Ciprofloxacin After Clinical Failure Of Ceftriaxone For Severe Salmonellosis In Children

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Citation

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Abstract

Background: Children with enteric fever or severe salmonella infections are usually treated with blactam antibiotics, particularly ceftriaxone. Due to their poor penetration into cells, blactam antibiotics, even if active in vitro, are sometimes clinically ineffective because they cannot reach the intracellular sites of Salmonella multiplication.

Objectives: To evaluate its usefulness in a retrospective study, the efficacy and safety of oral ciprofloxacin in patients with severe salmonellosis, including the clinical failure of ceftriaxone, was assessed.

Patients and Methods: From July 1, 1995 to 2000, the bacteriology laboratory of a French pediatric hospital had identified 215 patients between the ages of 1 month to 15 years with positive salmonella in blood or stools samples, 113 (53%) of them requiring hospitalization due to their clinical symptoms. Three (1%) were excluded for sickle-cell disease or poor nutritional status. None of the 110 isolated strains (including the 4 S typhi, 51 S typhimurium , 25 S enteritidis, 6 S hadar and 5 S heidelberg) was resistant to ceftriaxone or ciprofloxacin. Forty-one of the 110 strains (37.3 %) produced a beta-actamase. Twelve patients had a rapid recovery without antibiotic treatment, and 98 (mean age 3.9 years) were given antibiotics (ceftriaxone in 91 and amoxicillin in 7) for dysentery (43%), shock (15%) or persistent high fever and severe diarrhea (42%).

Results: In 72 children (mean age = 3.6 years) ceftriaxone treatment (amoxicillin in 5) for 5 or 7 days was rapidly effective: apyrexia was obtained in 1.5 days after the start of antibiotics and the number of stools per day was 4 or less in 2.2 days. Two to three weeks after clinical recovery, asymptomatic carriage was present in 22/38 patients (58%). In the 26 other patients, ceftriaxone (amoxicillin in 2) treatment was clinically ineffective, despite good in vitro activity, and was switch to oral ciprofloxacin (20 mg/kg/d, 5 days) after 2 to 7 days of fever and/or severe diarrhea. Clinical improvement with ciprofloxacin was obtained in less than 48 hours. The strains involved in these 26 patients included 4 S typhi and 15 S typhimurium ($p<.05$), 13/15 ($p<.01$) producing -- beta-lactamase. Asymptomatic carriage was found in 5/22 patients ($p<.05$) after recovery. None of the patient treated with ciprofloxacin had experienced side effect.

Conclusion: In severe salmonellosis, the clinical failure of ceftriaxone is not rare, particularly in S typhimurium producing beta-lactamase infection and short treatment with oral ciprofloxacin is safe and leads to rapid recovery.

INTRODUCTION

Fluoroquinolones, more than cephalosporins or other blactam antibiotics, are the treatment of choice for enteric fever and severe salmonellosis in adults because recovery is more rapid with a very low number of relapses and oral route is available ([1,2]). Fluoroquinolones are not licensed for use in children, but are sometimes required to treat serious infections, for compassionate reasons ([3,4,5,6]). Children with severe salmonellosis are treated with blactam antibiotics, particularly ceftriaxone ([7,8,9]). Due to their poor penetration into cells, blactam antibiotics, even if active in vitro, are sometimes clinically ineffective because they cannot reach the intracellular sites at which the Salmonella bacteria multiply. We previously showed that pefloxacin can lead to rapid recovery in cases of severe childhood salmonellosis in which treatment with beta-lactam has been unsuccessful ([10]).

However, pefloxacin, despite its remarkable efficacy, may have undesired secondary effects, affecting the joints in particular. Ciprofloxacin seems to be better tolerated: it is sometimes used in children, principally for the treatment of Pseudomonas aeruginosa infections in children with cystic fibrosis, and published data show that it is associated with a limited number of articular problems ([11,12,13,14,15,16,17]).

We report here the results of a 5-year clinical experience concerning children with severe salmonellosis, hospitalized in a pediatric unit. The clinical failure of ceftriaxone is not rare and subsequent compassionate use of ciprofloxacin can result in real benefits to the child and may shorten the duration of hospitalization.

MATERIALS AND METHODS

This retrospective study was carried out between July 1, 1995, and June 30, 2000. Children hospitalized in the general pediatric unit of the Saint Vincent de Paul Hospital, Paris, France, with acute, community-acquired salmonella infection were included in the study.

Patients: Children aged between 1 month and 15 years, hospitalized with community-acquired salmonella infection after routine examination in the emergency room were eligible for inclusion. Community-acquired salmonellosis requiring hospitalization was defined as an illness that started < 10 days before enrollment, and included one of the following: (1) acute diarrhea (>3 soft or liquid stools within the last 24 h), with fever, vomiting, or dehydration and no possibility of ambulatory treatment; (2) bloody-mucoid stools (dysentery) with fever and (3) persistent (3 or more days) temperature > 38.5 degree C, with soft or normal stools and no identifiable cause of fever other than salmonellosis;

Patients were excluded if they: (1) were at risk for salmonella infection (sickle cell disease, immune deficiency, malnutrition, etc.); (2) had salmonellosis that could only be identified serologically; (3) had a known previous history of renal impairment, liver damage, seizures or hypersensivity to blactam or fluoroquinolone antibiotics.

All of the children admitted to the pediatrics unit with acute gastroenteritis provided a stool sample, which was tested for rotavirus (ELISA, Dako Co.) and the main diarrhea-causing bacteria. Salmonella was identified (API 20E, Merieux Diagnostics, Marcy l'Etoile, France) and its serotype determined. Antibiograms were generated by the disk diffusion methods and we tested for blactamases.

The children presenting with severe clinical signs were treated with antibiotics after blood cultures and stool collection according to the standard methods used in our hospital (8). If the child's clinical condition improved rapidly after rehydration, with decrease in fever and diarrhea, no antibiotics were prescribed, even if Salmonella was isolated. Severe forms corresponded to those with symptoms of shock, dysentery-type syndrome (frequent bloody mucoid stools and fever), or persistent, severe diarrhea with fever (>38.5 degree C) that did not improve after at least 48 hours of oral or intravenous rehydration, or that worsened considerably. Finally, due to the risk of secondary infections, particularly of the meninges, all patients below the age of six months from whom Salmonella was isolated were treated with antibiotics ([18]).

The initial antibiotic treatment, in cases in which such treatment was considered necessary, was ceftriaxone (50 mg/kg i.v. for 5 days). During the first two years of the study, some children, whose treatment began before they were hospitalized in our unit, were given amoxicillin either orally or intravenously. Initial treatment with beta-lactams was considered to be ineffective if the fever and diarrhea persisted without improvement for three days or more, or if the child's state deteriorated during treatment. In such cases, after Salmonella identification, the child received oral ciprofloxacin (20 mg/kg/day), with a maximum total dose of 1g/day divided into two daily doses over five days. This treatment was given for compassionate reasons, to try to relieve patients rapidly, and the decision to give this treatment was approved by the ethics committee of Cochin Medicine School (Paris 5 University)

RESULTS

During the five-year study period, the bacteriology laboratory identified 215 patients positive for Salmonella, based on bacteriological tests prescribed by the doctor in charge of the emergency room or department in which the child was hospitalized. One hundred two (47%) of these patients received ambulatory treatment and their clinical condition did not necessitate hospitalization or specific treatment apart from the usual process of oral rehydration. One hundred thirteen (53%) children were admitted to hospital with salmonellosis during this period, accounting for 1.5% of all admissions during this period and 8.5% of admissions for acute gastroenteritis in the unit. In 26 cases, the children had just returned from a trip abroad, to Africa in 24/26 cases; the other patients (78%) acquired salmonellosis in France. In seven cases (three families), similar cases were

identified among the patient's close family and friends. Three children had conditions rendering them susceptible to severe salmonellosis (S. panama, S. shubra, S. enteritidis): sickle cell anemia in two cases (one developed osteomyelitis caused by Salmonella) and severe malnutrition in one child from French Guiana. All three were excluded from the study.

The study therefore concerned 110 patients who fulfilled the criteria defined above (Tables 1 & 2). The patients' initial symptoms and the strains isolated are summarized in table 1. None of the strains isolated was resistant to ceftriaxone or ciprofloxacin. Forty-one of the 110 strains (37.3 %) produced beta-lactamase and were thus resistant to amoxicillin, but none produced a cephalosporinase.

Figure 1

Table 1: Symptoms and Salmonella sp identification in patients hospitalised

N =	110 (60 M, 50 F)
Age [years] (m - range)	3.9 (0.2-14.9)
Dysentery	42
Schock	15
Isolated fever (< 3 soft stools / d)	10
Fever > 38.5°C + Diarrhea	33
Fever < 38.5°C + Diarrhea	10
S. typhi	4
S. typhimurium	51
S. enteritidis	25
S. hadar	6
S. heidelberg	5
S. virchow	2
S. branderup	2
Other *Salmonella sp*	15

Twelve of the patients (mean age = 2.3 years, range = 7 months to 13 years) hospitalized with acute gastroenteritis, six of whom were febrile (>38.5 degree C), were rapidly cured by oral (7/12) or intravenous rehydration. Salmonella was isolated from stools, but rapid clinical improvement was observed within two days, and no antibiotics were given.

Four children, aged between 4.5 and 14.9 years (mean age = 9.3 years), three of whom had recently returned from abroad (Morocco, Algeria, Pakistan), had typhoid fever. These children were treated with ceftriaxone after the isolation of S. typhi (by blood culture in two cases), which was sensitive to all blactams in all four cases. These four patients had high fever, with abdominal pain and very moderate diarrhea (<4 liquid stools per day).

The other 94 patients were given antibiotics upon admission or in the next few days. Blood culture was positive for 10 of the 67 samples taken. Forty-two children had dysentery with bloody, mucoid stools and fever. Upon admission, 15 children were diagnosed with clinical shock, with low arterial blood pressure, tachypnea and poor clinical tolerance due to the infection. Eight children, not including the four that were infected with S. typhi, had persistent fever with abdominal pain and soft stools without real diarrhea. Salmonella was isolated from the stools (6 cases) or by blood culture alone (2 cases), for all of these 8 children (6 cases of S. typhimurium, 1 case of S. hadar, 1 case of S. infantis). Ten other children had moderate fever, but severe diarrhea that persisted or worsened during the period of hospitalization, with more than eight stools per day, leading to the prescription of antibiotics. The remaining 19 patients received antibiotics due to the severity and persistence of their symptoms, as they had persistently high body temperature (>38.5 degree C) and diarrhea that lasted for more than three days. The clinical sign most frequently associated with diarrhea, and fever, was abdominal pains, which were intense in half the cases.

Four of the patients were aged six months or below on admission, but they presented with severe symptoms and were treated with antibiotics on the basis of clinical criteria. Thirteen children initially received amoxicillin and 75 initially received ceftriaxone. Five of the children treated with amoxicillin were found to be infected with a strain that was resistant to this antibiotic and were thus given ceftriaxone after the antibiogram results became available. The patients were assigned to two groups, depending on the clinical outcome of their treatment.

A) CLINICAL SUCCESS FOLLOWING TREATMENT WITH CEFTRIAXONE OR AMOXICILLIN

This group comprised 72 children (mean age = 3.6 years, range = 2 months to 15 years). On average apyrexia was obtained 1.5 days (range = 0.5 to 4 days) after the start of ceftriaxone treatment (or amoxicillin treatment in five cases in which the strain was sensitive) and the number of stools

per day decreased to 4 or less in 2.2 days (range = 1 to 6 days). Vesicular lithiasis was diagnosed in one patient: the patient recovered quickly following treatment with ceftriaxone and the control stool culture was negative.

The Salmonella strains isolated are listed in table 2: 29 S. typhimurium, 19 S. enteritidis, 4 S. hadar, 3 S. Heidelberg and 17 other non-typhoid strains. All of the amoxicillin-resistant strains belonged to the non-typhoid Salmonella group (27/72, 29.2%).

Figure 2

Table 2: Symptoms and Salmonella sp in patients without antibiotic treatment, treated with ceftriaxone or secondary treated with cipropfloxacin

	No antibiotics	Ceftriaxone[1]	Ciprofloxacine after Ceftriaxone[2]
N	12	72	26
Age (years) mean (range)	2,3 (0,7-13)	3,6 (0,2-14,9)	5,5 (0,7-14)
Dysentery	0	30	12
Isolated fever	0	6 (4 *S typhimurium*)	6 (4 *S typhi*, 2 *S typhimurium*)
Blood culture positive	0/2	6/48	4/20
S typhi Amox R	0	0	4 0
S typhimurium Amox R	7 3	29 (40,2%)* 5 (17,2%)**	15 (57,7%)* 13 (86,6%)**
S enteritidis Amox R	2 0	19 (26,4%) 6 (31,6%)	4 (15,4%) 1
Salmonella sp Amox R	3 0	24 5	3 3
Salmonella strains Amox R	3	21 (29,1%)**	17 (65,4%)**
Stool culture positive 1-3 weeks after treatment	ND	22/38 (58%)**	5/22 (22,7%)**
Chi square : * p < 0,05, ** p < 0,01 [1]Amoxicillin in 5 patients [2]Amoxicillin in 2 patients			

All of the children in this group were seen by a doctor following their release from hospital and had normal clinical symptoms and normal stools. A stool culture was carried out one to three weeks after the end of the treatment in 38 patients, and was positive in 22 cases (58%).

B) CLINICAL FAILURE AFTER TREATMENT WITH CEFTRIAXONE AND SUBSEQUENT TREATMENT WITH CIPROFLOXACIN

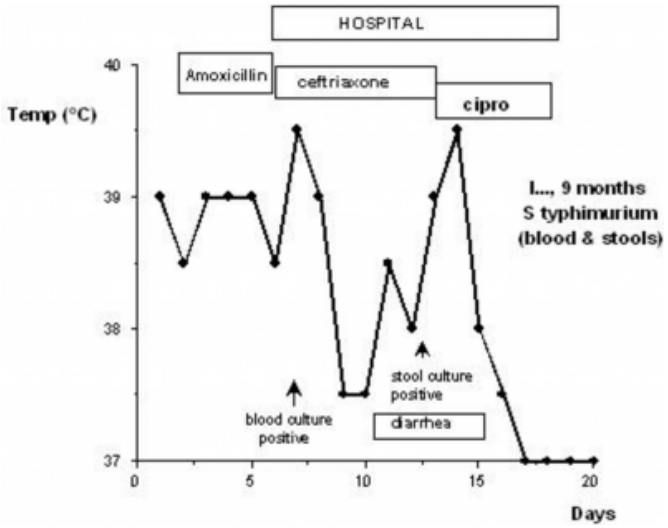
This group contains 26 children (mean age = 5.5 years, range = 0.7 to 14 years) whose initial treatment with ceftriaxone (or amoxicillin in two cases in which the strains were sensitive) did not lead rapidly to a clinical improvement. Ceftriaxone treatment lasted for two to seven days (mean = 2.7 days). The absence of a clinical improvement, and in four cases a deterioration, led us to use oral ciprofloxacin. Following this change of treatment, fever disappeared in a mean of 1.25 days and diarrhea in a mean of 1.8 days. The most spectacular improvement observed concerned abdominal pain. In the 12 cases in which abdominal pains were predominant, they totally disappeared within 12 hours of the first oral dose of ciprofloxacin.

The four patients with typhoid fever remained febrile despite treatment with ceftriaxone, which was active in vivo against the four strains. Three of these patients were given ciprofloxacin on the third day after the start of ceftriaxone treatment and one, on the sixth day. In two patients with mild fever, bloody, mucoid diarrhea worsened despite ceftriaxone treatment. The replacement of this treatment by oral ciprofloxacin after 48 hours led to a spectacular improvement: the bloody, mucoid diarrhea stopped within 24 hours. In two other children with soft stools (infected with S. typhimurium), fever remained high despite treatment for 2 days with ceftriaxone and apyrexia was observed within 24 to 48 hours of initiating ciprofloxacin treatment. The other patients were treated with beta-lactams for three or more days, but fever and diarrhea persisted: the absence of a clinical improvement led to the prescription of ciprofloxacin. In 16 (61%) patients, clinical signs improved rapidly, leading to rapid discharge from hospital and ambulatory ciprofloxacin treatment was continued.

The case of one 9-month-old patient is summarized in figure 1. This febrile patient, without severe diarrhea, was initially given ambulatory treatment with oral amoxicillin. Upon admission, blood culture was positive (amoxicillin-resistant S. typhimurium) and she received ceftriaxone, which initially seemed to be effective. However, during treatment, the patient developed febrile diarrhea and a stool culture tested positive for the same strain. After treatment with ciprofloxacin, the patient was cured both clinically and bacteriologically.

Figure 3

Figure 1: Evolution of body temperature of a young girl infected with S typhimurium (Amox-R) : ceftriaxone and ciprofloxacine were effective in vitro



These children were seen in consultation during the preceding months following their release from hospital. None suffered arthralgia during or after the acute episode, or any other secondary effects of ciprofloxacin. A stool culture was carried out one to three weeks after the end of the treatment for 22 of the patients of this group: it was positive in five cases (22.7%, $p<0.01$ vs. patients treated with beta-lactams). The four patients with S. typhi infection had negative stool cultures.

The distribution of the Salmonella stains in this group of 26 patients for whom treatment with beta-lactams resulted in clinical failure was very different from that of the patients in the group for which the treatment was clinically effective. Clinical failure of the treatment was observed in the four patients infected with S. typhi, although all of these strains were sensitive to all of the antibiotics. S. typhimurium was predominant (68.2%, $p<0.05$), and 13 of the 15 S. typhimurium isolates were amoxicillin-resistant ($p<0.01$). The ages of the patients infected with S. typhimurium were not significantly different in the two groups (3.3 and 4.5 years). Seventeen of the 26 Salmonella strains isolated (65.4%, $p<0.01$) were amoxicillin-resistant.

DISCUSSION

This retrospective clinical study was carried out in an infectious diseases and general pediatrics unit of a Parisian pediatric hospital. The decision to use antibiotics was based on clinical criteria ([11]), principally the initial severity (dysentery, symptoms of shock) or the persistence of signs, prolonged fever and diarrhea, leading to the perceptions that the infection would become generalized. The 12 patients who recovered rapidly and the 102 patients who were examined in the emergency room but not hospitalized did not receive antibiotics. It is possible that certain patients would have recovered spontaneously without antibiotic treatment, but with a risk of prolonged infection and severe general repercussions.

The series of 72 patients who recovered following treatment with ceftriaxone (or amoxicillin in six cases) and the 26 patients who were subsequently treated with ciprofloxacin were similar in terms of age and clinical symptoms, but differed in terms of the strains isolated. The four patients with antibiotic-susceptible S. typhi remained febrile under ceftriaxone treatment for three to six days, until the initiation of ciprofloxacin treatment. The number of patients infected with S. typhimurium was higher in the clinical failure group, particularly for amoxicillin-resistant strains (87%). In general, two-thirds of the Salmonella strains infecting patients treated with ciprofloxacin were resistant to amoxicillin, but susceptible to ceftriaxone and ciprofloxacin. If the S. typhi strains were excluded, more than three quarters of the Salmonella strains infecting patients treated with ciprofloxacin were resistant to amoxicillin (production of a blactamase) but susceptible to ceftriaxone and ciprofloxacin.

The use of ciprofloxacin led to the rapid disappearance of clinical symptoms, especially abdominal pains. The pains improved within 12 hours of the first oral dose of ciprofloxacin and the fever and diarrhea stopped rapidly. This rapid improvement led to a rapid discharge from hospital for two thirds of the children, as reported with typhoid fever ([19]) or with severe salmonellosis ([20,21]) .The frequency of bacteriological cure depended on the type of treatment. We found that 23% of stool cultures tested positive after ciprofloxacin treatment, a frequency similar to that reported by Leibovitz ([9]). The frequency was higher after treatment with ceftriaxone (>50%), and similar to that previously reported following treatment with beta-lactams ([10]). The meta-analysis carried out by Buchwald ([22]) showed that between 50 and 60% of young children become asymptomatic carriers of Salmonella in the two to three weeks following the initial episode.

Fluoroquinolones are not authorized for use in children due to the risk of side effects, principally problems concerning the joints. Such problems are more common in growing

subjects, and concern the major weight-bearing joints in particular, but the precise mechanism underlying these effects is unclear ([3,4,5,6,15,25,26,27,28,29]). The frequency of joint problems does not seem to differ much between adults and children, but very few pediatric series have been published ([5,25]). The problems seem to depend on the molecule used. Pefloxacin is the molecule causing the highest frequency of joint problems and tendinitis, whereas ciprofloxacin seems to be better tolerated ([27,28,29,30,31]). One pediatric series consisting of over 2000 patients receiving ciprofloxacin showed that transitory arthralgia occurs in 1.5% of cases and that 60% of these arthralgias occur in patients with cystic fibrosis([15]). Short-term treatments seem to be well tolerated ([16]): in the series studied by Leibowitz ([9]), in which invasive diarrhea was empirically treated with oral ciprofloxacin, no side effects were reported. Most pediatricians agree that fluoroquinolones should only be used in children with severe infections after the failure of initial treatments, when no other medication (particularly that can be taken orally) is available, and particularly in cases of salmonellosis ([3,4,5]).

There is no definitive consensus concerning non-typhoid salmonellosis treatment in children due to the large number of possible clinical forms. The usual recommendations are that apparently banal acute gastroenteritis should not be treated and that antibiotics should only be prescribed for severe forms. As the severity criteria are solely clinical, the decision depends largely on the experience of the doctor in charge. In this series, less than half of the patients infected with Salmonella who attended the hospital were considered to have a severe form and treated with antibiotics. This series shows that ceftriaxone is effective in three quarters of cases of severe childhood salmonellosis. However, in the case of clinical failure, the patients can be treated with oral ciprofloxacin for a short period of time. Ciprofloxacin leads to rapid recovery and ambulatory treatment can be continued. No side effects were observed in this limited series, but further studies are necessary.

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