No

...subjects clearly informed about:
(j) Nature and purposes of study (Yes) No
(k) Procedures to be followed including alternatives used (Yes) No
(l) Physical risks Yes No NA
(m) Sensitive questions Yes No NA
(n) Benefits to be derived (Yes) No
(o) Right to refuse to participate or to withdraw from study (Yes) No
(p) Confidential handling of data (Yes) No
(q) Compensation &/or treatment where there are risks or privacy is involved in any particular procedure Yes No NA

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 Committee:
   ___ Umbrella proposal - Initially submit overview (all other requirements will be submitted with individual studies
   ✓ Protocol (Required)
   ✓ Abstract Summary (Required)
   ✓ Statement given or read to subjects 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 complete 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 Ctte. for review.

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

81-044
Rec'd 7/10/81

SECTION 1 - RESEARCH PROTOCOL

1. Title: Protein losing enteropathy in post measles diarrhoea.

2. Principal Investigator: Dr. Md. Shafiqul Alam Sarker

   Co-Investigators: Dr. Asma Khanam, Mr. M. A. Wahed.

3. Starting Date: October, 1981

4. Completion Date: June, 1982

5. Total direct cost: US $ 13,299.00

6. Scientific Program Head:

   This protocol has been approved by the NWG working group.

   Signature of Scientific Program Head: [signature]

   Date: 30/9/1981

7. Abstract Summary:

Excessive loss of plasma protein into the gastrointestinal tract is a leading cause in the pathogenesis of kwashiorkwar. Protein losing enteropathy following measles has been described (1). The extent and duration of such protein loss in post measles gastroenteritis is not known.

In an attempt to better define such loss and the association of measles and malnutrition, we will measure protein loss from the gut, in 25 children between 1-4 years of age suffereing from diarrhoea following measles and 25 children with diarrhoea only. To measure protein loss in stool, a recently develop method (2), which measures the presence of α_1 antitrypsin, a glycoprotein, which resist enzymatic proteolysis in the gut, will be used. Longitudinal observation of protein loss in the faeces will be maintained for a period until diarrhoea stops and 4 weeks after discharge. If the ratio of α_1 antitrypsin in stool and serum is <1.0 the patient will be diagnosed as a case of protein losing enteropathy. In addition we will look for carbohydrate malabsorption by breath hydrogen test. The findings of the two groups will be compared. By this study, we hope to learn more about the contribution of protein loss and malabsorption to the development of malnutrition after measles.

Review:

1. Research involving human subject: _____
2. Research Review Committee: _____
3. Director: _____
4. BMRC: _____
5. Controller: _____

A. INTRODUCTION:

1. Objectives: The main objectives of this study are:

i) To measure the extent and duration of protein loss in post-measles diarrhoea and after recovery.

ii) To see whether carbohydrate malabsorption is associated with post-measles diarrhoea and has any association to protein losing enteropathy.

iii) To see the impact of gastrointestinal protein loss on subsequent nutritional status in post measles diarrhoea patients.

2. Background:

Measles is a disease of children with a high mortality and severe morbidity especially in developing countries where there is high level of malnutrition (3,4,5). Mortality rates vary in different countries. In Bangladesh data from studies carried out in Matlab suggested that measles is the number three killer among preschool children and ranks after diarrhoea and tetanus neonatorum (6). In India measles ranks among the most important causes of childhood mortality (7). In developed countries the rate of death due to measles ranged between 0.1 to 0.5 per thousand population (8).

In West Africa the case fatality rate of 0.36% has been recorded. In Mexico death rate was 85 times, in Guetamala 268 times and in Equador 274 times more than the US figure (9). Death rate from East Africa ranged from 5.33, but the studies from India have shown much lower rate. In another study by Koster et al in Bangladesh, a case fatality rate of about 4% has been recorded in under four population (10). In that study he observed measles associated death was the single most common cause of death in children during his twelve months observations.

Complication of measles: Complications of measles include extensive desquamation of skin, haemolytic skin rash, diarrhoea, respiratory tract infections including bronchopnumonia and laryagotracheobronchitis, ottitis media, conjunctivitis and encepalitis.

Measles and diarrhoea: An acute episode of diarrhoea with measles has described for over a century. Severe necrotizing gastroenteritis has been described at autopsy (11) Giant cells are known to occur in the mucosa of intestine (12). This is probably due to the invasion of lymphoid tissue of the gut by rapidly multiplying virus. Jaspal and Ramkrishnan reported from India that 36 - 40% of measles cases were complicated by diarrhoea (13,14). In Nigeria out of total 179 attacks of diarrhoea in 256 children in different infection, 105 attacks occured in children with measles i.e. about 61% was measles associated diarrhoea (15).

This finding was based on 3 years observation. Ghosh also reported from India that about 30% of diarrhoea cases were associated with measles (16). In Matlab,Bangladesh (1980) S.S Nigar noted various types of diarrhoea in 92% of measles cases (17). This similar figure has also been recoreded by authors in central America (4).

The relative risk of measles was greater in children having diarrhoea. Koster et al, in 1977 reported from Matlab area that out of 33% measles associated death, diarrhoea and dysentery was the major complication associated with death in 42% (10). The importance and frequency of diarrhoea as a complication can be explained by the fact that degree of desquamation of intestinal epithelium is much more in the malnourished than in well nourished child (18). The increased duration of diarrhoea is due to infalmmation of epithelial lining resulting non absorption of fluid by the vili. There is also inflammation of lymph channel and nodes causing increase in passage of stool (19).

Measles and Malnutrition: Measles and a complicating diarrhoea may be the precipating cause of keashiorkwar (20). Brown R. E. et al (21) in 1966 found that among 197 children hospitalized with kwashiorkwar in Uganda 62% had associated infection and the commonest of these was measles. Another study from Senegal showed that measles was a frequent precursor of severe malnutrition and a higher measles mortality was observed in those children who were under weight (18).

In Nigeria a longitudinal study shcwed that children lost more than 10% of former weight as a result of measles and did not recover their weight quickly after disappearence of rashes but took about 2 months. Children who had diarrhoea took twice as long to regain their lost weight than children who had nc diarrhoea with measles (3). Koster (10) also noted longer period to regain lost weight.

The high incidence of measles at 1-4years of age coincides with the age distribution of diarrhoeal disease with that for malnutration the later is due to inadequate supplementation of breast milk and reduced intake during an after weaning.

For children, nutritional status may be the key factor in determining the severity of measles and the likelihood of mortality. Malnutrition may cause a more severe attack of measles. A study from West Africa noted that the undernourished who suffer an attack of measles

often go on to develop Kwashiorkwar (22). The mortality rate from measles in malnourished rural Guetamalan children was 189 times that seen in US in 1959 (23). The high fatality rate occurs in the age group in whom malnutrition is most common, especially during the weaning period (24). Reduced intake or unavailability of food during this period are considered contributing factors. There is decrease in host resistance at this point and maternal immunity tends to decline. Also the nutritional requirement of this group of child by breast milk is not maintained at this point. Dossetor et al in 1977 (25) showed that malnourished children had more severe and prolong attacks than well nourished children. This observation suggests that defective immune response in malnourished children make them more susceptibility to secondary infection.

Post measles protein loss and malabsorption:

Excessive loss of plasma protein into the gastrointestinal tract may be major factor in the pathogenesis of Kwashiorkwor (26). Evidence of gastroentestinal protein loss in postmeasles gastroenteritis has been reported (1). Association of protein loss and malabsorption has also been reported in acute measles infection with diarrhoea in under weitht and malnourished children (1.27). Morely noted that many West African children had blood in their stool during the first few days following measles (3).

Since blood is present in the stool protein loss may also occur. Protein loss in the patient may be related to diarrhoea. Shukry et al in 1965 reported that children lost little protein in absence of diarrhoea (28). Hence, the development of malnutrition might be more common in post measles diarrrhoea than measles in it self.

It is not known whether measles virus has any specific role in the syndrome of post measles diarrhoea. Super infection by bacteria or fungi in the bowel is a possible explanation. As xylose absorption is deppressed by systemic bacterial infection (29). So it might also be present in measles and result in diarrhoea.

The extent and duration of protein loss and malabsorption has not yet been convincingly documented. Hence, it would be important to find out the contribution of such loss and malabsorption in postmeasles nutritional disorders.

Previously, the methods to detect the gastrointestinal protein loss required the use of radio active materials (30,31,32,33). These methods are expensive, cumbersome and introduce considerable technological handicaps and potential health hazards. In an attempt to learn the extent and duration of protein loss in post measles diarrhoea we will measure protein loss from the gut by measuring

α_1 antritrypsin in a random fecal sample and blood. This α_1 anti-trypsin is a glycoprotein and a serum protease inhibitor. It is synthesised by the liver and is responsible for nearly all the protease inhibiting capacity, hence the name. Its normal serum concentration is about 250 mg/dl and is reported to react as acute phase reactant protein (34,35,36)) and found with rapidly increased concentration in stress condition like any acute beneferial or viral infection, burn, post operative trauma etc (37,38,39)). It also appears that the observation of increased level of this protein is helful for indicating inflammatory bowel disease (40) . Recently many authors (41,2) , has documented endogenous protein loss by using this $\alpha_1$antitrypsin as a reliable index.

3. Rationale:

Malnutrition is a common consequence of post measles diarrhoea. The contribution of protein loss to the development of malnutrition following post measles should be studied in an attempt to develop strategies for preventing malnutrition post measles.

SECTION II - RESEARCH PLAN

B. Specific aims:

1. To measure the extent and maginude of protein loss in post-measles diarrhoea.

2. To see whether carbohydrate malabsorption is associated with protein losing enteropathy in post measles diarrhoea.

C. Methods and procedure:

There will be two groups of children of 1-4 years age of either sex and are non breast fed.

First group: 20 children attending outpatient department of ICDDR,B with 2-5 days history of diarrhoea following measles within three weeks will be selected. All patient will be examined clinically. All anthropometic measurement (Height, weight, Midarm circumference, Head circumference, Chest circumference) will be taken. The patient with followings will not be selected.

1. Severe malnutrition: 60% and below wieght for age, 70% and below weight for height of Matlab Standard and all cases with aedema irrespective of weight.

2. Gross electrolyte imbalance: Extreme lethargy, abdominal distension, convulsion, doughy skin, absent or sluggish bowel sound etc.

3. Severe bronchopneumonia: Breathlesness, dyspnoeia, hurried respiration, subcostal suction and diffuse bilateral crebs in lung.

4. Ottitis Media: Discharge of pus per ear.

5. Any patient who received antibiotic during past 4 weeks and patients whose clinical status indicate immediate antibiotic intervention.

After admission, dehydration will be corrected by intravenous infusion and on going losses will be replaced. After rehydration 3 ml blood will be drawn for CBC plasma protein, α_1 antitrypsin, electrolyte, urea and creatinin. Urine will be obtained for analysis, stool will be collective for microscopic examination and microbiological investigation for v. cholerae, salmonella, shigella and E. coli. Toxigenicity test of E. coli (ST & LT) will be performed by infant mouse assay and chinese hamster ovarian cell assay respectively. ELISA test will be performed for rotavirus. Usual hospital diet will be allowed.

A paediatric urine collector (PUC) bag will be fixed in the perineum to collect stool and urine separately. Total amount of stool and urine output in 24 hours will be recorded and the sample will be kept in ice surrounded bucket. The patient will be kept in the hospital until diarrhoea stops.

During this period .5 ml blood will be drawn by finger pick for estimation of $\alpha_1$antitrypsin in every alternate day till diarrhoea stops. Stool will be collected 24 hourly and will be homogenised and 20 c.c. aliquote will be taken for estimation of $\alpha_1$antripsin in each day of blood sampling.

Breath hydrogen test will be done twice, on admission and on day of stoppage of diarrhoea. For that, patient will be kept fasting from midnight for atleast 6 hour and 2 gm/kg (not exceeding 20 gm) of lactose dissolved in a glass of water will be fed to the children. L - BHT test will be performed using an intermittent sampling technique according to the protocol Ayesha Molla et al (81 - 027). Breath sample will be collected before ingestion of lactose and at 30 min and then at hourly interval for 3 hours. For colection of expired breath samples the subject blew directly into an anaesthesia bag through a plastic value or breath through a face mask and two way valve system in case of younger children and infants. The hydrogen concentration of expired air will be determined by a quintron gas chromalograph. A rise of more than 20 PPM at 2nd hour being considered as a case of lactose malabsorber (42). This test is recently practiced in our laboratory.

Appropriate antibiotic will be started just after second L-HBT if needed. The patient will be discharged when she/he becomes clinically well and free from obvious sign of infection.

Second group: This group will consist of 20 children attending the ICDDR,B outpatient department due to diarrhoea only and had no history of measles previously within last 6 months period. This group will be equally matched for age, etiological agents, socioeconomic and nutritional status of the first group. The mathodology and treatment will be same as applied in first group.

All patients will be requested to return or arranged to bring them back after 4 weeks of discharge for 3 days. During this period the above tests will be perfromed as well.

The total portein and albumin ancentration will be measured by electrophoresis. $\alpha_1$antritrypsin concentration will be measured by radial immunodiffision technique (Mancini). Urinary protein will be measured using sulphosalicyclic acid. Protein electrophoresis will be performed. Stool sample will be processed as per crossley et al (2).

$\alpha_1$antitrypsin in both stool and serum will be measured by using "M" Partgen plates manufactured by Boehringer. For each batch of plates a reference curne will be established with standard solution. We will determine the protein losing enteropathy (PLE) using the arbitary ratio (stool mg/gm dry weight over serum gm/L) 1.0 as the screening point.

Analysis of the result: We will first determine protein using ratio of 1.0 as the screening point. Difference of positive or negative protein loss within the groups and etiologies will be compared by students "t" test. The result between the stages will be compared by using paired "t" test.

D. SIGNIFICANCE:

Intestinal protein loss may be an important factor in protein energy malnutrition. Post measles diarrhoea is considered to be associated with such loss. The duration and extent of such loss is needed to evaluate its important and prognosis and to develop methods of therapy to curtail the malnutrition following post measles diarrhoea.

E. FACILITIES REQUIRED:

1) Only 6 dozen of "M" partigen plates will be required.
2) Office space: The present study ward will be used.
3) Laboratory space: Existing laboratory space in Biochemistry will be utilized.
4) Logistic Support: For data processing help of statistics branch will be required.

5. COLLABORATIVE ARRANGEMENT: none

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Figure 1

Daily Longitudinal observation of α_1-Antitrypsin ratio of serum and stool according to aetiology.

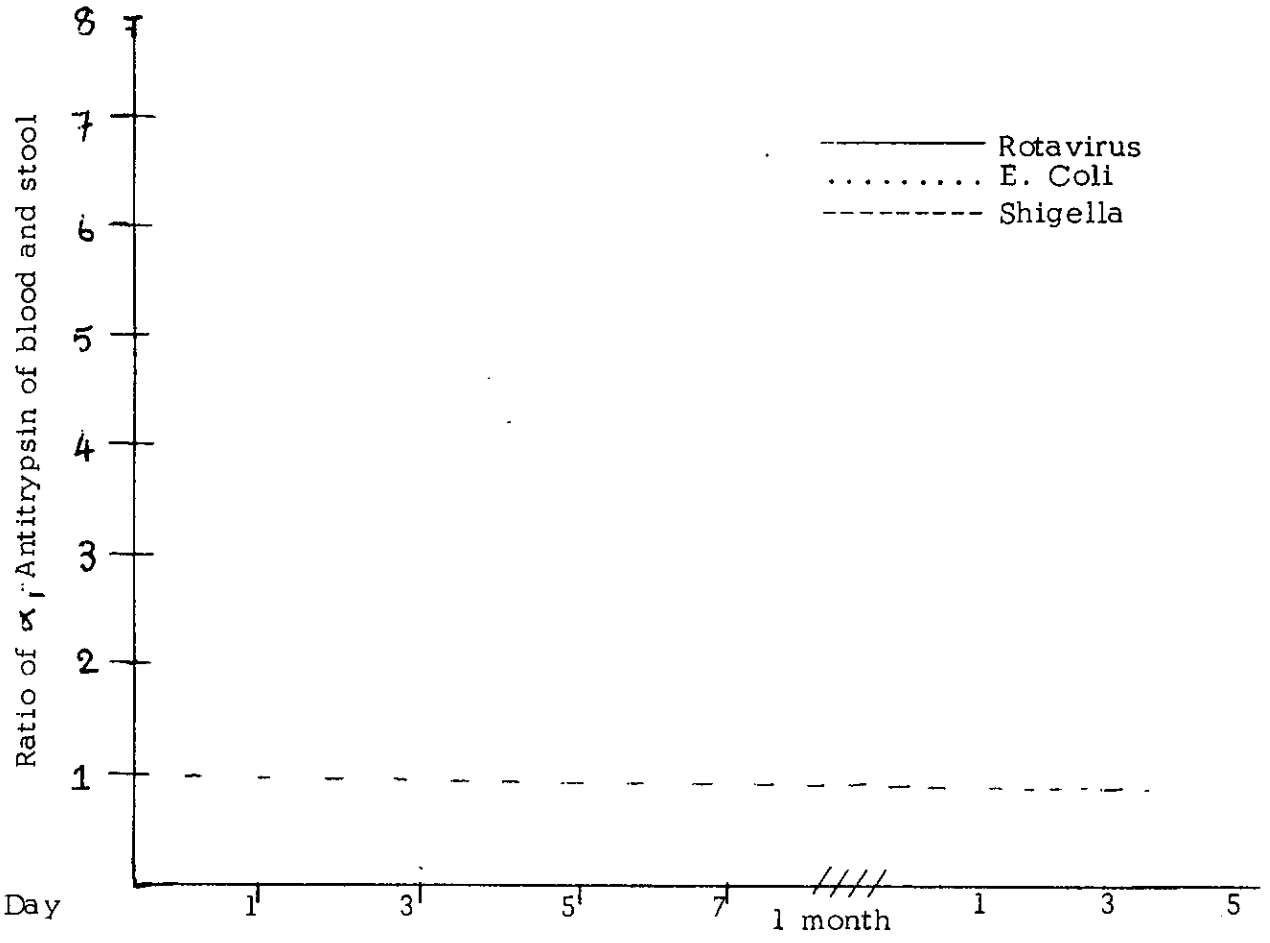

TABLE - 1

GENERAL PARTICULARS OF THE STUDY CHILDREN

	Post measles diarrhoea group	Only diarrhoea group
ɔ. of children		
·e in months		
ɔx		
ɔdy weight(kg)		
ɔight (cm)		
ɔight for age (%)		
ɔight for height(%)		
ration of diarrheea ɔore admission(Hrs)		
sma protein mg.(%)		

TABLE 2

RATIO OF α_1-ANTITRYPSIN (STOOL OVER BLOOD) IN TWO GROUPS OF ALL ETIOLOGY

Days	Post measles diarrhoea group	Only diarrhoea group	P.Value
1st day			
3rd day			
5th day			
7th day			
Recovery			

TABLE - 3

INCIDENCE OF PROTEIN LOSING ENTEROPATHY(PLE) AND CARBOHYDRATE(CHO) MALABSORPTION IN STUDY CHILDREN ACCORDING TO AETIOLOGY.

	Post Measles diarrhoea group(PM)				Only diarrhoea group (D)			
	PLE		CHO Malabsorption		PLE		CHO Malabsorption	
	Acute	Recovery	Acute	Recovery	Acute	Recovery	Acute	Recovery
ta Virus								
Coli								
igella								

TABLE - 4

CHANGE OF NETRITIONAL STATUS FROM ACUTE STAGE TO RECOVERY STATE.

	POST MEASLES DIARR. GROUP (PM)			ONLY DIARRHOEA GROUP (D)		
	Acute	Recovery	P value	Acute	Recovery	P value
weight						
or weight (%)						
ht for height (%)						
n protein mg (%)						
ıtitrypsin in serum						
ıtitrypsin in stool						
of rypsin of n & stool						

SECTION III

A. DETAIL BUDGET: (For 9 months):

1. PERSONNEL SERVICES:

Name	Position	% Effort	Annual Salary	Project Required Tk.	$
Dr. Shafiqul Alam Sarker	Principal Investigator	50%	34,500	12938	809
Dr. Asma Khanam	Co-Investigator	25%	55,392	10386	649
Mr. M. A. Wahed	do	20%	46,740	7011	438
One Sr. Staff Nurse		50%	24,000	9000	563
One Cleaner		25%	12,000	2250	141
One Sr. Lab. Technician		25%	34,800	8700	544
One Field Asstt.		50%	19,200	7200	450
Henry Ghose (Study Clerk)		20%	18,000	3600	225
			Sub Total	61,085	3,819

2. SUPPLIES AND MATERIALS:

Items:	Unit cost	Amount Required
6 dozens M. partigen plates (Antitrypsin)	$ 193.00	$ 1158.00
6 vials known standard	$ 5.00	$ 30.00
One box Electrophoresis membrane	$ 33.00	$ 33.00
One Roll scaning paper	$ 5.00	$ 5.00

	Unit cost	Amount Required	Project Tk.	Dollar
Rectal swab for V. cholera	Tk. 3.00	300	900	56
Rectal swab for salmonella and shigella.	Tk. 2.50	300	750	47
Culture for E. coli	Tk. 2.00	300	600	38
ST Assay Mice	Tk. 3.00	300	900	56
Rotavirus (Elisa)	Tk. 1.50	300	450	28
Syr. Ampicillin	$ 15.80/L	3 litres		47
Other drug (Syr. Paramex, Tixylis, Syr. M. Vitamine)			1000	63
		Sub Total	24,976	1,561

3. EQUIPMENT: Nil

4. PATIENT HOSPITALIZATION:

600 patient day 200 Tk./day — 1,20,000 — $7,500

5. OUTPATIENT CARE: Nil

6. ICDDR,B TRANSPORT: 800 miles land transportation Tk. 1600 $ 100

7. TRAVEL AND TRANSPORTATION: International Travel - Nil

8. TRANSPORTATION OF THINGS: Import of supplies - Tk. 4500 $ 281

9. RENT, COMMUNICATION AND UTILITIES: Nil

10. PRINTING AND REPORDUCTION: Memeograph Tk. 300 $ 19
Xerox cost Tk. 300 $ 19

11. OTHER CONTRACTUAL SERVICE: Nil

12. CONSTRUCTION: Nil

SECTION - IV

BUDGET SUMMARY

		Taka	Dollar
1.	Personnel	61085	3819
2.	Supplies	24976	1561
3.	Equipment	-	-
4.	Hospitalization	120000	7500
5.	Outpatient	-	-
6.	Transport	1600	100
7.	Travel	-	-
8.	Transport of thing	4500	281
9.	Rent	-	-
10.	Printing	600	38
11.	Contractual service	-	-
12.	Construction	-	-
	Total =	2,12,761	13,299

(Convertion rate $1.00 = Tk. 16.00)

ABSTRACT SUMMARY FOR ETHICAL REVIEW COMMITTEE

Excessive loss of plasma protein into the gastrointestinal tract is a leading cause in the pathogenesis of kwashiorkwar. The extent and duration of such protein loss in post-measles gastroenteritis is not know. In an attempt to find out such loss and to define more precisely the association of measles and malnutrition, we will measure protein loss from the gut. It is planned to carryout the study on 25 children between 1 - 4 years of age suffering from diarrhoea following history of measles

To measure protein loss in stool, a recently developed method [1] which measures the presence of $\alpha_1$antitrypsin, a glycoprotein, (which resists enzymatic proteolysis in the gut) will be used. Longitudinal observation of protein loss in the faeces will be maintained for a period until diarrhoea stops and after 4 weeks of discharge. If, the ratio of α_1 Antitrypsin in stool and serum is <1.0, the patient will be diagnosed as a case of protein losing enteropathy. Attempt will be made also to detect malabsorption by breath hydrogen test.

The findings of this group will be compared with another one group of 25 children with diarrhoea only matched for age, socioeconomic and nutritional status. By this study we will be able to find out the contribution of protein loss and malabsorption in the development of malnutrition after measles.

1. There will be two groups of patients of 1 - 4 yrs age:

   First group: 25 children with history of diarrhoea following measles.

   Second group: 25 children with history of diarrhoea only.

Measles is prevalent in children of 1-4 years of age group. Which are complicated by the onset of diarrhoea. In this condition the marked protein loss through the gastrointestinal tract is the usual accompaniment. This leads to malnutrition and thus carries on appreciable mortality and morbidity in children.

2. No potential risk.

3. Not applicable.

4. Confidentiality of the record of the patient will be maintained if necessary.

5. a) Though there is no such potential risk, still we will obtain a signed consent from legal guardian or patients.

   b) Not applicable.

   c) Not applicable.

6. No involvement of interview except to obtain the history of illness which is done routinely.

7. The society as a whole shall be potentially benifited from this study in future. At the time of post-measles diarrhoea, the continuous loss of protein through gastrointestinal tract along with malabsorption may leads to malnutrition. This study will help us to asses the extent and duration of such loss, and malabsorption, so that an effective therapy along with suitable nutritional intervention programme may planned to combat he malnutrition following post measles diarrhoea. So there will be general benifit to these patient and the society.

8. We will use the patient records. We shall take 1 ml of blood in every alternate day till diarrhoea stops from patient. On the 2nd day and day of stoppage of diarrhoea intermittent breath sample collection will be needed. These samples will ne needed in the follow-up period as well.

ICDDR,B

Protein losing Enteropathy in Post-measles Diarrhoea

CONSENT FORM

The International Centre for Diarrhoeal Disease Research, Bangladesh is carrying out studies on cholera and other diarrhoeal diseases to find out its most effective treatment and along with its nutritional consequences. It is learnt by us, that following measles, most of the children developed diarrhoea and in that case the protein loss through gastrointestinal tract along with malabsorption of carbohydrate is more marked, So that child become malnourished. We have planned to detect such loss and malabsorption. We like your child to participate in the study for well being of mankind.

If you allow your child to participate in our study, you can expect the followings:

1. Your child will be given best possible medical care for his diarrhoea and associated illnesses.

2. Your child will be kept for a period, until diarrhoe stop and a period of five days afer 4 weeks.

3. Routine investigation like blood, stool, and urine will be done to know the condition of your child.

4. 1 ml blood will be taken on every alternate day after admission to know the protein level of your child.

5. At moring of second day of admission and on the day of stoppage of diarrhoea, we will feed lactose (which exists in milk and like test of sugar) to your child and we will collect four breath sample at ½ hour and then at one hourly interval. By this test the absorption the absorptive capacity of milk by your child will be assess and thus we will be able to advise properly if your child is found to be malabsorber.

6. If you don't allow your child to participate in this study, there will not varation of usual treatment.

7. Above all, you will be at liberty, to witdraw your child from the study at any time, without any obligation.

If you are willing to participate in the study, please sign below:

Signature of Investigator: _____

Date: _____

Signature of Parent/Legal Guardian

Or Left Thumb Impression: -------