tachment 1.

Date November 1, 1990

ACE SHEET) ETHICAL REVIEW COMMITTEE, ICDDR,B.

5/11/90
209

Principal Investigator Dr M.A. Salam

Trainee Investigator (if any) _____

Application No. 90-019

Supporting Agency (if Non-ICDDR,B) _____

Title of Study "Double blind, randomized study of the treatment of childhood shigellosis comparing ciprofloxacin and pivamdinocillin"

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

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

1. Source of Population:
   (a) Ill subjects (Yes) No
   (b) Non-ill subjects Yes No
   (c) Minors or persons under guardianship (Yes) No
2. Does the study involve:
   (a) Physical risks to the subjects Yes (No)
   (b) Social Risks Yes (No)
   (c) Psychological risks to subjects Yes (No)
   (d) Discomfort to subjects (Yes) No
   (e) Invasion of privacy Yes (No)
   (f) Disclosure of information damaging to subject or others Yes (No)
3. Does the study involve:
   (a) Use of records, (hospital, medical, death, birth or other) (Yes) No
   (b) Use of fetal tissue or abortus Yes (No)
   (c) Use of organs or body fluids (Yes) No
4. Are subjects clearly informed about:
   (a) Nature and purposes of study (Yes) No
   (b) Procedures to be followed including alternatives used (Yes) No
   (c) Physical risks (Yes) No
   (d) Sensitive questions (Yes) No
   (e) Benefits to be derived (Yes) No
   (f) Right to refuse to participate or to withdraw from study (Yes) No
   (g) Confidential handling of data (Yes) No
   (h) Compensation &/or treatment where there are risks or privacy is involved in any particular procedure (Yes) No
5. Will signed consent form be required:
   (a) From subjects Yes (No)
   (b) From parent or guardian (if subjects are minors) (Yes) No
6. Will precautions be taken to protect anonymity of subjects (Yes) No
7. Check documents being submitted herewith to Committee:
   ___ Umbrella proposal - Initially submit an overview (all other requirements will be submitted with individual studies).
   ___ Protocol (Required)
   ___ Abstract Summary (Required)
   ___ Statement given or read to subjects on nature of study, risks, types of questions to be asked, and right to refuse to participate or withdraw (Required)
   ___ Informed consent form for subjects
   ___ Informed consent form for parent or guardian
   ___ Procedure for maintaining confidentiality
   ___ Questionnaire or interview schedule *

* If the final instrument is not completed prior to review, the following information should be included in the abstract summary:
1. A description of the areas to be covered in the questionnaire or interview which could be considered either sensitive or which would constitute an invasion of privacy.
2. Examples of the type of specific questions to be asked in the sensitive areas.
3. An indication as to when the questionnaire will be presented to the Cttee. for review.

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

A-032077

90-019
5/11/90

RESEARCH PROTOCOL

1. TITLE: DOUBLE BLIND, RANDOMIZED STUDY OF THE TREATMENT OF CHILDHOOD SHIGELLOSIS COMPARING CIPROFLOXACIN AND PIVAMDINOCILLIN

2. PRINCIPAL INVESTIGATOR: M.A. SALAM, M.B., B.S.
   CO-INVESTIGATORS: ALI MIRAJ KHAN, M.B., B.S.
   WASIF ALI KHAN, M.B., B.S.
   CONSULTANT MICHAEL L. BENNISH, M.D.

3. ANTICIPATED START DATE: OCTOBER 1, 1990

4. STUDY DURATION: TWO YEARS FROM INITIATION

5. TOTAL DIRECT COST: $190,822

6. SCIENTIFIC PROGRAM HEAD: This protocol has been approved by the Clinical Sciences Division.

Signature, Associate Director
Clinical Science Division

1-11-90.
Date

7. ABSTRACT SUMMARY

Dysentery, primarily due to Shigella infection, is the major cause of diarrhea related mortality in children age 1 to 15 in Bangladesh. Treatment of Shigella infections in Bangladesh is complicated by the high prevalence of resistance among Shigella to commonly used antimicrobial agents. Currently 90% of Shigella dysenteriae type 1 isolates at the ICDDR,B are resistant to both co-trimoxazole and ampicillin. More than 30% of Shigella flexneri isolates are resistant to both co-trimoxazole and ampicillin. Of crucial importance is that over 60% of S. dysenteriae type 1 isolates are now resistant to nalidixic acid, which until recently had been the drug of choice for treating patients with Shigella infection at the ICDDR,B

There are limited options available for the treatment of these multiresistant infection. It is thus imperative that additional effective therapies be identified. Ciprofloxacin is a second generation quinolone that has excellent in-vitro activity against Shigella, including those strains that are resistant to nalidixic acid. We have previously shown that it is effective in the treatment of shigellosis in adults, and we now propose to study its efficacy in childhood shigellosis. One-hundred-sixty children will be evaluated; 80 will be randomly assigned to receive ciprofloxacin, 10 mg per kilogram body weight every 12 hours for five days, and 80 patients will be assigned to receive pivamdinocillin, 20 mg per kg body weight every six hours for five days. Eighty study patients will be selected from

patients presenting to the outpatient unit, and 30 patients will be selected from patients admitted to the inpatient unit. This will allow us to judge the efficacy of the drug in both moderately as well as severely ill patients. The clinical and bacterial outcome, as well as any side effects of treatment in the two treatment groups (ciprofloxacin and pivamdinocillin), will be compared using pre-determined criteria.

8. Reviews:

   a. Ethical Review Committee ----------

   b. Research Review Committee ----------

   c. Director ----------

SECTION II: RESEARCH PLAN

A. INTRODUCTION

1. Objective.

The objective of this study is to compare the efficacy of ciprofloxacin and pivamdinocillin in the treatment of shigellosis in children.

2. Study Background.

Shigellosis remains a major cause of diarrhea associated mortality in children in many developing countries, including Bangladesh (Ronsmans, Bennish 1990, 1991). It is estimated that of approximately 3.8 million diarrhea related deaths that occur worldwide in children annually, 0.5 million (exclusive of China) are attributable to shigellosis (Anonymous: Burden of Disease Resulting From Vaccine Preventable Disease, National Academy of Sciences). In the Matlab field study area of ICDDR,B approximately two-thirds of all diarrhea related deaths are caused by dysentery (Bennish 1990). Based upon studies of other areas of Bangladesh it is likely that more than half of these children with dysentery are infected with Shigella (Ronsmans).

Treatment of children with shigellosis with an effective antimicrobial agent is known to shorten both the duration of symptoms as well as the duration that the organism is excreted in the stool (Haltalin, Salam and Bennish 1988, Salam and Bennish 1991). It is also likely that early treatment can prevent most

fatalities that occur with shigellosis (Haltalin, Gangarosa), especially those, such as toxic colitis, hemolytic-uremic syndrome (Koster), and sepsis (Struelens), that occur late in the course of the illness.

Effective treatment of shigellosis has been complicated by the recent emergence of multiresistant strains (Bennish 1985, Pal, Shahid). These strains are resistant to ampicillin, co-trimoxazole and nalidixic acid, which until recently had been the drugs of choice for treating shigellosis (Salam and Bennish, 1991). Indeed, 90% of S. dysenteriae type 1 isolates from patients presenting to the Clinical Research Centre of the ICDDR,B are now resistant to ampicillin and co-trimoxazole (Figure). Over thirty percent of Shigella flexneri isolates are resistant to ampicillin and co-trimoxazole (Figure). Over 60% of S. dysenteriae type 1 isolates are now resistant to nalidixic acid, which until recently had been the drug of choice for empiric treatment of patients with suspected shigellosis presenting to the ICDDR,B Clinical Research Center (Figure). Almost all S. flexneri resistant isolates, however, remain susceptible to nalidixic acid (Figure).

For patients infected with strains of Shigella resistant to ampicillin, co-trimoxazole and nalidixic acid there are currently few alternative treatment options. Indeed the only other antimicrobial agent that remains active in-vitro and that has been shown effective in a controlled clinical trial (conducted in adults) is pivamdinocillin (Kabir) (pivmecillinam was the previous name for this drug). It is likely that, as with the

other β-lactam agents, resistance will also develop to this agent once it is widely used. There thus is a pressing need to find additional effective antimicrobial therapies for shigellosis (Fontaine).

Among the most promising newer agents for the treatment of enteric infections are the fluorinated quinolones (Neu, Wolfson). The quinolones are a group of oral antimicrobial agents that block the action of bacterial DNA gyrase (Wolfson, Epstein). This enzyme, which is not present in human cells, is responsible for the supercoiling of bacterial DNA. The latter is essential for the functioning of bacterial DNA. Without the proper three dimensional DNA structure the cell is unable to replicate, and thus bacterial growth is rapidly halted.

The first generation of quinolones, including nalidixic acid and oxolinic acid, became available in the early 1960's (Buchbinder). These older quinolones are poorly absorbed from the gastrointestinal tract, achieve only marginal serum concentrations, and have a narrow spectrum of antimicrobial activity. As a consequence of these poor pharmacokinetic characteristics the older quinolones are mostly used in the treatment of urinary tract infections (Ronald). They have, however, been found effective in the treatment of other selected infections, including shigellosis (Salam and Bennish, 1988).

The newer quinolone agents, such as ciprofloxacin, norfloxacin, ofloxacin, enoxacin and pefloxacin are fluorinated "cousins" of the older quinolones. The slight change in chemical

configuration of the newer quinolones has resulted in markedly increased in-vitro activity against Enterobacteriaceae, as well as activity against gram-positive organisms. These agents are well absorbed orally, and serum concentrations are in excess of 20 times the minimum inhibitory concentration of most of the common Enterobacteriaceae (Davis, Hoffken, Bergan). Indeed, in the case of Shigella, over 90% of strains tested have been inhibited by 0.015 µg/ml or less of ciprofloxacin (Carlson, Goosens, Ling). Serum concentrations are usually in the range of 1.5 to 3.0 µg/ml, or 100 to 200 times the MIC 90% of Shigella.

In addition to high serum concentrations, the drugs also attain high concentrations in the stool. Median stool concentrations of 359 and 410 mg per gram of stool have been reported from patients in their third and fifth day of ciprofloxacin therapy respectively (Bennish and Salam). As the drug is well absorbed, this high stool concentration may in part be due to trans-intestinal elimination of the drug (Sörgel). An additional pharmacologic attribute of the quinolones is that many of them, including ciprofloxacin, have a relatively long half-life, allowing for dosing intervals of 12 to 24 hours.

Most Enterobacteriaceae, including Shigella, that are resistant to the older quinolones remain susceptible to the newer quinolones (Keusch and Bennish 1988, Parry). The reason for this is likely related to the basic mechanism of action of the quinolone agents. The older quinolones act at a single site on the DNA gyrase, while the newer quinolones act at two sites. Resistance to the quinolones usually develops by a chromosomal

change leading to an alteration in the gyrase. Because the newer quinolones act at two sites along the gyrase, the development of bacterial resistance requires two point mutations on the chromosome coding for the gyrase. This happens at a much lower frequency than the single point mutation required to confer resistance to the older quinolone agents (Smith, Sanders, Fisher).

The newer quinolones have been shown to be effective in the treatment of a variety of enteric infections in adults. These include salmonellosis, typhoid fever, and shigellosis (Keusch 1988B, Bennish and Salam 1990, Rodriguez-Noreiga, Rogerie, DeMol, Gotuzzo). In the study conducted here at the ICDDR,B, (Bennish and Salam, 1990) 60 ciprofloxacin treated patients, when compared to 35 ampicillin treated patients infected with an ampicillin susceptible strain of Shigella, were found to have an earlier resolution of clinical symptoms, as well as earlier eradication of Shigella from the stool.

The newer quinolones are, with the newer generations of cephalosporin agents, considered to be the most important new advances in antimicrobial therapy in the last 20 years. The quinolones are now marketed in most countries in the world, and ciprofloxacin is on the list of approved drugs of the Drug Administration of the Government of the People's Republic of Bangladesh. The quinolones are now among the most commonly prescribed antimicrobial agents in developed countries. They are used both in seriously ill in-patients (an intravenous

formulation is available) as well as for the treatment of outpatients. In addition to enteric infections, the quinolones are commonly used for deep-seated infections, such as osteomyelitis, which require long term therapy (Waldvogel). In such infections the quinolones have the advantage of achieving high serum and tissue concentrations after oral administration, as opposed to the parenteral administration required of most other broad spectrum agents. They are also used for the treatment of pyelonephritis (Naber), intra-abdominal sepsis (Shah), infection prophylaxis in neutropenic patients (Karp), and for the treatment of patients with cystic fibrosis (mucoviscidosis) who have an exacerbation of their pulmonary symptoms (Schaad 1989, Grenier).

The quinolones have proven to be remarkably safe agents. Indeed, in comparative studies examining the usefulness of quinolones with co-trimoxazole or nitrofurantoin in the treatment of urinary tract infections, the incidence of side-effects was higher with the two older drugs than it was with the quinolones (Sabaj). Gastrointestinal complaints are the most common side effects noted in patients receiving the quinolones. This includes mild diarrhea and nausea. Other reported side effects include dizziness, headaches and insomnia.

The agent is also approved by the United States Federal Drug Administration for clinical trials in children. Ciprofloxacin has already been extensively used in the treatment of children with cystic fibrosis (Schaad 1989, Douidar), as well as children with neutropenia (Infectious Disease in Children Newsletter), and

those with osteomyelitis due to Pseudomonas and other hard to treat organisms. Six-hundred thirty-four children age 3 days to 17 years who have received the drug on a compassionate use basis in Europe included children with respiratory tract illnesses, skin and soft tissue infections, urinary tract infections, and enteric infections (Kapila). The dosage range given to these children was 3.0 to 93.9 mg per kilogram per day, with the most common dose being 20 mg per kilogram per day. The range of adverse reactions possibly related to drug therapy was similar to that seen in adults. Loosening of stools, anxiety, and mild, transient elevations in transaminases were the most commonly noted side effects. Transient arthralgia was noted in 8 patients. No patient had arthropathy. In addition to this compassionate use basis, ciprofloxacin has been given under study protocol to a large number of pre-pubertal children without serious adverse effects (Cruciani, Schaad 1989). Ciprofloxacin is also being used extensively in the treatment of children infected with multiply drug resistant strains of Salmonella typhi (N.K. Jalan, personal communication).

Like all quinolone agents, including nalidixic acid, ciprofloxacin can cause arthropathy in the joints of juvenile animals of selected species who are given large doses of the drug (Ingham). On a weight for weight basis the arthropathy causing effect of ciprofloxacin is less than that of nalidixic acid (Pharma Report). In animals the arthropathy has been reversible when the drug is stopped. Long term experience with nalidixic

acid suggests that arthropathy is not a problem when used in humans (Schaad 1987, Salam and Bennish, 1988). There has been one report of arthropathy occurring in a 14 year old girl with cystic fibrosis who had been taking a relatively high dose of ciprofloxacin (45 mg per kg per day) for 3 weeks (Alfaham). Because arthropathy is known to occur in patients with cystic fibrosis, it is uncertain whether in this one case the arthropathy was truly related to treatment with ciprofloxacin, or, as seems more likely, was simply a complication of the primary illness.

C. METHODS OF PROCEDURE

1. Patient Selection.

The methods of this study will be similar to the previous three treatment studies of shigellosis that we have conducted (Protocol #'s 85-002, 86-013, 88-011). Patients eligible for study will be children age 1 to 15 years of age with a history of dysentery, who have frank bloody mucoid stools on naked eye examination of a stool sample. Patients will be divided into two groups - those with moderately severe shigellosis, who will be recruited from the patients presenting to the outpatient area and who will be admitted to the research ward, and patients with more severe disease, who will be selected from patients admitted to the inpatient unit. Eighty patients in each group will be selected.

Reasons for exclusion from the study will be:

a. Prior treatment for this illness with either of the two antimicrobial agents under study.

b. The presence of erythrophagocytic trophozoites of Entamoeba histolytica on stool microscopic examination.

c. For patients recruited from the outpatient department, illness of greater than 72 hours duration, or the presence of other infections requiring antimicrobial therapy in addition to that of the study drug.

d. Patients known to be allergic to β-lactam antibiotics, or to quinolone agents.

2. Treatment Regimens.

Patients will be randomized in equal numbers to receive either ciprofloxacin, 20 mg per kilogram body weight per day, or pivamdinocillin, 80 mg per kilogram body weight per day. The total daily dose of ciprofloxacin will be divided into two equal portions to be administered 12 hours apart. Pivamdinocillin will be divided into four equal doses to be given six hourly. Therapy will be double blinded. Treatment duration will be five days. For patients admitted into the inpatient unit, each set of medications will include both oral and intravenous forms, as some patients (usually less than 5% of patients admitted with shigellosis) develop ileus during their hospitalization, and are thus unable to continue to take oral medication.

Both medications will be prepared in identical appearing elixirs. In order to blind therapy patients receiving ciprofloxacin will receive identical appearing placebo

alternating with active drug. Concentrations of the two study drugs will be adjusted so that patients in each treatment group will receive an equivalent volume of drug.

3. Randomization.

Patients will be assigned a study number upon enrollment into the study. Such study numbers will be assigned consecutively, and a study medication will have been randomly pre-assigned to each study number. Randomization will be done using a block randomization method with a block size of six. There will be a separate randomization schedule for patients selected in the inpatient and outpatient areas.

4. Clinical Evaluation and Laboratory Studies.

Patients will be hospitalized for six full days following the initiation of therapy, and will be requested to return for a return visit 7 days after discharge. The following will be the schedule for the routine clinical and laboratory evaluations:

i. History and physical examination: On admission and daily. This will include specific evaluation of joint function.

ii. Determination of vital signs: 4 hourly throughout the study period.

iii. Enumeration and characterization of stools: Daily throughout the study period.

iv. Stool culture for identification of Shigella, Salmonella, Campylobacter jejuni: Admission.

v. Stool culture for identification of Shigella. Study day 3 and follow-up visit.

vi. Rectal swab culture for identification of Shigella: Admission and study days 2, 4, 5, and 6.

vii. Blood culture (1.5 ml): on admission.

viii. Complete blood count, platelet count, serum electrolytes, creatinine, bilirubin and aspartate aminotransferase (total 2.5 ml of blood): on admission and on study day five.

ix. Peak serum concentration of antimicrobial agent (1 ml blood): 90 minutes after the first dose of medication on the second study day.

x. Trough serum concentration of antimicrobial agent (1 ml of blood): To be drawn 11.5 hours after the last dose of medication on study day five. This sample will be drawn simultaneously with the other laboratory samples to be drawn on that day.

xi. Stool concentration of the antimicrobial agents: determined on the first stool passed on study days 2, 4 and 6.

xii. Urinalysis: Obtained on admission and study days 3 and five.

5. Evaluation of Outcome.

Both bacteriologic and clinical outcome will be evaluated with pre-determined criteria similar to those used in our previous study of shigellosis.

Clinical outcome will be judged on the basis of the patient's status on study day five, and will be defined as follows:

Resolution of illness:	No frank dysenteric stools. ≤ 3 total stools within 24 hours. Afebrile.
Marked improvement:	≤ 1 watery stool. ≤ 6 total stools. Afebrile.
Slight improvement:	≤ 3 watery stools ≤ 9 total stools. Afebrile
Failure:	> 3 watery stools, or > 9 total stools, or Febrile.

Bacteriologic cure will be defined as the eradication of Shigella by study day 3, with all subsequent stool samples remaining culture negative for Shigella.

6. Sample Size Determination.

To be able to determine a difference between treatment groups in the proportion of successfully treated patients of 30% (95% versus 65%) with a power of .80, and with an α of .05, a sample size of 80 (40 in each treatment group) is required. For this purpose successful treatment is defined as marked improvement or resolution of illness. Outcomes in the inpatient and the outpatient group will be compared both separately and in a combined fashion. Thus 160 patients (80 inpatients and 80

outpatients) will be required. We estimate that, after accounting for patients who are initially enrolled but who do not have Shigella isolated from their stool sample and for patients who withdraw from study, it will be necessary to enroll 240 patients to achieve the desired sample size.

7. Handling of Treatment Failures.

If the study treatment is judged to have failed by either clinical or bacteriologic criteria, the study code will be broken and the patient treated with an alternative agent, (if available), to which the isolate of Shigella is susceptible. In addition to the day five evaluation, therapy will be considered to have failed if after 72 hours of therapy patients have not shown symptomatic improvement and continue to have frank dysenteric stools, fever and tenesmus. During the study period patients in the inpatient group will be treated, if indicated, with other antimicrobial agents for infections in addition to shigellosis. This will not constitute an indication for removal from the study. The development at any time during the study of an adverse reaction (skin rash, arthropathy, altered mental consciousness) that is possibly or probably related to drug therapy will be an indication for stopping of the study drug and starting alternative therapy.

8. Statistical Methods.

Difference in means will be tested for significance using

the Student's t test if the data is normally distributed, and the Mann-Whitney U test if the data is non-normally distributed. Differences in proportions will be tested for significance using the chi-square test. Statpac Gold version 5.5 will be used for data entry, and both Statpac Gold and SPSS-PC^{+} will be used for data analysis.

9. Laboratory Methods.

All cultures and hematologic and biochemical examinations will be done using routine methods now available in our laboratories. Determination of serum and stool antimicrobial concentrations will be done using a chromatographic method. For this study 8.5 ml of blood will be required for the tests listed in the methods section.

D. SIGNIFICANCE

This study is intended to identify another antimicrobial agent that is likely to be effective in the treatment of shigellosis in children. There is currently a crucial need for identifying such agents, as the majority of S. dysenteriae type 1 isolates, which are responsible for the most severe forms of shigellosis in childhood, are resistant to all commonly used drugs except for pivamdinocillin. Although ciprofloxacin has been shown to be effective in adults, we do not know its effectiveness in childhood, and this study plans to examine that issue. The issue of efficacy in children is an extremely important one, as the majority of morbidity and mortality related

to shigellosis occurs in this age group.

E. Facilities Required.

This study will be done using the current facilities of the Clinical Research Center.

SECTION III: REFERENCES

1. Anonymous. The burden of disease resulting from diarrhoea. In: Division of Health Promotion and Disease Prevention, Division of International Health, Institute of Medicine, New vaccine development: establishing priorities. Vol.2. Diseases of importance in developing countries, Washington, D.C. National Academy Press, 1986:159-69.
2. Alfaham M, Holt ME, Goodchild MC. Arthropathy in a patient with cystic fibrosis taking ciprofloxacin. Br Med J 1987;2:699.
3. Bennish M, Eusof A, Kay B. Multiresistant Shigella infections in Bangladesh. Lancet 1985;2:441.
4. Bennish ML, Harris J, Wojtyniak BJ. Death in shigellosis: incidence and risk factors in hospitalized patients. J Infect Dis 1990;161:500-6.
5. Bennish ML. Mortality from shigellosis. Community and hospital data. Rev Infect Dis. 1991;12: In press.
6. Bennish ML, Salam MA, Haider R, Barza M. Therapy of shigellosis. II. Randomized, double blind comparison of ciprofloxacin and ampicillin. J Infect Dis. 1990;162:September. In press.
7. Bergan T, Dalhoff A, Rohwedder R. Pharmacokinetics of ciprofloxacin. Infection 1988; 16(suppl 1):S3-S13.
8. Bomhard E, Ruhl C, Krotlinger F. Bay O 9867, nalidixic acid, Am-715, DL-8280. Comparative investigations on the arthropathogenic effect and occulotoxicity in juvenile

Wistar rats. Pharma-Report. 1984;July 27:12826.

9. Buchbinder M, Webb JC, Anderson L, McCabe WR. Laboratory studies and clinical pharmacology of nalidixic acid (WIN 18,320). Antimicrob Agents Chemother 1962;308-17.

10. Carlson JR, Thornton SA, DuPont HL, West AH, Mattewson JJ. Comparative in vitro activities of ten antimicrobial agents against enteropathogens. Antimicrob Agents Chemother 1983;24:509-13.

11. Cruciani M, Concia E, Navarra A, et. al. Prophylactic co-trimoxazole versus norfloxacin in neutropenic children-prospective randomized study. Infection 1989;17:65-69.

12. Davis RL, Koup JR, Williams-Warren J, Weber A, Smith Al. Pharmacokinetics of three oral formulations of ciprofloxacin. Antimicrob Agents Chemother 1985;28:74-7.

13. De Mol P, Mets T, Lagasse R, Vandepitte J, Mutwewingabo JP. Treatment of bacillary dysentery: a comparison between enoxacin and nalidixic acid. J Antimicrob Chemother 1987;19:695-8.

14. Douidar SM, Snodgrass WR. Potential role of fluroquinolones in pediatric infections. Rev Infect Dis 1989;11:878-89.

15. Epstein RJ. Topoisomerases in human disease. Lancet 1988;1:521-23.

16. Fisher LM, Lawrence JM, Josty IC, Hopewell R, et al. Ciprofloxacin and the fluoroquinolones: new concepts on the mechanism of action and resistance. Am J Med 1989;87 (Supp 5A): 2S.

17. Fontaine O. Antibiotics in the management of shigellosis in children: what role for the quinolones? Rev Inf Dis 1989;11 (Supp 5):S1145-S1150.

18. Gangarosa EJ, Perera DR, Mata LJ, et. al. Epidemic Shiga Bacillus dysentery in Central America. II. Epidemiologic studies in 1969. J Infect Dis 1970;122:181-90.

19. Goossens H, De Mol P, Coignau H, Levy J, Grados O, Ghysel G, Innocent H, Butzler JP. Comparative in vitro activities of aztreonam, ciprofloxacin, norfloxacin, ofloxacin, HR 810 (a new cephalosporin), RU28965 (a new macrolide), and other agents against enteropathogens. Antimicrob Agents Chemother 1985;27:388-92.

20. Gotuzzo E, Oberhelman RA, Maguna C, Berry SJ, Yi A, Guzman M, Ruiz R, Leon-Barua R, Sack KB. Comparison of single-dose treatment with norfloxacin and standard 5-day treatment with trimethoprim-sulfamethoxazole for acute shigellosis in adults. Antimicrob Agents Chemother 1989;33:1101-4.

21. Grenier B. Use of the new quinolones in cystic fibrosis. Rev Inf Dis 1989;11(Suppl 5):S1245-S1252.

22. Haltalin KC, Nelson JD, Ring R, Sladoje M, Hinton LV. Double-blind treatment study of shigellosis comparing ampicillin, sulfadiazine, and placebo. J Pediatr 1967;70:970-81.

23. Hoffken G, Lode H, Prinzing C, Borner K, Koeppe P. Pharmacokinetics of ciprofloxacin after oral and parenteral administration. Antimicrob Agents Chemother 1985;27:375-9.

24. Ingham B, Brentnall DW, Dale EA, McFadzean JA.

Arthropathy induced by antibacterial fused N-alkyl-pyridone-3-carboxylic acids. Toxicol Lett 1977;1:21-6.

25. [Newsletter] Infectious disease in children. October 1988;1(10):1.

26. Kabir I, Rahaman MM, Ahmed SM, Akhter SQ, Butler T. Comparative efficacies of pivmecillinam and ampicillin in acute shigellosis. Antimicrob Agents Chemother 1984;25:643-5.

27. Kapila K, Chysky V, Hullmann R, Arcieri G, Schacht P Echols R. 3rd International symposium on new quinolones. Worldwide clinical experience on safety of ciprofloxacin in children on compassionate use basis. Vancouver, Canada, 1990.

28. Karp JE, Merz WG, Hendricksen C, et. al. Oral norfloxacin for prevention of gram-negative bacterial infections in patients with acute leukemia and granulocytopenia: a randomized, double-blind, placebo-controlled trial. Ann Intern Med 1987;106:1-7.

29. Keusch GT, Bennish ML. Shigella. In: Farthing MJG, Keusch GT, eds. Enteric infection. Mechanisms, manifestations, and management. London: Chapman and Hall Ltd., 1988:265-282.

30. Keusch GT. Antimicrobial therapy for enteric infections and typhoid fever. Rev Infect Dis 1988;10(suppl 1):S199-205.

31. Koster F, Levin J, Walker L, et al. Hemolytic-uremic syndrome after shigellosis: relation to endortoxemia and circulating immune complexes. N Engl J Med 1978;298:927-33.

32. Ling J, Kam KM, Lam AW, French GL. Susceptibilities of Hong

Kong isolates of multiply resistant Shigella spp to 25 antimicrobial agents, including ampicillin plus sulbactam and new 4-quinolones. Antimicrob Agents Chemother 1988;32:2-23.

33. Naber KG. Use of quinolones in urinary tract infections and prostatitis. Rev Infect Dis 1989;11 (suppl 5):S1321-37.

34. Neu HC. Clinical use of the quinolones. Lancet 1987;2:1319-22.

35. Pal SC. Epidemic bacillary dysentery in West Bengal, India, 1984. Lancet 1984;1:1462.

36. Parry MF, Panzer KB, Yukna ME. Quinolone resistance: susceptibility data from a 300-bed community hospital. Am J Med 1989;87(Supp 5A):12S.

37. Rodríguez-Noriega E, Andrade-Villanueva J, Amaya-Tapia G. Quinolones in the treatment of Salmonella carriers. Rev Infect Dis 1989;11 (suppl 5):1179-87.

38. Rogerie F, Ott D, Vandepitte J, Verbist L, Lemmens P, Habiyaremye I. Comparison of norfloxacin and nalidixic acid for treatment of dysentery caused by Shigella dysenteriae type 1 in adults. Antimicrob Agents Chemother 1986;29:883-6.

39. Ronald AR, Turck M, Petersdorf RG. A critical evaluation of nalidixic acid in urinary-tract infectious. N Engl J Med 1966;275:1081-9.

40. Ronsmans C, Bennish ML, Wierzba T. Diagnosis and management of dysentery by community health workers. Lancet 1988;2:552-5.

41. Sabbaj J, Hoagland VL, Shih WJ. Multiclinic comparative study of norfloxacin and trimethoprim-sulfamethoxazole for treatment of urinary tract infections. Antimicrob Agents Chemother 1985;27:297-301.

42. Salam MA, Bennish ML. Therapy for shigellosis: I. Randomized, double blind trial of nalidixic acid in childhood shigellosis. J Pediatr 1988; 113:901-7.

43. Salam MA, Bennish ML. Antimicrobial therapy of shigellosis. Rev Infect Dis. 1991;13: In press.

44. Sanders CC, Sanders WE, Goering RV, Werner V. Selection of multiple antibiotic resistance by quinolones, β-lactams, and aminoglycosides with special reference to cross-resistance between unrelated drug classes. Antimicrob Agents Chemother 1984;26:77-801.

45. Schaad UB, Wedgwood-Krucko. Nalidixic acid in children: retrospective matched controlled study for cartilage toxicity. Infection 1987;15:165-67.

46. Schaad UB, Wedgwood-Krucko, Guenin, K, Buehlmann U, Kraemer R. Antipseudomonal therapy in cystic fibrosis: aztreonam and amikacin versus ceftazidime and amikacin administered intravenously followed by oral ciprofloxacin. Eur J Clin Microbiol Infect Dis 1989;8:858-865.

47. Shahid NS, Rahaman MM, Haider K, Banu H, Rahaman N. Changing pattern of resistant Shiga bacillus (Shigella dysenteriae type 1) and Shigella flexneri in Bangladesh. J Infect Dis 1985;152:1114-9.

48. Shah PM. Use of quinolones for the treatment of patients with bacteremia. Rev Inf Dis 1989;11 (Suppl 5):S1155-9.

49. Struelens MJ, Patte D, Kabir I, Salam A, Nath SK. Shigella septicemia: prevalence, presentation, risk factors, and outcome. J Infect Dis 1985;152:784-90.

50. Smith JT. Mutational resistance to 4-quinolone antibacterial agents. Eur J Clin Microbiol 1984;3:347-50.

51. Sörgel F, Naber KG, Jaehde U. Reiter A. Seelmann R. Sigl G. Brief report: gastrointestinal secretion of ciprofloxacin: evaluation of the charcoal model for investigations in healthy volunteers. Am J Med 1989;87(Suppl 5A):62S.

52. Waldvogel FA. Use of quinolones for the treatment of osteomyelitis and septic arthritis. Rev Inf Dis 1989;11 (Suppl 5):S1259-S1263.

53. Wolfson JS, Hooper DC. The fluoroquinolones: structures, mechanisms of action and resistance, and spectra of activity in vitro. Antimicrob Chemother 1985;28:581-86.

SECTION IV: BUDGET

LOCAL SALARY	: US$	80,400.00
SUPPLY & MATERIAL(STOCK & NON-STOCK)	:	8,000.00
OTHER CONTRACTUAL	:	4,000.00
Dhaka transport	:	500.00
Xerox	:	200.00
Pathological tests	:	6,232.00
Microbiological tests	:	19,804.00
Biochemical tests	:	10,406.00
X-Ray	:	3,280.00
Patient study	:	37,500.00
Medical Illustration	:	200.00
Telex	:	500.00
Maintenance	:	600.00
Staff clinic	:	500.00
Bioengineering	:	200.00
Transport subsidy	:	500.00
INTERDEPARTMENTAL	:	80,422.00
REIMBURSEMENT FOR FOLLOW-UP TRANSPORT COST	:	3,000.00
INTERNATIONAL TRAVEL	:	10,000.00
CAPITAL EXPENDITURE	:	5,000.00
TOTAL DIRECT COST	:	190,822.00
OVERHEAD(31%)	:	59,155.00
TOTAL PROJECT COST	:	US$=249,977.00

SECTION V: CONSENT FORMS

Your child is suffering from dysentery which is probably due to infection with a germ named Shigella. Management of this infection requires the use of an antimicrobial agent effective against this germ. Unfortunately the Shigella germs in our country have gradually become resistant to most of the drugs once useful in its treatment. Therefore, we are attempting to identify alternative drugs which are likely to be effective for treating this infection.

In a previously conducted study at this Centre we have tested the effectiveness in adults of a drug named ciprofloxacin. The results of that study show that ciprofloxacin is as, or more effective, than previously used drugs for treating this condition. Children, however, are the worst sufferers from this disease in our country. Therefore it is necessary for us to determine the effectiveness of ciprofloxacin in children suffering from dysentery due to Shigella infection. We have undertaken this study to see if this drug is effective and safe for use in children suffering from shigellosis. You can contribute to the society by allowing us to enroll your child for this study. If you allow your child to participate in the study;

1. Your child will be required to be admitted for a total of 6 days in the research ward, or in the general ward of this hospital, and to come back 7 days after discharge from the hospital. If, however, the results of the stool and rectal

swab culture tests do show that your child is not suffering from shigellosis your child may be discharged, subject to improvement in his/her condition. Results of these studies are usually available 48 hours after admission.

2. On admission into the study, and on each of the six subsequent study days, we will take a detailed history of the symptoms that your child has, do a thorough physical examination, and record the findings.

3. On admission to the study, and on each of the subsequent six study days, we will insert a small cotton tipped swab into the rectum of your child. This will enable us to obtain a sample which will let us know if he/she is still infected with the Shigella germ that caused his/her illness. This is not painful - on occasion it may cause slight, momentary discomfort.

4. We will obtain a stool sample from your child on admission and on study days 3 and 5 for the same purpose - to determine if he/she still is infected with the Shigella germ. A portion of these stool samples, as well as stool samples collected on study days 2, 4 and 6 will be used for determination of the drug concentrations in the stool.

5. Purely on chance, your child will receive either pivamdinocillin every 6 hours, or ciprofloxacin every 12 hours, in appropriate doses. Pivamdinocillin is a drug, which, like ciprofloxacin, has been shown to be an effective drug for the treatment of shigellosis in adults.

6. During the six study days a total of 8.5 ml (approximately 2

teaspoons) of blood will be drawn for different tests which will mostly be required to determine the status of your child. This amount of blood will be drawn on three occasions; on the day of admission and on study days 2 and 5. Other than a little pain there is no risk involved with withdrawal of this amount of blood from your child.

7. We will record the number of times your child passes stool, and characterize every stool on each of the six study days. These will be required to assess progress of your child's condition.
8. If required any time during the study period, we will perform radiologic investigations of his/her chest and or joints.
9. Urine of your child will be tested on admission day and on study days 3 and 5.
10. You are the one to decide if your child will participate in this study. Even if you do not want your child to participate in the study, he/she will receive the standard treatment of this hospital.
11. You may at any time during the study withdraw your consent.
12. All information obtained from the history, physical examination and laboratory tests of your child will be kept confidential and no one other than the investigators of this study will have access to these records.
13. If you wish to know the result of any or all the tests done during the study, or the overall study results, those will

be provided to you upon your request as and when these become available.

If you agree to allow your child to participate in the study please put your signature or left thumb impression below:

_____	_____
Signature of the Investigator	Signature/LTI of the guardian
Date:_____	_____
	Relationship with the patient
Signature of witness:_____	Date: _____
Date: _____	

শিশুদের রক্ত আমাশয়ে সিপ্রোফ্লোক্সাসিন ও
সিফ্রিএকসোনের তুলনামূলক কার্যকারিতা গবেষনা।
সম্মতি পত্র

মুখী,

আপনার শিশু রক্তআমাশয়ে ভুগছে, যার কারন, সম্ভবত: 'সিগেলা' নামক রোগজীবানুর সংক্রমন। এ রোগের চিকিৎসায় জীবানু ধ্বংসী ঔষধের প্রয়োজন। দু:খজনক এই যে, এ জীবানুর বিরুদ্ধে একসময় কার্যকর বেশীর ভাগ ঔষধই তাদের কর্মক্ষমতা হারিয়ে ফেলেছে। এ কারনে, আমরা এ রোগের বিরুদ্ধে কার্যকর ঔষধ খুজে বের করার চেষ্টা করছি।

এ কেন্দ্রে, এর আগে এক গবেষনায় আমরা প্রান্ত বয়স্ক 'রক্ত আমাশয়ের রোগীদের উপর' সিপ্রোফ্লোক্সাসিন' নামক এক জীবানু ধ্বংসী ঔষধের কার্যকারিতা প্রমান করেছি। কিন্তু, শিশুরাই এ রোগে সবচাইতে বেশী ভুগে থাকে। এজন্যে, শিশুদের ক্ষেত্রে এ ঔষধটি কার্যকারিতা নির্নয় করা প্রয়োজন। আমরা শিশুদের ক্ষেত্রে এ ঔষধ কার্যকর এবং নিরাপদ কিনা, তা জানবার জন্যে এ গবেষনা কার্যক্রম হাতে নিয়েছি। আপনি এ গবেষনায় আপনার শিশুর অংশগ্রহনের অনুমতি দিয়ে সমাজে অবদান রাখতে পারেন। আপনি যদি এ গবেষনায় আপনার শিশুর অংশগ্রহনে রাজী থাকেন তাহলে;

① আপনার শিশুকে পুর্ন ৫ দিন এ হাসপাতালের গবেষনা/সাধারন প্রকোষ্ঠে ভর্ত্তি থাকতে হবে, এবং, ছুটির সাত দিন পর সামান্য সময়ের জন্যে তাকে এ হাসপাতালে আনতে হবে। অবশ্য, যদি পরীক্ষার ফলে প্রমানিত হয় যে, আপনার শিশু 'সিগেলা' আমাশয়ে ভুগছেনা, সেক্ষেত্রে, তবে অবস্থা ছুটি দেয়ার উপযুক্ত বলে বিবেচিত হলে ৫ দিনের আগেই তাকে ছুটি দেয়া যেতে পারে। প্রাথমিক পরীক্ষায় সাধারনত: ৪৮ ঘন্টা সময়ের প্রয়োজন।

② ভর্ত্তির সময় এবং প্রতিদিন মাথায় তুলা লাগানো সরু কাঠির সাহায্যে রোগীর মলাশয় থেকে পরীক্ষা সামগ্রী নিতে হবে। এতে সামান্য অস্বস্তি ছাড়া কোন ক্ষতির সম্ভাবনা নেই। এ পরীক্ষার সাহায্যে আমরা রোগী সংক্রমন থেকে মুক্ত হলো কিনা এবং কবে মুক্ত হলো তা জানতে পারবো।

③ ভর্ত্তির সময় এবং প্রতিদিন রোগীর অবস্থা সম্বন্ধে জিজ্ঞাসাবাদ এবং পুর্ন শারীরিক পরীক্ষা করা হবে। প্রাপ্ত তথ্যাদি লিপিবদ্ধ করা হবে।

④ ভর্ত্তির পর এবং ভর্ত্তির তৃতীয় ও পঞ্চম দিনে সামান্য পরিমান মল ২ নম্বর অনুচ্ছেদে বর্নিত কারনে নিতে হবে। এ ছাড়া মলে ঔষধের পরিমান নির্নয়ের জন্যে দ্বিতীয়, চতুর্থ এবং ৬ষ্ঠ দিনে সামান্য পরিমান মলের প্রয়োজন পড়বে।

(৫) ঔষধ নির্ভর হয়ে আপনার শিশু প্রতি ১২ ঘন্টা পর পর পরিমিত পরিমানে সিপ্রোফ্লক্সাসিন অথবা প্রতি ৬ ঘন্টা পর পর পরিমিত পরিমানে অন্য ঔষধ-সিপ্রোফ্লক্সাসিন ও মেট্রোনিডাজল দুটি পাঁচ দিনের জন্যে পাবে। দ্বিতীয় ঔষধটির কার্যকরীতা প্রাপ্তবয়স্কদের সিগেলা আমাশয়ে প্রমানিত হয়েছে।

(৬) হাসপাতালে ভর্তির সময়, দ্বিতীয় ও পঞ্চম দিনে, অর্থাৎ সর্বমোট তিন বারে ৮ মিঃলিঃ বা ২ চা-চামচেরও কম পরিমান রক্ত রোগীর শিরা থেকে বিভিন্ন পরীক্ষার জন্যে নিতে হবে। এত সূচের সামান্য ব্যথা ছাড়া আর কোন ক্ষতি হবেনা।

(৭) ভর্তি থাকা কালীন প্রতিদিন রোগী কতবার এবং কি ধরনের মল ত্যাগ করছে তা নির্ণয় এবং লিপিবদ্ধ করা হবে। এ থেকে চিকিৎসায় উন্নতি হচ্ছে কিনা তা বোঝা যাবে।

(৮) রোগীর প্রয়োজনে যে কোন সময়ে তার রক্ত বা শিরার এক্সরের ব্যবস্থা করতে হতে পারে।

(৯) ভর্তির দিন, তৃতীয় দিন এবং পঞ্চম দিনে মূত্রের পরীক্ষা করা হবে।

(১০) আপনিই একমাত্র ব্যক্তি যিনি এ গবেষনায় আপনার শিশুর অংশ গ্রহনের অথবা অংশগ্রহন থেকে বিরত থাকার সিদ্ধান্ত নেবার অধিকার রাখেন। আপনি প্রস্তাবে রাজী না হলেও আপনার শিশু এ হাসপাতালের প্রচলিত সুচিকিৎসা পাবে।

(১১) অংশ গ্রহনের পরেও যে কোন সময়ে আপনি সম্মতি প্রত্যাহার করতে পারেন।

(১২) আপনার শিশুর থেকে প্রাপ্ত সকল তথ্য এবং যাবতীয় পরীক্ষার ফলাফল গোপন রাখা হবে। শুধুমাত্র এ গবেষনার গবেষক ও তত্ত্বাবধায়ক জড়িত ব্যক্তি ছাড়া আর কেউই এসব তথ্যাদি জানতে পারবেনা।

(১৩) আপনি আপনার শিশুর কোন বা সমস্ত পরীক্ষার ফলাফল জানতে চাইলে যদি ফলাফল জানা থাকে তাহলে তা আপনাকে জানানো হবে। এমনকি, আপনি গবেষনার ফলাফল জানতে চাইলে ফলাফল জানা সাপেক্ষে আপনাকে তা জানানো হবে।

আপনি যদি আমাদের আবেদনে সাড়া দিয়ে এ গবেষণা কার্যক্রমে আপনার শিশুর অংশ গ্রহনের প্রস্তাবে যদি রাজী থাকেন তাহলে দয়া করে নীচের নির্দিষ্ট স্থানে আপনার স্বাক্ষর অথবা টিপসই দিন।

আপনার সহযোগীতার জন্যে অসংখ্য ধন্যবাদ ॥

গবেষকের স্বাক্ষর: _____

তারিখ: _____

অভিভাবকের স্বাক্ষর/ টিপ সই : _____

তারিখ: _____

সাক্ষীর স্বাক্ষর: _____

তারিখ: _____

রোগীর সাথে সম্পর্ক : _____

ABSTRACT SUMMARY

1. Requirements for Study Population.

This study will require children 1-15 years of age who are ill with dysentery caused by infection with Shigella. This is the population that is most at risk of suffering morbidity and mortality from shigellosis, and it is essential to identify effective antimicrobial therapies for this population. Ciprofloxacin has been shown to be both effective and safe in the treatment of shigellosis in adults. It is now necessary to determine if it is also effective in the treatment of shigellosis in childhood.

2. Potential Risks.

The major potential risk from the this, as with any drug study, is adverse reaction to the drugs under study. Both pivamdinocillin and ciprofloxacin are known to be quite safe. The major adverse reactions to pivamdinocillin are similar to those seen with other β-lactam agents. The most serious of these are allergic reactions, including, rarely, anaphylaxis. Other reported adverse reactions to pivamdinocillin include nausea, dyspepsia and other gastrointestinal complaints in less than 5% of patients who receive the drug, and slight increases in liver enzymes. Allergic reactions to ciprofloxacin are less common than for pivamdinocillin. Side-effects reported include anxiety, nausea, and mild elevations in liver enzymes. As with nalidixic

acid, arthropathy has been reported when the drug is given in high doses to certain types of animals. However arthropathy has not been a problem in either the adults or the children who have been treated with ciprofloxacin or other quinolone agents including nalidixic acid.

Aside from adverse effects of the drugs, the only other risk associated with this study is the blood drawing. The volume of blood drawn for study purposes will be quite small and will therefore pose no risk to the study patients.

3. Methods for minimizing potential risks.

Patients will have a detailed physical examination done daily. Any patient with signs of possible adverse effects from the study drugs will receive alternative therapy.

4. Methods for safeguarding confidentiality.

Patients will be assigned a study number, and all data entry and computer records will be identified using this study number, rather than the patient's name.

5. Informed consent.

Informed consent will be obtained from the parent or guardian of all patients enrolled in the study. Bangla and English language versions of the informed consent form are attached.

6. Interview

Patients and their parents will have routine medical interviews and examinations done on a daily basis.

7. Benefits to the individual and society.

The individual will benefit because they will receive treatment for shigellosis with one of two drugs that are both likely to be effective in its therapy. Given the widespread resistance of Shigella to other antimicrobial agents, and the seriousness of the morbidity (and mortality) that is associated with Shigella infections that are not treated or are treated ineffectively, the benefits of therapy with these two drugs far outweigh the risks.

Society will benefit because we will determine the effectiveness of these two drugs, pivamdinocillin and ciprofloxacin, in the treatment of children with shigellosis. This will allow us to plan more rational therapy for patients with this disease, which is a major cause of the childhood mortality and morbidity in Bangladesh.

8. Samples required.

This study will make use of patient records, as well as stool, urine and blood.

CIPROFLOXACIN IN CHILDHOOD SHIGELLOSIS STUDY
JOINT ASSESSMENT CHART

PATIENT'S NAME: _____ AGE : | | | | | SEX : | M | F |

Y Y M M

ADMISSION # : | | | | | | | STUDY # : | | | | DATE : | | | | | | |

D D M M Y Y

STUDY DAY(AD, AND DAY 1-6) | |

JOINT EXAMINATION SCALE (FOR SWELLING, PAIN, AND TENDERNESS)

0= NONE, 1= MILD, 2= MODERATE, 3= MARKED

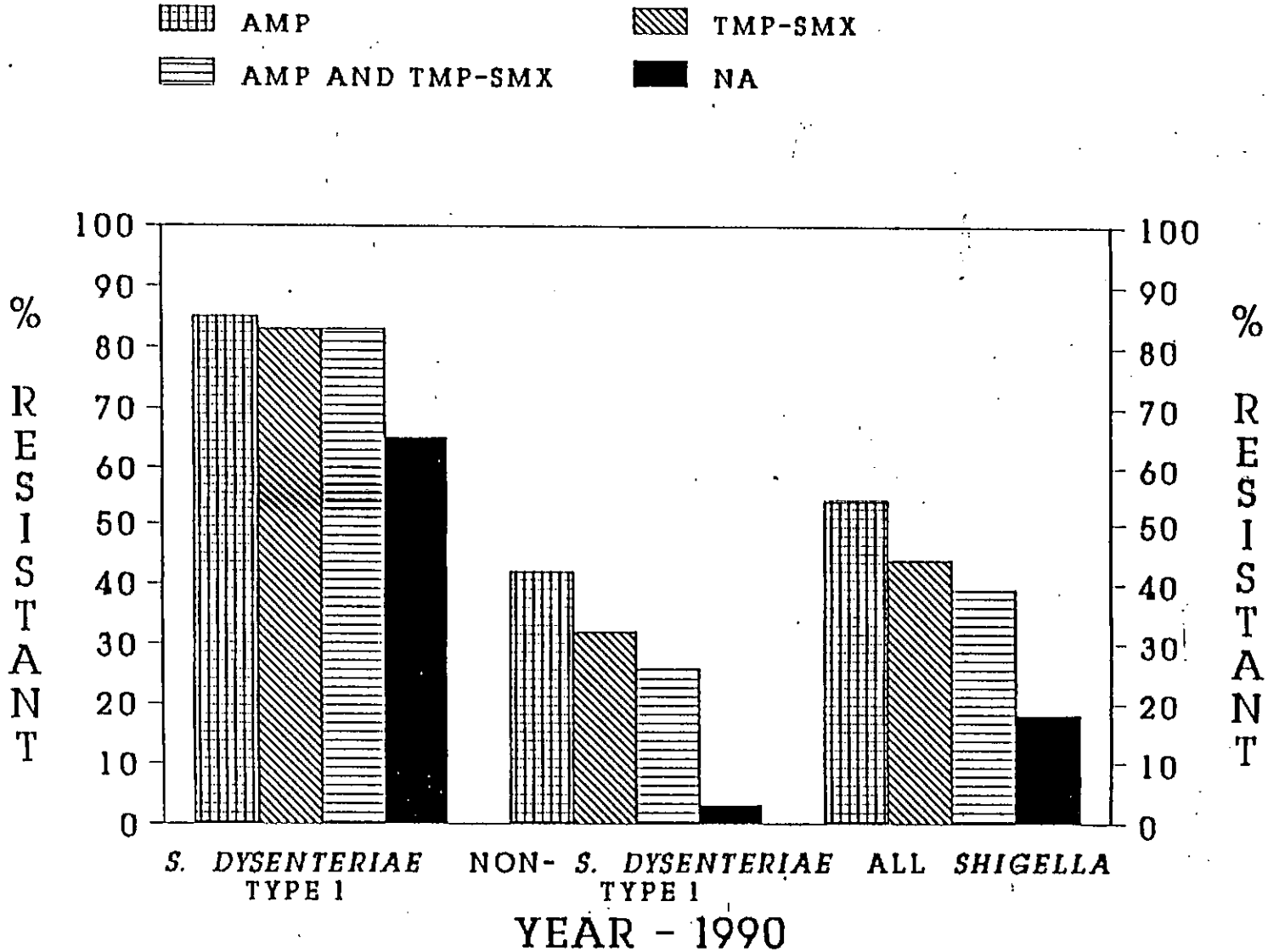
LIMITATION OF MOTION SCALE

0=FULL RANGE, 1=25% LIMITATION, 2=50% LIMITATION, 3=75% LIMITATION, 4=100%LIMITATION

JOINTS	SWELLING		PAIN ON MOTION		TENDERNESS		LIMITATION OF MOTION	
	RIGHT	LEFT	RIGHT	LEFT	RIGHT	LEFT	RIGHT	LEFT
HIP								
KNEE								
ANKLE								
WRIST								
ELBOW								
SHOULDER								

GAIT 0 = NORMAL 1=LIMPING

% OF *SHIGELLA* ISOLATES RESISTANT TO:



Project Title: Double blind, randomized study of the treatment of childhood shigellosis comparing ciprofloxacin and sulfadimidine

Summary of Referee's Opinions: Please see the following table to evaluate the various aspects of the proposal by checking the appropriate boxes. Your detailed comments are sought on a separate, attached page.

	Rank Score		
	High	Medium	Low
Quality of Project		X	
Adequacy of Project Design		X	
Suitability of Methodology	X		
Feasibility within time period	X		
Appropriateness of budget			X
Potential value of field of knowledge		X	

CONCLUSIONS

I support the application:

a. without qualification ___

b. with qualification

- on technical grounds X
- on level of financial support X

I do not support the application ___

record these data should be provided.

5. The monitoring of appearance of side effects should be presented in the

This research proposal presents a double-blind, controlled clinical trial comparing the efficacy of ciprofloxacin, a new quinolone antibiotic, and pivmecillinam in the treatment of acute shigellosis in children. During the last 20 years, bacillary dysentery due to antibiotic-resistant strains of Shigella has become a major public health problem in many developing countries. Thus, the identification of alternative antibiotics for use in the treatment of severe shigellosis in these areas is a very important research topic. I recognise that ciprofloxacin, as other quinolones, has not been licensed for use in children below 15 years of age because of cartilage toxicity observed in young rats. Nalidixic acid, however, which has similar toxicity, has been licensed for use in children, and is widely recommended for treatment of shigellosis in young children. I also feel that the toxic effects are related both to the amount of drug given and the duration of therapy. As the amounts to be given in this study are far below those that cause toxic signs in experimental animals and the duration of therapy is brief (5 days), I consider the use of ciprofloxacin to treat shigellosis in children justified.

Ciprofloxacin has been shown to achieve high concentration in stools, even 48 hours after a single dose administration and a single dose treatment with norfloxacin was shown to be as efficacious as a 3 day treatment with TMP-SMX for acute shigellosis in adults. I would therefore recommend that the authors evaluate the efficacy of a single dose therapy (or perhaps a daily dose given for 2 days) instead of a 5 day therapy. A single treatment of this type would be advantageous for the provision of effective therapy under conditions where the reliable delivery of medication for a longer period is very difficult.

Other comments:

1. The criteria to distinguish between moderately severe shigellosis and severe shigellosis should be provided.

2. The blinding of the study might be more difficult than suggested in the protocol - taste and physical aspects of the two drugs are very different and obtaining identical elixirs might be impossible. If this is the case, I would suggest that the authors use a "double-dummy" technique:

   Group A = ciprofloxacin + placebo pivmecillinam
   Group B = pivmecillinam + placebo ciprofloxacin

3. In the determination of the sample size, provision should be made for patients harbouring Shigella resistant to pivmecillinam or ciprofloxacin.

4. More details on data collection techniques and on the forms to be used to record these data should be provided.

5. The monitoring of appearance of side effects should be presented in more detail. A sample form to collect daily information on a number of possible side effects should be provided with the proposal.

5. The proposed budget appears to be unrealistically high (cost US$ 1050/patient) and is not at all justified; especially with regard to the following items:

- local salary US$ 80 000
- patient study US$ 37 500
- interdepartmental US$ 80 422
- international travel US$ 10 600

Despite the fact that this proposal is presented "anonymously", I presume that the authors are experienced researchers in this field. I therefore support their application provided a revised proposal taking into account the above-mentioned comments and suggestions is prepared.

Project Title: Double blind, randomized study of the treatment of childhood shigellosis comparing ciprofloxacin and addinocillin

Summary of Referee's Opinions: Please see the following table to evaluate the various aspects of the proposal by checking the appropriate boxes. Your detailed comments are sought on a separate, attached page.

	Rank Score		
	High	Medium	Low
Quality of Project		✓	
Adequacy of Project Design		✓	
Suitability of Methodology		✓	
Feasibility within time period	✓		
Appropriateness of budget			✓
Potential value of field of knowledge		✓	

Not mentioned

CONCLUSIONS

I support the application:

a. without qualification ☐

b. with qualification

- on technical grounds ☒
- on level of financial support ☒

Review of double blind randomised study of the treatment of childhood.....
PI Dr. MA Salam

July 18, 1990

The authors (no names of investigators are given) propose to study the efficacy of ciprofloxacin and pivamdinocillin in children with shigellosis. The need for alternative anti-microbial therapy in childhood shigellosis is clear, and these two drugs are promising candidates, since both have been shown to be highly effective in adults. The main reluctance to study them in children is the presumed toxicity to cartilege growth in young children, and the manufacturer presently prohibit their use in children.

The protocol needs some major alterations to accomplish its objectives.

1. Both the drugs need to be compared against a "standard" which is presently in use. I presume this is naladixic acid, although this is not stated in the protocol. I would therefore suggest a 3-cell trial, in which one of the cells is the standard drug now being used. (It is of course impossible to have a placebo group.) If done without a standard, one is only comparing the two "unknons" against each other, and both may be less effective than the present therapy.

2. As a result of the above reasoning, the sample size needs to be recalculated;

3. I don't see the advantage of using half outpatients and half in-patients. I would suggest using only in-patients, so that the dose of medicine given can be validated, and the appropriate samples taken. (No study protocol is given for the out-patients anyway).

4. I don't understand the differences between stool and rectal swabs for cultures of Shigella during followup.

5. Where will the assays of antimicrobial levels in blood (peak and trough) and stool be done ? No methodologies are given.

6. The outcome of illness should be determined on a longitudinal basis, not on a fixed definition on day 5. A response to treatment should definitely be seen by day 3 (with decrease in fever and blood in the stool) (allowing a child to be treated for 5 days while not clinically responding would be judged as poor medical care !).

7. I suspect about 50% of children (at the most) with a dysentery syndrome will have SHigella isolated; therefore whatever sample size is calculated, twice as many will have to be entered into the study.

8. Urine samples are mentioned in the consent form, but not in the protocol. (NO consent forms for outpatients are included).

9. The statement that the US FDA is allowing the use of ciprofloxacin in clinical trials in children needs to be validated. I was not aware that was the case, and no reference is given.

10. The cost of the study is outrageously high. Such studies can usually be done with much less money. There should be a more detailed listing of the budget, particularly for the items:

local salary	$80,400	
lab tests	35,000	
X_rays (not mentioned in protocol)		
patient study	37,500	
interdepartemntal	80,422	
international travel	10,000	(nothing of this is mentioned in the protocol).

11. I should mentioned that the figures mentioned in the text were not supplied to me.

12. An estimate of the time needed to finish the study should be given, based on current admission rates to the hospital.

13. The MIC's of the Shigella isolates to the 2 drugs should be included.

IN summary I support the concept of the study, but the design should be radically modified, and the budget markedly decreased.

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TO: Chairmen, ERC/IRRC

FROM: M.A. Salam, MB., BS., Michael Bennish, M.D.

RE: Response to Reviewers Comments on the Protocol Entitled "Double Blind, Randomized Study of the Treatment of Childhood Shigellosis Comparing Ciprofloxacin and Pivamdinocillin".

DATE: 6 August, 1990

Thank you for sending us the reviewers comments, which were quite helpful. Most of their suggestions have been incorporated in the revised protocol, a copy of which is attached.

Since the reviewers are anonymous and the reviews we have received are not numbered, we have numbered the two reviews as 1 and 2. Our response to the specific comments of the reviewers is as follows:

Review # 1:

In the second paragraph of the reviewer's comments, he/she suggests that a short course of ciprofloxacin, using either a single dose or two doses of ciprofloxacin, be evaluated. He/she cites as support for this a study that showed that single dose norfloxacin was as effective as five days of trimethoprim-sulfamethoxazole in treating adults with shigellosis. Although the reviewer does not cite the specific reference, we assume that it is Gotuzzo et al "Comparison of Single-Dose Treatment with Norfloxacin and Standard 5-Day Treatment with Trimethoprim-Sulfamethoxazole for Acute Shigellosis in Adults" Antimicrobial Agents and Chemotherapy, 1989;33:1101-4.

There are a couple of reasons why that study is not directly

comparable with our proposed study here at the ICDDR,B. Primary among them is that patients enrolled in that study had mild illness, and that a short course of therapy is much more likely to be effective in persons with mild illness. The two treatment groups in the Gotuzzo study, norfloxacin and trimethoprim-sulfamethoxazole, had a mean of 9.7 and 7.6 unformed stools, respectively, in the five days following the initiation of therapy. In our previous study of the treatment of shigellosis in children (Salam MA, Bennish ML, Therapy for Shigellosis. I. Randomized, Double-blind Trial of Nalidixic Acid in Childhood Shigellosis, Journal of Pediatrics, 1988;113:901-7), nalidixic acid treated patients had a mean of 40 stools following the initiation of therapy, and ampicillin treated patients had a mean of 53 stools in the five days following the initiation of therapy. This difference may be attributable in part to the presumed absence of patients with S. dysenteriae type 1 in the study from Gotuzzo et al, and because they had no limit on the duration of illness prior to entry into their study.

In our opinion, it would be wiser to initially evaluate the efficacy of ciprofloxacin in children by first starting with a standard five day treatment regimen. If that is effective, than shorter courses of therapy could be evaluated; the reverse sequence of events might not so easy.

1.1. Distinction between moderately and severely ill patients.

The distinction between moderately ill patients and severely ill patients will be made by regular staff physicians using their standard criteria. Among the criteria used are height of fever, and severity of abdominal pain and tenesmus. Severely ill patients will be selected from those patients who will have already been admitted to the inpatient unit by the physician on duty. Moderately ill patients will be selected directly from the outpatient area, or the short term treatment ward.

1.2. Blinding of the study.

We faced a similar problem with the blinding of the drugs in the nalidixic-ampicillin study. Ampicillin has quite a distinctive penicillin smell, whereas nalidixic was a bit bitter. After trying a couple of different flavors, we found that mint was able to neutralize the difference in taste and smell between the two drugs. Thus the study was well blinded. We anticipate that the same will be true with this study.

Because pivamdinocillin will be given on an every six hour regimen, there is no need for a placebo in this group. Ciprofloxacin, which is given on a 12 hourly basis, will

alternate with placebo. This was noted in the protocol (page 11 of the protocol). The placebo will be identical in composition to the ciprofloxacin and pivamdinocillin elixirs, except that it will not contain active drug.

1.3. Sample size.

The sample size calculated in the study was based on patients infected with strains of Shigella that are susceptible to the two study drugs. Fortunately, no ciprofloxacin resistant strains have yet been identified in Dhaka, and amdinocillin resistant strains are very rare (5 of 2005 Shigella isolates in 1989, Mitra et al, Lancet 1990;1:1461-2).

1.4 & 1.5. Forms for data collection, and for monitoring adverse reactions.

The forms for data collection will be similar to forms used in our previous study, and are attached. A from for assessing joint function, the major potential toxic effect, is also attached.

1.6. Budget

We do not consider the budget to be unrealistic. It is based on the charges in effect at the ICDDR,B.

Local salary: This is the exact amount that will be required to support local staff.

Patient study: We have no control over this. The figure has been calculated on the basis of the number of days a patient will be required to be hospitalized X the total patients enrolled X the cost of a patient day in the Clinical Research Center.

International travel: This is based on economy fare travel and lodging in the United States for two persons to attend a scientific congress, and for two visits to Bangladesh by one of the consultants.

Review # 2.

Although the proposals are supposed to be submitted to the reviewers anonymously, we see that at the top of the review our names were listed. Were the reviews really anonymous, and the names added at a later date?

In the first paragraph of the review, in reference to ciprofloxacin and pivamdinocillin, the reviewer states that "the manufacturer presently prohibit their use in children". This is not true. First, it is drug control authorities who approve or disapprove the particular use of a drug, and not manufactures. Pivamdinocillin is approved for use in children. In most countries ciprofloxacin is approved for use in children based on a decision by the treating physician of the risk- benefit ratio for using the drug (see attached package insert from Great Britain).

2.1. The use of a control group using a "standard" drug.

We agree that a newer drug should always be tested against a standard drug. Pivamdinocillin is now one of two standard therapies for the treatment of shigellosis at our institution. The other is nalidixic acid. For the first six months of 1990, however, 65% of all S. dysenteriae isolates were resistant to nalidixic acid, thus severely limiting its usefulness in the empiric therapy of shigellosis. The proportion of resistant isolates can be expected to continue to increase. Thus if nalidixic acid were used as the control drug we would be treating many children with a drug that is known to be ineffective. Thus the selection of pivamdinocillin.

2.2. Sample size.

For reasons explained in 2.1 we do not feel there is a need to add a third treatment group and thus no need to redo the sample size calculation.

2.3. In-patients vs. out-patients.

We did not propose treating patients on an outpatient basis. Perhaps the reviewer misunderstood. We will recruit patients who present initially to the outpatient clinic, but they will be treated as inpatients.

2.4. Differences between stool and rectal swab cultures.

A stool culture is performed from stool that a patient has passed. A rectal swab culture is performed by putting a cotton-tip application in the rectum, and gently but firmly rotating it against the epithelial surface. Although a stool sample for culture is preferred, during follow-up visits this may be difficult to obtain because patients are likely to be having only one or two stools a day.

2.5 Assay of antimicrobial concentrations.

This will be done at the laboratory of Dr. Michael Barza, New England Medical Center, by chromatographic methods.

2.6 Determination of outcome.

The outcome measures we have enumerated have worked well for us in previous study. We agree with the reviewer that a response to treatment should be seen by day three, and it is for that reason that we have included a provision for withdrawing from the study patients who have not improved by that time (page 15 of the protocol). Such patients will be considered treatment failures and placed on open therapy with an appropriate drug.

2.7 Proportion of patients enrolled who will have Shigella isolated from their stool or rectal swab culture.

The reviewer suggests that only 50% of patients enrolled in the study will have Shigella isolated. This has not been our previous experience. In our previous study in children (J Pediatr 1988;113:901-7) 88% (79 of 90) children enrolled in the study had Shigella isolated. The percentage in our study in adults (J Infect Dis, September 1990) was only slightly less. In any case, only patients who have Shigella isolated will be continued in the study, and included in the analysis.

2.8 Urine sampling.

This is mentioned on page 13 of the protocol.

2.9. FDA approval of ciprofloxacin for trials in children.

This was approved at a meeting Anti-Infective Drug Advisory Committee of the United States Federal Drug Administration on 29 November, 1990. The IND is 21804. This can be verified with the FDA.

2.10. Budget.

Please see 1.6 above.

2.11. Figure.

Apparently a copy of the figure was not included with the proposal that went to the reviewer. A copy is attached to the current version.

2.12 Period of study.

The time period for this study has been mentioned in the appropriate section of the protocol (front page). Perhaps the reviewer was not given the front page. The study duration will be two years from the enrollment of the first patient.

2.13. MIC determinations.

We do not think that determination of MIC's is a necessity. Previous susceptibility testing, done at this Centre, of the susceptibility of Shigella to these two drugs did not show any discrepancy between MIC and Kirby-Bauer testing. Performing MIC tests would only add further to the costs of the study.

Conclusion: We believe that we have answered all the questions raised by the reviewers in a satisfactory way, and hope that the Research Review Committee will judge in favor of the protocol.

Thank you.