Attachment 1.

Date 29.9.80

ETHICAL REVIEW COMMITTEE, ICDDR,B.

550

Principal Investigator Dr. R. Islam. Trainee Investigator (if any) _____

Application No. 80-038(P) Supporting Agency (if Non-ICDDR,B) _____

Title of Study LEUKEMOID REACTION IN SHIGELLOSIS AND ITS RELATION TO HAEMOLYTIC UREMIC SYNDROME

Project status: Limited Study.
(✓) 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).

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 — N.A. Yes (No) NA
(b) Social Risks — Yes (No) NA
(c) Psychological risks to subjects — Yes (No) NA
(d) Discomfort to subjects — Yes (No) NA.
(e) Invasion of privacy — Yes (No) NA
(f) Disclosure of information damaging to subject or others — Yes (No) NA

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: NA
(a) Nature and purposes of study — Yes No N.A
(b) Procedures to be follow[illegible] including alter[illegible]ces used — Yes No NA
Pl[illegible] ti[illegible]sks — Yes No NA
[illegible]estions — Yes No NA
[illegible]be derived — Yes No NA
[illegible]e to
[illegible] to with- — Yes No NA
[illegible]ling — Yes No NA
[illegible]reat-
[illegible]risks
[illegible]in
Yes No NA

5. Will signed consent form be required: N.A.
(a) From subjects — Yes (No) NA
(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 NA
___ 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.

Ethical Review Committee for any changes subjects before making such change.

80-038(P)
Rece'd.
30.9.80.

SECTION I - LIMITED STUDY PROTOCOL

1) Title: LEUKEMOID REACTION IN SHIGELOSIS AND ITS RELATION TO HAEMOLYTIC UREMIC SYNDROME

2) Principal Investigator: Dr. M. Rafiqul Islam

Associate Investigators: Dr. Thomas C. Butler and Dr. P.K. Bardhan

3) Starting Date: August 1980

4) Completion Date: September 1980

5) Total Direct Cost: $ 1938

6) Scientific Program Head:

This protocol has been approved by the Pathogenesis and Therapy Working Group.

Signature of Scientific Program Head: K. M. I. S. Aziz

Date: 24/9/80

7) Abstract Summary:

The purpose of this limited study is to review charts of about 300 patients admitted to the Hospital Ward of the ICDDR,B from 1975 to 1980 who had white blood cell counts in excess of 50,000 per cu mm^3. The reason for examining the clinical data gathered on these patients is to explore the relationships between leukemoid reactions in this patient population and development of the hemolytic-uremic syndrome of shigellosis.

SECTION II - RESEARCH PLAN

A. INTRODUCTION

1. Objective: The purpose of this work is to carry out a retrospective review of patients' charts to obtain clinical data on the relationships between leukemoid reactions in children and 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). 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 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 (2), and postmortem examinations of the kidneys revealed depositions of fibrin in renal glomeruli and renal artieries (3). Thus, a role for endotoxemia being found significantly more frequently in HUS cases than in the non-HUS shigellosis cases, 2) the temporal association of endotoxemia and onset of hemolysis, and 3) 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.

The role of leukocytosis in producing the HUS has not been adequately investigated, but blood leukocytes are a well-known source of tissue thromboplastin (4) and could be instrumental in provoking the disseminated intravascular coagulation that is observed during the HUS of shigellosis. Furthermore, endotoxin has been shown to cause blood leukocytes to produce additional quantities of thromboplastin (5).

SPECIFIC AIMS:

1. To review about 300 charts of patients admitted to ICDDR,B from 1975-1980 with white blood cell counts 50,000 per cu mm.^{3}
2. To record on data sheets information regarding age, sex, date of admission, history of illness, physical examination, laboratory data, diagnoses, 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 leukemoid reactions, what are the distributions of age, sex, symptomatology, diagnoses, physical findings, stool picture urine analysis means of laboratory data, incidence of the HUS, and the clinical outcomes.

   b. What was the incidence of HUS (defined by a fall of Hct by 10% fall in plateret count and rise in creatinine to 2 mg per 100 ml) in patients with S. dysenteriae and other diagnoses.

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

   d. Divide cases into HUS, hemolysis only, Thrombocytopenic only, uremia only, and uncomplicated shigellosis. Ask same questions.

METHODS AND PROCEDURE

1. Chart Collection and Review.

   (a) Total member of patients admitted with history of diarrhoea from 1975-1980 will be stratified according to age (1, 1-3, 3-5) yrs and above), sex with shigella and non-shigella infection.

(b) Number of patients developed Leucomoid reaction among those groups. When the relationship between etiology, age, sex with Leucomoid reaction is established then detail analysis of these cases will be studied focusing on associated HUS, other complications and outcome.

2. Available data will be recorded in the data sheet, attached with the procol, 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 leukemoid reactions, 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.

BUDGET

1. Personnel

Name	Position	% Effort	Taka	Dollar
Dr. M.R. Islam	Chief Physician & Assoc. Scientist. (Principal Investigator)	20%	3500	-
Dr. Thomas C. Butler	Consultant (Co-investigator)	10%	-	1000
Dr. P.K. Bardhan	Medical Officer (Co-investigator)	30%	2250	-
H.B. Ghosh	Clerk	20%	620	-
			6370	

	Taka	Dollar
2. Supplies and Material	Nil	1200
3. Equipments	Nil	-
4. Hospitalization cost	Nil	-
5. Travel	Nil	-
6. Animal Resources	Nil	-
7. Logistic support	Nil	-
8. Printing and Reproduction	Nil	-
9. Computer time - 5 hours @ Taka 1000 per hour	5000	-
	11370	
	$938	

Conversion rate $ 1 - Tk. 15

Total = $ 1938

Data Sheet - Shigella Leukemoid Study

Stat 219 (1-3) Card A (4)

Patient Name _____ Patient 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)

Locality _____ (21-22) (Write out - plan identifying code)
Police Station

Days of illness _____ (23-24)
Prior to Admission

Fever _____ (25) (Yes = 1, No = 2, Not known = 9)

Diarrhea duration _____ (26-27) (Days)

Diarrhea frequency _____ (28-29) (Stools per day)

Diarrhea character _____ (30) (Watery = 1, Bloody = 2, Mucoid = 3, semi-solid = 4, water-bloody =5, watery-mucoid = 6, bloody-mucoid = 7, unknown = 9)

Abdominal pain _____ (31) (Yes = 1, No = 2)

Received antibiotic before admission _____ (32) (Yes = 1, No = 2, unknown = 9)

Received rehydration before admission _____ (33) (I.V. = 1, oral = 2, both = 3, None = 4, unknown = 9)

Temperature on admission ____ | ____ (34-36 | 37) (Degrees)

Pulse rate _____ (38-40) (per minute)

Blood pressure _____ | _____ (41-43 | 44-45) (Systolic / diastolic)

Nutritional status _____ (46) (Obese = 1, normal = 2, thin = 3, malnourished = 4)

Dehydration status _____ (47) (None = 1, mild = 2, moderate = 3, severe = 4)

Abdomen tender _____ (48) (Yes = 1, No.= 2, unknown = 9)

distended _____ (49)

absent bowel sound _____ (50)

(cont'd...page 2)

Proctoscopy _____ (51) (Not done = 1, normal = 2, mild colitis = 3, severe with bleeding = 4, pseudomembrane = 5)

Other findings:

_____ (52) pheumonia

_____ (53) meningismus

_____ (54) convulsions

_____ (55) petechiae

_____ (56) unconscious

Stool culture _____ (57) (Shigdys = 1, Shig flex = 2, Shig boydi = 3, Shig sonnei = 4, Salmonella = 5, ETEC/LT = 6, ETEC/ST = 7, Vibrio cholerae = 8, Negative = 9)

Blood culture _____ (58) (Not done = 1, Neg = 2, pos = 3, if possitive record bacterial species)

Fecal WBC _____ (59-61) (No WBC/HPF, not done 999)

Fecal RBC _____ (62-64) (No RBC/HPF, not done 999)

Fecal pH _____ (65) (Acid = 1, alk = 2, not done = 3)

Hematocrit _____ (66-67) (percent)

WBC _____ (68-70 . 71) (in thousands/hundred)

Differential _____ (72-73) Bands

_____ (74-75) Polys

_____ (76-77) Lymphs

_____ (78-79) monos

_____ (80-81) eosinophils

RBC fragmentation: _____ (82) (Yes = 1, no = 2, unknown = 9)

Spec gravity _____ (83-86) (9999 - not done)

(cont'd....page 3)

Urinalysis _____ Sp Gravity (9999 - not done)
87-90

_____ Protein (1 = 1+, 2 = 2+, 3 = 3+, 4 = 4+, 5 = negative, 9 = not done)
91

_____ WBC (no/HPF, 9 = not done)
92-94

_____ RBC (no/HPF, 9 = not done)
95-97

_____ Casts (none = 1, granular = 2, hyaline =3, not done = 9)
98

Bun _____ (mg/100 ml, 999 - not done)
99-101

Creatinine _____ (mg/ml, 99/9 - not done)
102-103 104

Sodium _____ (meq/L, 999 - not done)
105-107

Potassium _____ meq/L, (9/9 - not done)
108-109

Cholride _____ meq/L (999 - not done)
110-112

CO_2 _____ meq/L (99/9 - not done)
113-114 115

Max fall in Hct _____ (per cent)
116-117

Highest WBC _____ (thousand / hundreds)
118-120 121

Platelets on admission _____ (thousands / hundreds)
122-124 125

Max fall in platelets _____ (thousands / hundreds)
126-128 129

Oliguria _____ (yes = 1, No = 2, unknown - 9)
130

Max rise in BUN _____ (mg/100 ml)
131-133

Max rise in creatinine _____ (mg/100 ml)
134-135 136

Duration diarrhea in hospital _____ (Days)
137-138

Antibiotic _____ (Ampicillin = 1, Chloro = 2, tetracycline = 3, TMP-SMZ = 4, none = 5, other = 6)
139

Transfusion _____ (Yes = 1, no = 2, unknown = 9)
140

Outcome _____ (1 = discharge, 2 = died)
141