Date 20 August 1984

ETHICAL REVIEW COMMITTEE, ICDDR,B.

Principal Investigator Dr. M.R. Islam

Application No. 84-037P

Trainee Investigator (if any) _____

Supporting Agency (if Non-ICDDR,B) _____

Title of Study "Role of Antibiotic Resistance and Treatment in Hemolytic Uremic Syndrome of Shigellosis". (Pilot study).

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: N.A.
   - (a) Ill subjects — Yes No
   - (b) Non-ill subjects — Yes No
   - (c) Minors or persons under guardianship — Yes No

   NA

2. Does the study involve: N.A.
   - (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

   NA

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: N.A.
   - (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

   NA.

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

   NA

6. Will precautions be taken to protect anonymity of subjects — Yes No — NA

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.

   NA.

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

Principal Investigator

Trainee

21 AUG 1984

84-037P
21/8/84

SECTION 1 - RESEARCH PROTOCOL

(Limited study)

1.	TITLE:	ROLE OF ANTIBIOTIC RESISTANCE AND TREATMENT IN HEMOLYTIC UREMIC SYNDROME OF SHIGELLOSIS.
2.	PRINCIPAL INVESTIGATOR:	Dr. M.R. Islam
	CO-INVESTIGATORS:	Dr. Thomas Butler, Dr. A.K. Azad.
3.	STARTING DATE:	August 1984
4.	COMPLETION DATE:	October 1984
5.	TOTAL INCREMENTAL COST:	US $ 700.00
6.	SCIENTIFIC PROGRAMME:	This protocol has been approved by the Pathogenesis and Therapy Working Group.

Signature of Scientific Programme Head: T Butler

Date: 19-8-84

7. ABSTRACT SUMMARY:

The purpose of this limited study is to review charts of about 30 patients admitted to the Hospital Ward of the ICDDR,B from 1980 to 1984 who had shigellosis with hemolytic uremic syndrome. The reason for examining the clinical data gathered on these patients is to explore the relationships between antibiotic resistance and treatment, development of the hemolytic-uremic syndrome of shigellosis.

8. REVIEWS:

(a) Research involving human subjects: _____

(b) Research Review Committee: _____

(c) Director: _____

SECTION II - RESEARCH PLAN

A. INTRODUCTION:

1. Objective:

The purpose of this work is to carry out a retrospective review of patient's charts to obtain clinical data on the relationships between antibiotic resistance and treatment in the development of the hemolytic-uremic syndrome of shigellosis.

2. Background:

In 1975, Rahaman and co-workers at the ICDDR,B described a devastating complication of shigellosis in Bangladeshi children, now called the hemolytic-uremic syndrome after shigellosis (1). Similar syndrome had been reported from South India in 1978 (2). It occurred in about 10% of children admitted to the hospital with shigellosis. Patients with the HUS differed from other patients by being usually less than 2 years old, having a severe grade of colitis by proctoscopy, having leukemoid reactions (WBC 50,000 per cu mm), and having stool cultures positive for shigella dysenteriae type 1 (shiga bacillus). The complication occurred most often in the second week of illness when the patients were afebrile and their diarrhea was diminishing in intensity. It was marked by a falling hematocrit and platelet count, erythrocyte fragmentation and reticulycytosis, oliguria, and a rising blood urea nitrogen. More than half of oliguria, and a rising blood urea nitrogen. More than half of these children died. Investigations by Koster and co-workers at the ICDDR,B showed that most of these patients had endotoxemia

(as defined by the limulus test), intravascular coagulation, and circulating immune complexes (3), and postmortem examinations of the kidneys revealed depositions of fibrin in renal glomeruli and renal artieries (4). Thus, a role for endotoxemia being found significantly more frequently in HUS cases than in the non-HUS shigellosis cases, the temporal association of endotoxemia and onset of hemolysis, and the autopsy finding of renal glomerular thrombosis which is the hallmark of the generalized Shwartzman reaction, that is produced experimentally in rabbits by two intravenous injections of endotoxin spaced about 24 hours apart (5).

Antibiotic resistance is common in shigella isolates in Bangladesh and other countries. The complication of HUS could result from inadequately treated shigellosis due to antibiotic resistance. Alternatively, rapid killing of bacteria by effective antibiotic could release endotoxin from dying bacteria to trigger the complication.

B. SPECIFIC AIMS:

1. To review about 30 charts of patients admitted to ICDDR,B from 1980-1984 with hemolytic uremic syndrome and shigellosis.

2. To record on data sheets information regarding age, sex, date of admission, history of illness, physical examination, laboratory data, diagnosis, hospital course, and outcome.

3. To enter these data onto discs for computer storage and analysis.

4. To seek answers to the following questions:

   (a) For the entire group of patients with hemolytic uremic syndrome what are the distributions of age, sex, symptomatology, diagnoses, physical findings, stool picture, antibiogram, antibiotic treatment, and the clinical outcome.

   (b) How did the HUS cases differ from non-HUS controls in regard to incidences of clinical findings and means of laboratory data and clinical outcomes.

C. METHODS AND PROCEDURE:

1. Chart Collection and Review.

   (a) 30 charts of admitted patients will be selected as cases of HUS. They must have Shigella species isolated from stool or blood. They must have a 10% or greater decrease in Hct or a single Hct determination <20% plus a creatinine value >200 µmoles per 100 ml.

   (b) 30 control charts will be selected from admitted patients with shigellosis that matched for age to the nearest year and matched for species of shigella.

2. Available data will be recorded in the data sheet, attached with the protocol, for entering onto computer discs. Specific questions will be asked for interrelationships and interpretations of these datas.

D. SIGNIFICANCE:

Examination of charts in this retrospective review will provide valuable information on the magnitude of the problem of the HUS of shigellosis, the relationship of the HUS to antibiotic resistance and treatment, and further details of the clinical features and outcome in the HUS. This study can provide the basis for planning new prospective studies of shigellosis in Bangladesh.

E. FACILITIES REQUIRED:

No extra facilities required.

SECTION III - BUDGET

1. Personnel

Name:	Position	% effort	Project Requirements Taka	Dollar
Dr. M.R. Islam	Principal Investigator	20%	10,000	-
Dr. Thomas Butler	Co-investigator	5%		1200
Dr. A.K. Azad	Co-investigator	30%	5,400	-
Mr. H.B. Ghose	Clerk	20%	1,600	
			17,000	

2. Supplies and Materials: Nil
3. Equipments: Nil
4. Hospitalization cost: Nil
5. Travel: Nil
6. Ani,al Resources: Nil
7. Logistic support: Nil
8. Printing and Reproduction: US $ 500
9. Computer time - 5 hours (@ Tk. 1000 per hour) Tk. 5000

TOTAL: US $ 2580

(Conversion rate US $ 1 = Tk. 25)

Personnel salary: US $ 1880

Total Budget excluding personnel salary: US $ 700

REFERENCES:

1. Rahaman MM, Alam AKMJ, Islam MR et al. Shiga bacillus dysentery associated with marked leukocytosis and erythrocyte fragmentation. Johns Hopkins Med J.; 136 : 65-70, 1975.

2. Raghupathy P, Date A, Shastry JCM et al. Hemolytic-ureamic syndrome complicating shigella dysentery in South Indian children, Br. Med. J.; 2 : 1518, 1978.

3. Koster F, Levin J, Walker L, et al: Hemolytic uremic syndrome after shigellosis: Relation to endotoxemia and circulating immune complexes. N. Eng. J. Med.; 298 : 927, 1978.

4. Hammond D, Lieberman E. The hemolytic uremic syndrome: renal cortical thrombotic microangiopathy. Arc Intern Med.; 126 : 816-821, 1970.

5. Gaynor E. Bouvier C, Spaet TH. Vascular lesions ' possible pathogenic basis of the generalized shwartzman reaction. Science; 1970 : 486, 1981.

Date sheet: Role of antibiotic resistance in H.U.S.

Stat: 219 (1-3) · Card: A (4)

Patient's Name: _____ Patient's No.: / / / / / / (5 - 9)

Date of admission: / / / / / / / / (10 11 12 13 14 15) Day/month/year

Age: / / / / / / (16 17 18 19) Years/months

Sex: / / (20) Male = 1, Female = 2

Other family members affected: / / (21) Yes = 1, No = 2

Days of illness prior to admission: / / / (22 23)

Weight: / / / / / (24 25 26) (kg)

Weight/age Percentile (NCHS): / / / (27 28)

Jaundice: / / (29) (Yes = 1, No = 2, Not recorded = 9)

Oedema: / / (30) (Yes = 1, No = 2, Not recorded = 9)

Abdominal pain: / / (31) (Yes = 1, No = 2, Not recorded = 9)

Tenesmus: / / (32) (Yes = 1, No = 2, Not recorded = 9)

Rectal prolapse: / / (33) (Yes = 1, No = 2, Not recorded = 9)

Duration of diarrhoea: / / / (34 35) (Days)

Frequency of diarrhoea: / / / (36 37) (Stools/day)

Character of stool: /___/ (38)
(Watery = 1, Bloody = 2, Mucoid = 3, Semi solid = 4, Watery bloody = 5, Watery mucoid = 6, Bloody-mucoid = 7, Not recorded = 9).

Stool culture: /___/ (39)
(Shig. dys 1 = 1, Shig dys 2 = 2, Shig flex = 3, Shig boydii = 4, Shig sonni = 5).

Antibiogram: (Sens = 1, Res = 2, Not done 9)

Ampicillin /___/ (40)

SMZ /___/ (41)

Tetracycline /___/ (42)

Chloromycetin /___/ (43)

Gentamicin /___/ (44)

Other (specify) /___/ (45)

Antibiotics given in hospital:

Ampicillin	/___/ (46)	(Yes=1, No=2)	Date started	/___/ (47 48)	Date stopped	/___/ (49 50)
TMP-SMZ	/___/ (51)	(Yes=1, No=2)	Date started	/___/ (52 53)	Date stopped	/___/ (54 55)
Genta	/___/ (56)	(Yes=1, No=2)	Date started	/___/ (57 58)	Date stopped	/___/ (59 60)
Chloro	/___/ (61)	(Yes=1, No=2)	Date started	/___/ (62 63)	Date stopped	/___/ (64 65)
Penicillin	/___/ (66)	(Yes=1, No=2)	Date started	/___/ (67 68)	Date stopped	/___/ (69 70)
Other (specify)	/___/ (71)	(Yes=1, No=2)	Date started	/___/ (72 73)	Date stopped	/___/ (74 75)

Blood culture: / / (Not done = 1, Neg = 2, Pos = 3, if possitive record bact. species)
76

Fecal WBC: / / / / (No. WBC/hpf, Not done = 999)
77 - 79

Fecal RBC: / / / / (No. RBC/hpf, Not done = 999)
80 - 82

Haematocrit (%):

First sample: / / Hosp. day: / /
83 84 85 86

2nd / / Hosp. day: / /
87 88 89 90

3rd / / Hosp. day: / /
91 92 93 94

4th / / Hosp. day: / /
95 96 97 98

5th / / Hosp. day: / /
99 100 101 102

Initial WBC: / / / / / (thousands/hundred)
103 - 105 106

Differential: / / Bands
107 108

/ / Polys
109 110

/ / Lympho
111 112

/ / Monos
113 114

/ / Eosinos
115 116

Platelets: (thousands/hundred)

First sample: / / / / / Hosp. day: / /
117 - 119 120 121 122

2nd / / / / / Hosp. day: / /
123 - 125 126 127 128

3rd / / / / / Hosp. day: / /
129 - 131 132 133 134

4th / / / / / Hosp. day: / /
135 - 137 138 139 140

5th / / / / / Hosp. day: / /
141 - 143 144 145 146

RBC fragmentation: / / (147) (Yes = 1, No=2, Not recorded=9)

Adm. Specific gravity: / / / / / (148 - 151) (999 = not done)

Adm. Plasma protein: / / / (152 153) gm%

Adm. Urea: / / / (154 155) (mmols/l)

Creatinine (mmols/1):

Sample: / / / / (156 - 158) Hosp. day: / / / (159 160)

2nd / / / / (161 - 163) Hosp. day: / / / (164 165)

3rd / / / / (166 - 168) Hosp. day: / / / (169 170)

4th / / / / (171 - 173) Hosp. day: / / / (174 175)

5th / / / / (176 - 178) Hosp. day: / / / (179 180)

Adm. Blood sugar: / / / / (181 - 183) (mmols/1, 99/9= not done)

Adm. Serum sodium: / / / / (184 - 186) (mmols/1, 999 = not done)

Adm. Potassium: / / / (187 188) (mmols/1, 9/9 = not done)

Adm. Chloride: / / / / (189 - 191) (mmols/1, 999 = not done)

Adm. CO_2: / / / (192 193) / / (194) (mmols/1, 99/9 = not done

Urine analysis: / / / / / (195 - 198) Sp. gravity (9999 = not done)

/ / (199) Protein (1=1+, 2=2+, 3=3+, 4=4+, 5=negative, 9=not done).

/ / / (200 201) WBC(no/hpf, 99=not done)

/ / (202) Casts (none=1, granulab=2, hyalone=3, WBC cost=4, RBC cast=5, Not done=9).

Max fall in HCT: / / / (percent)
203 204

Highest WBC: / / / / / (thousands/hundred)
205 - 207 208

Max fall in platelet: / / / / / (thousands/hundred)
209 210 211

Max rise in Urea: / / / (mmols/l)
212 213

Max rise in creatinin: / / / / (µmol/l)
214 - 216

Duration of diarrhoea in Hosp. / / / (days)
217 218

Antibiotics used in Hosp. / / (Yes=1, No=2) (Amp.=1, Chlor=2, Peni=3, TMP-SMZ=4, Genta=5, Furoxone=6, Nalidexic-acid=7, More than one=8, None=9).
219

Transfusion: / / (Yes=1, No=2, Unknown=9)
220

Effect of dialysis: / / (Cured=1, Died=2, Unknown=9)
221

Outcome: / / (Cured=1, Referred to other hosp. = 2, Died=3, Unknown=9).
222