58

Date 21/11/85

ETHICAL REVIEW COMMITTEE, ICDDR,B.

Principal Investigator DR.ABDUS SALAM

Application No. 85-002

Title of Study "Double Blind Randomized Trial of Nalidixic Acid and Ampicillin in the Treatment of Childhood Shigellosis"

Trainee Investigator (if any) ____

Supporting Agency (if Non-ICDDR,B) ____

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 a 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.

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

Principal Investigator

Trainee

SECTION I - RESEARCH PROTOCOL

1. TITLE — DOUBLE BLIND RANDOMIZED TRIAL OF NALIDIXIC ACID AND AMPICILLIN IN THE TREATMENT OF CHILDHOOD SHIGELLOSIS

2. PRINCIPAL INVESTIGATOR — DR. ABDUS SALAM

COINVESTIGATORS — DR. SHAHADAT HOSSAIN
DR. MAHABUBUR RAHMAN
DR. M. BENNISH

3. STARTING DATE — March 1, 1985

4. COMPLETION DATE — November 1, 1985

5. TOTAL DIRECT COST — $23,666

6. SCIENTIFIC PROGRAM HEAD — This protocol has been approved by the pathogenesis and therapy working group.

Signature of programme head: _____

Date: 24/1/85

ABSTRACT

The increasing frequency with which shigella isolates at our Dhaka station hospital are resistant to the two first line drug therapies, ampicillin and trimethoprim-sulfamethoxazole (STX), neccesitates a search for alternative effective drugs. In an effort to determine the efficacy of nalidixic acid (NA) in comparison to ampicillin in the treatment of shigellosis we propose to study the alternative therapies in sixty children: half will be randomly assigned to therapy with nalidixic acid (60 mg/kg/day divided into four equal doses and given for five days) and the other half will be randomly assigned to receive ampicillin (100 mg/kg/day divided into four equal doses and given for five days). Patients selected for study will be children who come to the Dhaka station hospital with a history of dysentery, and who on physical examination are febrile (rectal temperature > 38.0), and who have > 20 WBC's/hpf on microscopic examination of the stool. Children with complicating illnesses will be excluded from the study. On admission and prior to treatment, all patients will have two stool cultures and one blood culture taken, a chest x-ray performed, and a blood count and blood chemistries determined. Children will be hospitalized for a total of seven days. Stool cultures will be performed daily, and a repeat blood count and serum will be done on days three and five. Blood culture and other tests

will be repeated if indicated. Serum drug levels will be performed after the third, twelfth and twentieth doses of medicine. Outcome will be judged by the two standard methods - bacteriologic cure as determined by time to eradication of shigella from stool, and clinical cure, as judged by duration and volume of diarrhea and fever index. In addition we will determine on alternate days two other possibly useful indicators of efficacy of therapy - stool concentrations of alpha 1-antitrypsin and shigella toxin.

OBJECTIVE

To assess the effectiveness of NA relative to ampicillin in achieving clinical and bacteriologic cure of shigella infections in children with the dysenteric form of the illness.

BACKGROUND

Shigella infections remain the major definable cause of morbidity and mortality in patients admitted to the Dhaka station hospital of the ICDDR,B. During the calender year 1983 4,338 patients were admitted to the general, study or intensive care wards of the hospital: 16.9% had cholera infections, 15.1% had shigella infections, 1.9% had typhoid fever, and 66.1% had another or no pathogen identified. However the death rates for the different infections varied markedly: 68 (10.3%) of patients with shigella infections died, compared to seven (8.6%) with typhoid fever and 8 (1.1%) with cholera. In reality the death rate for patients admited with shigellosis was probably much higher as another 16.1% of admitted patients

with shigellosis were discharged on risk bond: it is thought by most of the physicians working in the hospital that these patients are likely to die at home.

This morbidity and mortality occured almost exclusively in children; only one of the 68 patients who died from their shigella infections in the hospital was more than ten years of age, and 62 (91%) were less than five years old. In a number of different studies antiobiotic therapy has been shown to shorten and ameliorate the course of the disease in patients treated with an effective drug when compared to patients treated with placebo, (1-3) and antibiotics have had a central place in the treatment of the more severe forms of the disease ever since sulfonamides were first used for this purpose over forty years ago. However as each new drug has been introduced for the treatment of shigellosis, resistance to the drug has eventually emerged and become a major obstacle to effective therapy. This was first noted in the late nineteen-fifties when Japenese researchers found that resistance to sulfonamides and other antibiotics could be transmitted from one bacteria to another by "R factors". Soon after ampicillin replaced sulfonamides as standard therapy for shigellosis, large scale outbreaks of shigella which contained R factors or other extrachromasomal transferable genetic elements coding for resistance to ampicillin occured in Central America, Bangladesh, and elsewhere.(4-5) STX was shown in studies done here at the ICDDR,B (6) and elsewhere to be an effective and perhaps superior alternative to ampicillin in the treatment of shigella infections, but resistance to this drug combination also rapidly appeared.

Our situation here at ICDDR,B reflects the current dilemma involved in deciding upon initial empiric therapy when a child is suspected of having a shigella infection. During 1983 approximatly 15% of the shigella isolates from inpatients were resistant to ampicillin when measured by the disk method, and 23% were resistant to SXT (7). Patients with a shigella infection resistant to ampicillin were 1.9 times more likely to die from their infection than those infected with an ampicillin sensitive strain. (7) Although this difference was not quite statistically significant (95% confidence intervals for the odds ratio was .86 to 4.12) the trend for a worse outcome if no effective antibiotic was given was clear. (7) This problem of antibiotic resistant shigellois is a problem that is of current importance in a number of different countries, as the recent reports of multiply antibiotic resistant shigella shiga epidemic in West Bengal indicate.

Naladixic acid is a member of the quinolone group of synthetic antimicrobial agents. (8) It is bacteriacidal for most of the common gram-negative organisms. It appears to act by inhibiting DNA synthesis, although recent studies suggest that it has an independent effect on RNA synthesis. It is well absorbed from the gastrointestinal tract and acheives serum levels of 20-50 micrograms per milliliter. It is approved for use in children by the Federal Drug Administration of the United States. (9) It's side effects and toxicities in humans are rare and include hypersensitivity reactions, CNS effects such as drowsiness, dizziness and vertigo, increased intracranial pressure, and nausea and vomiting. All the side effects are reversible upon discontinuation of the medication. In juvenile animals of many species the

drug has been shown to cause arthropathy (erosion of cartilage in weight bearing joints), but this has never been observed in humans and, as noted above, it remains an FDA approved drug for use in children. Resistance to NA has not been shown to be transferable via R factors.(10) Chromasomally mediated resistance, either by selection of resistant clones or by mutation during therapy, does occur. A number of studies have examined the in-vitro sensitvity of shigella isolates to NA and have found them to be almost universally sensitive. (11,12) During February, March and April of 1984 246 shigella isolates from our lab were tested by a disc method for sensitivity to Naladixic acid: all 246 were found to be sensitive. In contrast 13.8% were resistant to ampicillin (including 21.8% of 110 shigella flexneri isolates), and 35.4% were resistant to STX (including 84.5% of 97 shigella dysenteriae type I isolates).

Only three studies have examined the usefullness of NA in treating shigellosis in humans. The best of these studies was done by Nelson and Hatalin, (13) who in the late 1960's and early 1970's performed the most systematic evaluation of the role of anti-microbial therapy in the treatment of shigellosis. They randomly assigned children aged three months to ten years to treatment with 55 mg/kg/day of NA (17 patients) or 100 mg/kg/day of ampicillin (19 patients). Both groups were treated for five days. They found that the ampicillin group defervesced earlier (mean of 1.0 vs 2.4 days) and that eradication of shigella from the stool also occured more quickly (1.7 vs 2.9 days). They concluded that NA might have a limited use in patients who have an infection with a shigella species resistant to standard therapies. In contrast two other studies have found NA to be as

effective as alternative therapies in the treatment of shigellosis. In one (3) 18 patients (children and adults) with shigellosis were treated in a double blind fashion with naladixic acid and compared with 11 patients who received lactulose (thought to have some effectiveness in the treatment of the disease) and 14 patients who received placebo. The authors defined a cure as "when all signs of the infection had disappeared....and culture of the fecal specimen had given no growth during a follow-up period of two months". Using those standards 13 (72%) of 18 patients treated with naladixic acid were cured, which was significantly better than the 3 (21%) of the 14 patients treated with placebo, but not significantly different from the 6 (55%) of thirteen patients cured with lactulose. In the third and earliest study reported (14) Moorhead et al looked retrospectively at all the 1,392 patients with dysentary due to shigella sonne who had been admitted to their Birmingham hospital during the period January 1958 through September 1964. All patients were cultured for three consecutive days starting 24 hours after the end of therapy. There was no systematic manner of assigning therapy. Patients who did not have shigella sonne present in any of the three post-treatment stool cutures were considered cured. Using this standard, 88.5% of 112 patients treated with Naladixic acid were cured, compared to 90.0% of 963 patients treated with oral streptomycin and 68.5% of 57 patients treated with tetracycline.

Our current drug dosing practices here at ICDDR,B, and in the rest of the less developed world are based on studies done among well nourished children in the developed world. Little information is available about the pharmocokinetics of the commonly prescribed drugs, including antibiotics, in

children who are malnourished or who have gastroenteritis. However in their study (13) Nelson and Hatalin showed that the clinical response of children with shigella treated with 100 mg/kg/day of ampicillin differed considerably depending on their absorbtion and peak serum levels of the drug: both clinical and bacteriologic response was slower in those patients who had lower serum levels. This suggests that determining appropriate antibiotic dosing schedules might be critical to acheiving cure.

Dysenteric illness can have prolonged effects on the nutritional status of children (15), and cessation of fever and diarrhea does not necessarily mean resolution of the disease. Loss of protein into the gut in patients with dysentery has been one explanation for the nutritional impact of dysentery, and measurement of a protein marker, alpha 1-antitrypsin, has been used an indicator of the amount of protein loss in the gut.(16) This might then be a more important measure of the efficacy of therapy than the more standard measures of duration of diarrhea and time to defeverscence.

The ability of shigella to produce a protein toxin in vitro has long been known (17), but whether it is produced in vivo and what role it might play in actual disease has not been known. Recently an ELISA has been developed that makes measurement of the toxin more practicable (18), and preliminary studies found that it was present in relatively high levels in 12 of 12 patients with dysentary due to infection with S. dysenteriae type I, but in only two of six patients infected with shigella flexneri.(18) Looking for the presence of toxin in these patients followed prospectively will help us to understand whether there is a correlation between the presence and amount

of toxin in stool and clinical symptoms, and what effect the different therapies have on toxin production.

RATIONALE

Shigella infections are a major cause of morbidity and mortality in children in the developing world, as evidenced from our own hospital figures and reports from many areas of the world. Patients with shigella treated with an effective antimicrobial agent do substantially better than those who do not have such treatment. Resistance to ampicillin and sulfamethoxazole-trimethaprim, our current two 'first-line' drug therapies, is frequent and increasing. Effective alternative therapies need to be found. Naladixic acid is a synthetic antimicrobial agent that is inexpensive, available in Bangladesh, and safe. In vitro studies have shown that almost all shigella strains are sensitive. Three previous, small scale studies of it's use in treating shigella infections have shown varying degrees of efficacy. The drug is currently being used in the hospital, despite lack of definative proof of it's efficacy. We propose to do a larger, double blind, randomized study of it's efficacy in comparison with ampicillin, and hopefully finally define what role this drug should have in the treatment of shigellosis.

SPECIFIC AIMS

1. To determine the efficacy of naladixic acid in comparison to ampicillin in the treatment of shigella infections of children. Efficacy will be judged by fever index, time to eradication of shigella from stool cultures, duration and volume of diarrhea and effect on stool concentrations of alpha 1-antitrypsin and shigella toxin.

2. To study the pharocokinetics of these two drugs in patients with shigella infections, and see if altered pharocokinetics have an inpact on outcome in any or all of the patients studied.

METHODS of PROCEDURE

A total of sixty-six patients will be studied. This sample size was obtained by assuming a cure rate of 95% in ampicillin treated patients (a fair estimate based on previous studies), an alpha value of .05 and a beta value of .20. The power of showing a difference if the cure rate in the nalidixic acid group is 65% will be .80. Because only patients with pre-treatment stool cultures positive for shigella will be eligible for inclusion in the anlysis, we estimate that it will be neccesary to enroll 130 children in order to obtain the required 66 patients for the study.

Criteria for entry into the study will be:

1. Age three months through nine years.
2. History of diarrhea for less than 72 hours, with a minimum of three unformed stools in the preceding 24 hours.
3. A history of blood or mucous in the stools.
4. A history of fever or temperature > 38.0 rectally when examined.

5. More than 20 WBC's per HPF on microscopic examination of the stool.

Reasons for exclusion from the study will include:

1. Prior use of medicines for this illness.

2. Complicating illnesses. These will include pneumonia (infiltrate on chest x-ray), evidence of hemolysis or anemia (hematocrit less than 20% or fragmented RBC's >1%), uremia (serum creatinine > 150 micromoles/liter), systemic sepsis (positive blood culture, evidence of hemmorhagic diathesis), leukomoid reaction, (WBC >50,000), peritonitis or toxic megacolon (absent bowel sounds, rebound tenderness on palpation), severe malnutrition (<60% of weight for age) or alteration in conciousness (seizure or obtundation).

3. Known allergy to either of the medicines.

On admission a complete history and physical examination will be done and recorded. (see attached sheet)

The following laboratory evaluations will be done on admission and prior to the initiation of therapy:

1. Two stool samples. The first will be cultured for shigella, salmonella, campylobacter and vibrios. A portion of this stool sample will be used for Rotavirus and LT ELISA, and for stool microscopic examination. The second sample will just be cultured for shigella.

2. Chest roentgneogram.

3. Complete blood count and differential count.

4. Blood electrolytes, creatinine, and total serum protein.

5. Blood culture.

Treatment: Treatment will be with with either naladixic acid given in a dose of 60 mg/kg/day divided into four equal doses given six hourly for five days, or ampicillin given in a dose of 100 mg/kg/day divided into four equal doses and given six hourly for five full days. Both will be given in an elixir preperation. The drug will be supplied as a powder to be mixed with 60 cc's of water. The concentration of the naladixic acid will be 45 mg/ml, and that of the ampicillin will be 75 mg/ml. Thus the volume of elixir given with the two drugs will be equal. The drugs will be supplied and prepared free of charge my Medimpex, the international marketing arm for the Hungarian drug company, Chenoin, which manufactures the two drugs. Treatment will be randomized and double blind. The powdered medicine (ampicillin or nalidixic acid) will be distributed into 130 different sets of bottles according to a random number table. This will be done by the manufacturer who will then maintain a copy of the code. When a patient is

entered into the study a number will be selected from a box containing the numbers 1 through 130, and the set of medicine corresponding to the number selected will be assigned to that patient. The medicine will be kept in the pharmacy, and the pharmacist will dilute the medicine with 60 ml of sterile water.

Measurement of antibiotic levels: One and two hours after the administration of the fourth, twelfth and twentieth (last) doses of antibiotics 1 ml of blood will be drawn for determination of peak antibiotic levels. This will be done, when possible, at the same time that blood is drawn for other studies. Nalidixic acid will be measured by an HPLC method, and ampicllin by means of a bioassay. Both will be performed by Chenoin, the Hungarian manufacturer of the drugs.

Further data:

The number of stools and volume thereof will be recorded daily. Urine bags will be used for incontinent children so that stool can be seperately quantified. Vital signs will be measured and recorded every four hours. Pertanent physical examination findings will be recorded daily.

Bacteriological procedures and Methods: Cultures for bacterial enteric pathogens will be done on the first morning stool sample for all seven days that the children are hospitalized. Cultures will be done according to the routine methods in practice at the Centre, and shigella sensitivities will be determined by both the disc and MIC methods. Repeat ELISA for LT and

rotavirus will be performed on a stool sample obtained on the fifth day. These will also be done by ELISA methods in current use at the Centre.

Alpha -1 anti-trypsin and shiga toxin measurements: Alpha-1 antitrypsin and shigella toxin levels will be measured on homogenized 24 hour stool stool samples collected on the first, third and fifth days. Shigella toxin will be measured by an ELISA method using a mouse monoclonal antibody to purified shigella toxin.

A complete blood count will be repeated on the third and fifth days of study, as will a total serum protein, electrolytes and creatinine. These will be drawn at the same time on the third and fifth days that a drug level is being drawn. Thus blood drawing will be performed on only four of the seven days that the child is in the hospital.

Exclusion from study after patient has initially been entered:

Patients will be entered into the study if they meet the admission criteria. If after 24 hours in the study there are no non-lactose fermenters growing on either the SS or MacConkeys plates, the patients will be withdrawn from the study. Any patient who has a marked clinical deterioration while in the study will also be withdrawn. Clinical deterioration will be defined similarly to the complications that were used to initially exclude patients into the study, and will include the development of hemolysis, uremia, septicemia, alteration in consciouness, or the development of peritonitis or toxic megacolon.

Definitions for these will be as above. Another reason for withdrawal will be the development of a rash that is suspected to be drug related. For patients who are withdrawn from the study the treatment code will be broken and the patient given such therapy as is routinely indicated.

Monitoring of side effects: Patients will be examined daily for evidence of rash, alteration in conciousness, signs of increased intracranial pressure or other untoward findings, and these will be recorded.

Data analysis: Information will be recorded on abstracting forms (see attached) and will be entered into a stat-pac data based and statistical program designed for a Kaypro micro-computer. Comparison between the two groups will be done mainly by means of chi-square analysis.

DAILY SUMMARY OF DATA COLLECTION

DAY OF ADMISSION:

1. History and physical examination

2. Stool One: Culture for shigella, salmonella, campylobacter, vibrios. Elisa for E.coli LT on picks of E. Coli. Rotavirus ELISA. Microscopic examination.

3. Stool Two: Culture for shigella.

4. Five ml's of blood drawn for culture, TC, DC, HCT, platelets, electrolytes, creatinine, protein.

5. Chest x-ray.

6. TREATMENT BEGINS

7. Every four hours vital signs, enumeration of stool frequency and volume.

DAY 1:

1. Physical examination.

2. Vital signs every four hours, and enumeration of stool volume and frequency.

3. Alpha-one anti-trypsin and shiga toxin meausrement on 24 hour collection of stool.

4. One ml of blood drawn for antibiotic measurement one and two hours after fourth dose of antibiotics (25 and 26 hours after initiation of therapy).

5. Culture of stool for shigella.

DAY 2:

1. Physical examination

2. Vital signs every four hours, and enumeration of stool volume and frequency.

3. Culture of stool for shigella.

DAY 3:

1. Physical examination

2. Vital signs every four hours, and enumeration of stool volume and frequency.

3. Stool for culture of shigella and microscopic examination.

4. Four ml's of blood drawn one hour after twelfth dose of antibiotics (73 hours after first dose) for antibiotic level, TC, DC, platelets, HCT, electrolytes, protein, creatinine.

5. One ml of blood drawn two hours after twelfth dose of antibiotic (74 hours after first dose) for antibiotic level.

6. Measurement of alpha-one anti-trypsin level and shiga toxin level on homogenized 24 hour collection of stool.

DAY 4:

1. Physical examination

2. Vital signs every four hours, and enumeration of stool frequency and volume.

3. Culture of stool for shigella.

DAY 5:

1. Physical examination

2. Vital signs every four hours, and enumeration of stool frequency and volume.

3. Culture of stool for shigella, salmonella, vibrios, campylobacter, and picking of E. coli colonies for ELISA testing for LT production. Testing for rotavirus antigen by ELISA.

4. Microscopic examination of stool.

5. Four ml's of blood drawn one hour after twentieth dose of antibiotics (121 hours after first dose) for measurement of antibiotic level, TC, DC, HCT, platelets, electrolytes, protein, and creatinine.

6. One ml of blood drawn two hours after twentieth dose of antibiotics (122 hours after first dose), for measurement of antibiotic level.

7. Alpha-one anti-trypsin and shiga toxin measurement on homogenized specimen of 24 hour stool collection.

8. END OF ANTIBIOTIC THERAPY

DAY 6:

1. Physical examination

2. Vital signs every four hours, and enumeration of stool frequency and volume.

3. Culture of stool for shigella

DAY 7:

1. Physical examination

2. Vital signs every four hours, and enumeration of stool volume and frequency.

3. Discharge

SIGNIFICANCE

With increasing resistance of shigella to antibiotics currently used for treatment of shigella infections, alternative effective therapies need to be found. Naladixic acid is an inexpensive, safe, available antimicrobial agent that is currently being used in our hospital to treat patients who have shigella infections resistant to ampicillin or SXT. It's efficacy is not known with certainty however, and this study aims to determine that. If it is effective in the therapy of shigellosis it can then be used in a more rational and effective manner than it is currently being used, and hopefully help us to reduce the considerable morbidity and mortality we see from this infection.

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Detailed Budget

1: Personnel Services

Name	Position	%Effort	Taka	$
Dr. A Salam	Prin. Investigator	25%	15,098	
Dr. Shahadat	Co-Investigator	15%	10,784	
Dr. Mahabob	Co-Investigator	15%	10,256	
Dr. Bennish	Co-Investigator	15%		6,198
	Study Nurse	25%	12,684	
	Lab Technician	25%	6,5000	

2: Supplies and Materials

Item	Taka	$
Ampicillin and Naladixic Acid	No cost	
Needles, Syringes, Vials for Serum Collection	500	
Urine and Ostomy Bags	2,000	

Laboratory Tests

For One Patient Who Completes the Study

Test	Cost/test	No. of Tests	Costs(Taka)
MIC to Ampicillin and Naladixic acid	75	2	150
Bacterial Stool Cultures	45	8	360

Rotavirus Elisa	45	2	90
LT and ST Testing	50	2	100
Hct, TWBC and Differential Count	9	3	27
Blood Culture	66	1	66
Electrolytes	70	3	210
Serum Protein	45	3	135
Creatinine	64	3	192
Platelet Count	3	3	9
Chest X-Ray	25	1	25
Alpha 1 Anti-trypsin	373	3	1119
Shiga Toxin Assay	60	3	180
Total Lab costs for one patient			2663
Cost for 66 Patients			175,750 ($7,030)

Costs for a Patient who is entered into the Study but who does not have shigella

Test	Cost	No. tests	Total (Taka)
Chest X-Ray	25	1	25
Stool Culture	45	3	135
Blood Culture	66	1	66
Electrolytes	70	1	70
Creatinine	64	1	64
Serum Protein	45	1	45
HCT, TC, DC	9	1	9
Total Costs for			414

Patient Entered but not completing Study	
Costs for approx. 66 such patients	27,324 ($1,093)
Total Costs Material, supplies and Tests	$10,623
3. Equipment	No costs
4. Patient hospitalization	$3,168
5. Outpatient care	No cost
6. ICDDR,B Transport	$300
7. Travel and Transportation of Persons	No costs
8. Transportation of Things	$1,500
9. Rent, Communications and Utilities	No cost
10. Information services	No cost
11. Printing and reproduction	No cost
12. Other contractual services	No cost
13. Construction, renovation alteration	No cost

BUDGET SUMMARY

1. Personnel Services	$8075
2. Supplies and Materials	$10,623
3. Equipment	0
4. Patient Hospitalization	$3,168
5. Outpatient Care	0
6. ICDDR,B Transport	$300
7. Travel and Transportation of Persons	0
8. Transportation of Things	$1,500
9. Rent, Communications and Utilities	0
10. Information Services	0
11. Printing and Reproduction	0
12. Other contractual Services	0
13. Construction, Renovation and Alteration	0
TOTAL COSTS EXCLUSIVE OF OVERHEAD	$23,666
30% OVERHEAD	$7,100
TOTAL COSTS INCLUDING OVERHEAD	$30,766

ENGLISH CONSENT FORM

Your child is suffering from bloody dysentary. This disease can be dangerous, especially for children. Among other things it can cause your child to become malnourished. Available medicines are gradually becoming inefective for treating this condition. This forces us to search for alternative and effective drugs which can be used to treat this disease. To dc that ICDDR,B has undertaken a study to determine the effectiveness of a drug not commonly used in this condition, naladixic acid. If you agree we shall include your child in our study. We will take a detailed history from you concerning your childs medical problems, and will examine your child touroughly and record the findings. We shall take a small amount of blood and stool for diffrent investigations and an x-ray of the chest will be done. Your child will receive a measured dose of the standard medicine for treating shigella (ampicillin), or naladixic acid, every six hours for five days. Both of these medicines are effective in treating dysentary due to shigella. That means that your child will not remain without medicine. After getting the third and 12th doses of medicine a small amount of blood will be taken one and two hours after the doses to measure the level of drug in the blood. This amount of blood will not cause any harm to your child. Seven days will be needed to complete the study and every day stool samples should be taken

for investigation and amount of stool passed meausred.

All appropriate measures will be taken to treat your child. During the study your child will not get any physical injury other than little pain at the time of taking blood. Your consent to take your child in our study will help us finding effective drug to treat this condition.

You are free to withdraw your child from the study any time you desire so. Even if you do not give consent for the study your child will get the usual and appropriate treatment from the centre.

We shall let you know the reports of the investigations done if and when you desire so.

Signature of the Investigator

Signature (LTI) of the Guardian

Date

Date

[illegible]
[illegible]
[illegible]

সম্মতিপত্র

আপনার শিশু এক অসুখে ভুগছে। শিশুদের মধ্যে এ রোগ [illegible] হয়ে থাকে। [illegible] আপনার শিশু [illegible] পারে। এ রোগের [illegible] এখনো [illegible] আমরা [illegible]। [illegible] এ রোগের [illegible] (ঢাকা মেডিকেল কলেজ হাসপাতাল) এ রোগের [illegible]। [illegible] আপনার শিশুকে আমরা গবেষণার জন্য ভর্তি করেছি। [illegible] আপনাদের [illegible], রোগীর [illegible] পরীক্ষা [illegible] করা হবে। [illegible] আপনার শিশুকে [illegible] পরীক্ষার জন্য [illegible] দেওয়া হবে। [illegible] পরীক্ষা করা হবে এবং [illegible] করা হবে। আপনার শিশুকে [illegible]। [illegible] আপনার শিশু [illegible]। [illegible] আপনার শিশুকে [illegible] দেওয়া হবে। [illegible] আপনার শিশুর [illegible] এ হাসপাতালে [illegible] থাকতে হবে। [illegible] এবং [illegible] পরীক্ষা করা হবে।

আপনার শিশুকে তিন মাস পর্যন্ত ফলো আপ করা হবে। [illegible] আপনার শিশুর আর কোন প্রকারের [illegible] হবে না। আপনার সম্মতি আমাদেরকে এ রোগের চিকিৎসা [illegible] সাহায্য করবে।

আপনি যে কোন সময় আপনার শিশুকে গবেষণা থেকে প্রত্যাহার করতে পারবেন। আপনি যদি এ গবেষণায় সম্মত না থাকেন তাহলেও আপনার শিশু এ হাসপাতালে প্রচলিত চিকিৎসা পাবে।

আপনি ইচ্ছা করলে বিভিন্ন প্রকারের পরীক্ষার ফলাফল আপনাকে জানানো হবে।

ধন্যবাদ।

সাক্ষীর স্বাক্ষর

তারিখ: –

অভিভাবকের স্বাক্ষর / টিপসই

তারিখ: –

ABSTRACT SUMMARY

1. Our subject population will be children with shigellosis. Because almost all morbidity and mortality due to shigellosis occurs in children less than 10 years of age, it is important to study the effect of therapy in this age group.

2. The only invasive procedure that we will do during this study is blood drawing. The amount of blood that will be drawn during the study will pose no risk to the patient. Since we do not include a placebo group in the study no child will go untreated. If there is any significant deterioration in the clinical condition of any of the children, the code will be broken and they will be withdrawn from the study.

3. The only risks are that drug therapy might be ineffective, either because Naladixic acid is not effective in a particular patient, or becuase a patient randomly assigned to treatment with ampicillin might be infected with an ampicillin resistant strain of shigella. There will be close 24 hour monitoring of the patients condition, and if any significant deterioration in the patients condition (defined in methods section) occurs, the code will be broken and they will be withdrawn from the study.

4. All patients enrolled in the study will be assigned a study number and that number will be used throughout when analyzing information collected from such patients.

5. Informed consent will be obtained from the parent or guardian of each child entered into the study. As the study is double blinded, we will not be able to tell the parent exactly which of the two drugs their child will receive. This is the only information that will be withheld.

6. A standard medical history will be taken at the time of entry into the study.

7. Each individual will receive the best care available for thier infection, and this is the major benefit that will accrue to them through the study. The main disadvantage is that they will, in most cases, be hospitalized for a longer period than they ordianrily would be. Society will benefit because we will have the opportunity to see if there is an effective therapy for what is now a major cause of morbidity and mortality in children.

8. This study will require the use of hospital records, (which we will record ourselves), stool, and blood.

NALIDIXIC ACID STUDY

VITAL SIGN FORM

Form No. _____ Date: _____ Drug: _____

Protocol No.: _____ Admission No.: _____

Patient's Name: _____ Age: _____ Sex: _____

	4:00 a.m.			8:00 a.m.			12:00 noon		
	Pulse	Temp.	Resp.	Pulse	Temp.	Resp.	Pulse	Temp.	Resp.
Day - 0									
Day - 1									
Day - 2									
Day - 3									
Day - 4									
Day - 5									
Day - 6									
Day - 7									

	4:00 p.m.			8:00 a.m.			12:00 M.N.		
	Pulse	Temp.	Resp.	Pulse	Temp.	Resp.	Pulse	Temp.	Resp.
Day - 0									
Day - 1									
Day - 2									
Day - 3									
Day - 4									
Day - 5									
Day - 6									
Day - 7									

NALIDIXIC ACID STUDY

INVESTIGATION (FORM - 1)

From No.: _____ Date: _____ Drug: _____

Protocol No.: _____ Admission No.: _____

Patient's Name: _____ Age: _____ Sex: _____

A. STOOL CULTURES

	Day - 0		Day-1	Day-2	Day-3	Day-4	Day-5		Day-6
	S - 1	S - II							
Shigella									
Salmonella									
Campylobacter									
Vibrio									
E. coli									
Rotavirus									

B. STOOL M/E, SHIGELLA TOXIN AND ALPH, ANTITRYPSIN

		Day - 0	Day - 1	Day - 3	Day - 5
Stool $_1$ antitrypsin					
Stool Shig. toxin					
STOOL MICROSCOPY	pH				
	Puscells/hpf				
	RBC/hpf				
	Macro/hpf				
	Veg. E.H.				
	Ova				
	Cyst.				

NALIDIXIC ACID STUDY

INVESTIGATION FORM-2

Form No. _____ Date: _____ Drug: _____

Protocol No.: _____ Admission No.: _____

Patient's Name: _____ Age: _____ Sex: _____

A. BLOOD COUNT

Days:	Hct	TWBC	Poly	Band	Lymp	Mono	Baso	Eosi	Reti	Frag RBC	Myel	Meta Myel	Toxic vac.	Platelet
Day - 0														
Day - 3														
Day - 5														

B. BLOOD CHEMISTRY

Days:	Na	K^+	Cl^-	TCO_2^-	Urea	Creat	Glucose	Prot	Sp. Gr.	
Day - 0										
Day - 3										
Day - 5										

C. OTHERS

Days:	X-Ray chest	Blood C/S	BLOOD ANTIBIOTIC		
			Sample - 1	Sample - 2	
Day - 0					
Day - 1					
Day - 3					
Day - 5					

NALIDIXIC ACID STUDY.

SAMPLING FORM

FORM NO.

DATE:

DRUG:

PROTOCOL NO.

ADMISSION NO.

STUDY NO.

PATIENT'S NAME:

AGE:

SEX: M ☐ F ☐

1

	DAY-0	DAY-1	DAY-2	DAY-3	DAY-4	DAY-5	DAY-6
	1 2						
	6 ml	1 ml + 1 ml		5·5		5·5	

NALIDIXIC ACID STUDY

CLINICAL INFORMATION (FORM -A)

Form No.: _____ Date: _____ Drug: _____

Protocol No.: _____ Admission No.: _____

Patient's Name: _____ Age: _____ Sex: _____

	WEIGHT	DEHYDRATION		ABD. DIST.		ABD. TENDERNE	
	8:30 a.m.	8:30 a.m.	4:30 p.m.	8:30 a.m.	4:30 p.m.	8:30 a.m.	4:30 p.m.
Day - 0							
Day - 1							
Day - 2							
Day - 3							
Day - 4							
Day - 5							
Day - 6							
Day - 7							

	BOWEL SOUND		NO. OF VOMITUS		NO. OF STOOLS		AMOUNT OF STOOL	
	8:30a.m.	4:30p.m.	8:30a.m.	4:30 p.m.	8:30 a.m.	4:30 p.m.	8:30 a.m	4:30 p.m.
Day - 1								
Day - 2								
Day - 3								
Day - 4								
Day - 5								
Day - 6								
Day - 7								
Day - 8								