Ciprofloxacin Use in Neonates

A Systematic Review of the Literature

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Background: Ciprofloxacin has no marketing authorization for use in neonates worldwide but it is prescribed for the treatment of neonatal life-threatening infections, mainly in developing countries and in Europe. Given the concerns about its toxicity in this population and the necessity for its use in specific clinical situations, we conducted a systematic review of the use of ciprofloxacin in neonates.

Methods: We performed a systematic search of PubMed, Embase, and the Cochrane Database of Systematic Reviews and bibliographies of relevant articles. We included all studies, regardless of design, that reported efficacy, safety, and pharmacokinetics of ciprofloxacin for the treatment of any neonatal infectious condition. We excluded letters, editorials, preliminary reports, and abstracts.

Results: Observational cohort studies, case reports, and descriptions of patient series account for all literature reviewed. Ciprofloxacin was administrated in neonates as a salvage therapy for sepsis due to multidrug-resistant strains or with signs of clinical deterioration under first-line antibiotic treatment. Initial administration was always intravenous with variable dosing schedule. Clinical response to treatment was estimated at 64% and 91% in 2 cohort studies, with a median of 83% in case series. Of the 14 case reports, 12 yielded positive clinical outcomes. No serious adverse events, particularly joint toxicity, were observed, although evaluation was predominantly clinical and follow-up limited to few months after the end of treatment.

Conclusions: The current literature provides some information to support the use of ciprofloxacin in neonates. Additional high quality studies should be undertaken to provide reliable data on pharmacokinetics, efficacy, and long-term safety.

Key Words: ciprofloxacin, antibiotics, neonates, safety, pharmacokinetics

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Infection in neonates is frequently complicated by systemic sepsis and therefore may become rapidly life-threatening.[1] A significant number of hospital-acquired infections are generally caused by gram-negative bacteria which are responsible for high neonatal morbidity and mortality.[2] Nosocomial infections are related to neonatal immune immaturity and the frequent use of invasive life sustaining devices mainly in preterm neonates. Also, the injudicious use of broad-spectrum antibiotics in neonatal units has led to high rates of resistance in first line empiric antibiotics like penicillin and cephalosporin.[3,4] As multidrug-resistant organisms become more of a problem in neonatal intensive care units, there is a need to evaluate the use of other available antibiotics to treat serious neonatal infections.

Fluoroquinolones (FQ) are potent, bactericidal antimicrobials against a broad spectrum of Gram-negative and Gram-positive bacteria. They have been widely used in adult patients because of their excellent tissue penetration, including the cerebrospinal fluid (CSF).[5] Although resistance to FQ is reported to be increasing, this group of antibiotics remain active against approximately 90% of Gram-negative organisms encountered in the community.[6] Restrictions in its use result from concerns about the potential of joint toxicity, observed in juvenile animals, and the risk of emergence of drug-resistant pathogens.[6–8] Despite these concerns, ciprofloxacin has been successfully prescribed "off-label" in several pediatric infections. It is the only fluoroquinolone to be included on the list of "Essential Medicines for Children" prepared by the WHO.[9] In neonatology, the use of ciprofloxacin in life-threatening infections, although rare, is justified by the fact that clinical benefits largely overweight the potential risks. Thus, the aim of this paper is to present a systematic review of all available literature on the use of ciprofloxacin in neonates.

METHODS

Search Strategy

We performed a systematic literature search of PubMed (from 1966 to July 2009), Embase (from 1980 to July 2009), and the Cochrane Database of Systematic Reviews (up to July 2009) for all studies evaluating the efficacy, safety, and pharmacokinetics of ciprofloxacin in neonates.

We combined the following key words (MeSH and free text) in our search strategies: newborn, infant, preterm, ciprofloxacin, fluoroquinolones, therapeutic(s), toxicity, adverse event(s), drug toxicity, drug reaction, clinical trial, meta-analysis, randomized controlled trial, review (search strategies are available in the Appendix). The search limits included English and French languages and humans. Reference lists of identified articles were also manually screened for additional relevant studies.

Study Selection

We included all studies, regardless of design, which reported outcomes after use of ciprofloxacin for the treatment of any neonatal infectious condition, defined as any condition appearing in the first 28 days of life. Treatment by ciprofloxacin had to be initiated in the first 3 months of life. Only studies published as a full article were included in the systematic review. Abstracts, letters, editorials, replicate or preliminary reports, and review

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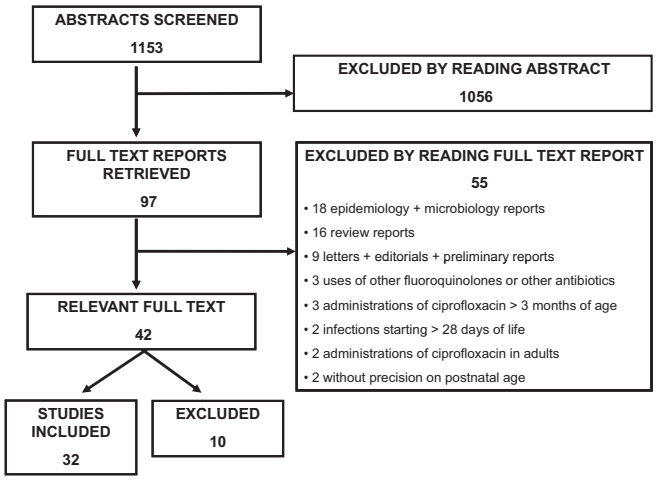

FIGURE 1. Study flowchart.

articles were excluded from the analysis. The first author (F.K.) assessed study eligibility, under the supervision of 2 senior authors (E.J.A. and M.T.).

Data Extraction

The following data were extracted: year of publication, study location, study design, neonatal condition treated and causal organism, total number of participants, number of neonates that received ciprofloxacin, gestational age (GA) at birth, age at study inclusion, age at isolation of causal organism, age at start of ciprofloxacin treatment, dosing schedule, administration route duration of ciprofloxacin treatment, and length of follow-up.

Outcomes included in the systematic review concerned the efficacy and toxicity of ciprofloxacin in neonates and all available pharmacokinetic data. Response to treatment was evaluated either clinically and/or microbiologically (bacteriologic eradication). Clinical response was defined as the survival and/or the clinical improvement of the neonate under ciprofloxacin without need for antibiotic modification, during initial hospitalization. Reasons for treatment failure were also retrieved. Ciprofloxacin toxicity was defined as any unintended adverse consequence of its use, observed in the treated neonates.

Any problems raised in the data extraction and quality assessment were resolved by discussion with the 2 senior authors (E.J.A. and M.T.).

Data Analysis and Presentation of Results

The studies are described in narrative and tabular forms. In view of the heterogeneity of study designs and clinical contexts, we have not conducted any pooled analyses of outcomes.

RESULTS

Literature Search

The search yielded 1153 potentially eligible reports. Of these, 1056 were excluded after a first screening based on title and/or abstract, leaving 96 articles for full article review. Manual searching of the reference lists of these articles identified 1 additional article to be included. Of the 97 articles for full-text review, 55 were subsequently excluded (reasons for exclusion are presented in Fig. 1). However, 10 papers were further excluded from analysis because these studies also included infants or older children treated by ciprofloxacin[10–17] or neonates treated by antibiotics other than ciprofloxacin[18,19] and in both cases outcomes of ciprofloxacin-treated neonates alone could not be identified. Of note, one of these studies excluded was the only RCT that was identified in the search which evaluated the efficacy and safety of topical ciprofloxacin compared with topical tobramycin for the treatment of bacterial conjunctivitis.[17]

In total, 32 reports met all eligibility criteria and were included in the review. Of these, 5 were cohort studies[20–24] and 27 were single case reports (n = 14)[25–38] or series of 2 to 29 patients (n = 13)[39–51] treated with ciprofloxacin.

Pharmacokinetics

Only one study primarily evaluated the pharmacokinetic parameters of ciprofloxacin in neonates.[39] This study recruited 24 preterm neonates with sepsis (mean GA: 32 weeks; range: 28–36

TABLE 1. Summary of Cohort Studies

Publication (Reference)	Population	Condition	No. Treated by Ciprofloxacin/ No. of Participants	GA at Birth (wk), Mean (±SD) or/ and (Range)	Age* (d), Mean (±SD) or/ and (Range)
Ahmed et al[20]	Bangladesh	Culture proven or clinically suspected septicemia	92/492	<33	Cipro: 7.5 (range: 3–16)
Chaudhari et al[21]	India	Blood culture proven septicemia due to multidrug-resistant organisms (Cipro group) et septicemia (control group)	30/60	Cipro: 33.2 (±3.83)/control: 33.6 (±3.43) (global range: 28–40)	Cipro: 8.06 (range: 5–13)
Drossou-Agakidou et al[22]	Greece	Culture proven or clinically suspected sepsis	116/216	Cipro: 31 (±4) (range: 25–40)/ control: 31 (±4) (range: 24–40)	Cipro: 19 (±14) (range: 1–44)/ control: 12 (±8) (range: 1–31)
Dutta et al[23]	India	Culture-proven multidrug-resistant nosocomial sepsis	61/205	Cipro: 30.2 (±2.9)/ control: 31.9 (±1.9)	NS‡
Gurpinar et al[24]	Turkey	Blood culture proven sepsis sensitive to ciprofloxacin or sensitive to cefotaxime or healthy neonates (control)	9/27	Cipro: 35/controls: 35 and 36	NS‡

*Age at study inclusion or age at start of ciprofloxacin treatment or age at isolation of multiresistant organism.

†Global survival (during and after hospitalization).

‡Received ciprofloxacin during neonatal period without other precisions.

No. indicates number; NA, not applicable; NS, not stated; bid, twice a day; IV, intravenous administration; No. evaluated, total number − patients who left hospital against medical advice (no outcome information available).

weeks) aged between 3 and 25 days at study inclusion. They received intravenous (IV) ciprofloxacin at the dose of 10 mg/kg/dose, 12 hourly. Data on serum ciprofloxacin were available for 20 patients. Peak ciprofloxacin levels at days 1, 3, and 7 of treatment were comparable (mean [±SD]): 2.3 (±0.39 μg/mL), 3.0 (±0.44 μg/mL), and 2.7 (±0.39 μg/mL), respectively. Trough values on the same days were also comparable (mean [±SD]): 0.7 (±0.14 μg/mL), 0.8 (±0.14 μg/mL) and 1.0 (±0.21 μg/mL), respectively. Based on knowledge of ciprofloxacin's MIC90 at the time, the authors concluded that the evaluated dose resulted in sufficient serum concentrations to eliminate common Gram-negative pathogens but would have been insufficient for the treatment of *Staphylococcus aureus* and *Pseudomonas aeruginosa* infections. No differences were observed between neonates <1500 g and >1500 g or those <7 days and >7 days of postnatal age, with respect to corresponding peak and trough levels on sampling days. Seventeen neonates improved clinically and outcome was unknown for 2 patients lost to follow-up during treatment. No adverse events were observed during therapy.

Two short reports reported serum and CSF ciprofloxacin concentrations in a total of 7 neonates. A case series of 6 septic preterm neonates (24–29 weeks GA), aged between 9 and 49 days at the start of ciprofloxacin treatment, received 10 mg/kg/dose twice daily.[40] Serum concentrations at the third IV dose ranged from 0.04 to 2.6 mg/L (predose) and from 1.45 to 5.7 mg/L (postdose). Also, in 1 neonate with ventriculitis, serum and CSF concentrations were estimated at 0.04 and 0.88 mg/L, respectively, before the third dose, and at 0.52 and 1.45 mg/L, respectively, before the 14th dose of ciprofloxacin. Ciprofloxacin concentrations were measured in an 8-day-old neonate with meningitis at different days of treatment (2, 4, 7, 15, 21 days).[42] Serum concentrations ranged from 1.6 to 2.6 mg/L and CSF concentrations from 1.3 to 2.7 mg/L.

Efficacy and Safety

Cohort Studies

Of the 5 observational cohort studies, 2 were prospective,[20,22] one was an historic cohort study[23] and 2 did not provide further details on study design.[21,24] Characteristics of these 5 cohort studies and major conclusions are shown in Table 1.

Altogether, 1000 neonates were included, 308 had received ciprofloxacin, and 692 were considered as controls because they had either received other antibiotics (n = 683) or no antibiotic treatment (n = 9). Indications for ciprofloxacin treatment included a culture (blood or CSF) proven multidrug-resistant sepsis or a clinically suspected sepsis with signs of deterioration under first line antibiotics. The mean duration of intravenous therapy ranged from 11 to 15 days in the ciprofloxacin-treated group and 13.3 days in the control group (reported in 1 study only).[20] After hospital discharge, all initially included neonates were followed-up in 3 studies whereas the proportions of controls and ciprofloxacin-treated neonates followed-up in the remaining 2 studies were different (Table 1).[20,22]

Measures of treatment efficacy were available in only 2 cohort studies. The first study[20] reported a clinical response rate of 64% among the ciprofloxacin-treated neonates compared with 27% among the controls. The second study[22] reported a global survival rate of 91% for the ciprofloxacin group and 89% for the control group. However, in this study, neonates who died within 15 days of treatment initiation or who did not complete laboratory follow-up were excluded from the analysis. The remaining 3 studies[21,23,24] included only neonates who survived and had complete medical records up to the end of the predefined follow-up period, thus estimation of the clinical response rates was not possible.

No serious side-effects were reported during treatment or follow-up in either of the groups. The only adverse event reported was a greenish coloration of teeth in the first year of life, in one neonate of each group (ciprofloxacin and control).[22] During treatment, routine hematologic and biochemical parameters[20,22] measured were not different between the 2 groups. Data on the short- and long-term impact of ciprofloxacin on cartilage damage and growth were analyzed with no significant differences observed between ciprofloxacin and control groups. However, in all studies joint toxicity was evaluated clinically and only 1 study performed radiologic exams (ultrasound scan, x-ray).[21] Multiple regression models adjusting for common neonatal characteristics like weight

TABLE 1. (*Continued*)

Dosing Schedule; Duration of Treatment by Ciprofloxacin (Mean ± SD)	Treatment of Control Group	No. With Clinical Response/ No. Evaluated (%)		No. Followed-up After Discharge/ Mean Follow-up (mo, Mean [±SD])	
		Cipro	Control	Cipro	Control
15 mg/kg/d bid IV; 11 ± 3 d	Other antibiotics (ampicillin, gentamicin, cefotaxime)	55/86 (64%)	94/344 (27%)	48/(24.7 [±18.3])	66/(21.6 [±18.8])
20 mg/kg/d bid IV; 14 d	Other antibiotics (cefotaxime, amikacin)	NA	NA	30/(6)	30/(6)
10 mg/kg/d bid IV; 15 d	Other antibiotics	106/116† (91%)	89/100† (89%)	77/(12)	83/(12)
10 mg/kg/d bid IV; >3 d	NS	NA	NA	61/(12)	144/(12)
20 mg/kg/d bid IV; 14 d	Cefotaxime (n = 9)/ no antibiotics (n = 9)	NA	NA	9/(42)	18/(42)

and gestational age at birth, were used in 2 studies[21,23] and found no significant relation between the use of ciprofloxacin and the cartilage size of the right knee measured in ultrasound examination[21] or the height at 12 months corrected age.[23]

Finally, 2 studies undertook evaluation of the motor and mental development during follow-up using the Bayley Scales of infant Development[20] and the Denver Development Test[24] but no differences in the development of infants were noted between the 2 groups. One study[21] performed an ophthalmic check that was reported normal in all infants.

Case Reports and Case Series

Twenty-seven case reports and patients' series are summarized in Tables 2 and 3. Approximately half of these studies were performed in low and lower middle income countries (15/27; 55.5%) and the remaining half, in high income countries (12/27; 45.5%). Ciprofloxacin was exclusively administered for the treatment of invasive neonatal infections with central nervous system (CNS) involvement (meningitis, meningoencephalitis, ventriculitis) in 15 (55.5%) reports.[25–28,30,34,36–40,42,43,45,50] Overall, 143 neonates were treated with ciprofloxacin out of the 256 neonates and infants that participated in these studies (56%). Ciprofloxacin was administered intravenously in 2 divided daily doses (only 1 study[50] reported 3 daily IV infusions) but daily dose varied widely between 5 and 60 mg/kg. Duration of treatment was usually 2 or 3 weeks (12/20; 60%) but ranged from 5 to 75 days in total, depending on clinical condition and presence of a CNS infection. Ciprofloxacin was prescribed almost exclusively in combination with other antibiotics, mainly aminoglycosides and third generation cephalosporins, although details on these combinations are not available for all reports. Of interest, in 3 studies the initial IV administration of ciprofloxacin was followed by an oral administration of FQ.[30,42,50]

Clinical response to treatment was reported in 12 of 14 (86%) case reports. In patients' series, median clinical response was 83% (range: 0%–100%) of treated neonates. Overall, 19 of 33 failures of treatment were reported as being related to infectious complications. Cases of neurologic sequelae were described in 3 studies: 4 hydrocephalus (1 irreversible with severe neurologic injury,[45] 1 associated with a slightly delayed psychomotor development,[36] and 2 reversible[45]) and a hemiplegia of left extremities.[30] All of these neonates presented with meningitis and/or cerebral abscesses.

Rate of bacteriological eradication was evaluated in only 2 series of patients. The first one reported an eradication rate of 100% in 6 cases of neonatal *Enterobacter cloacae* septicemia (clinical response = 50%)[40] and the second one a rate of 93% (27/29) in a multiresistant nosocomial *Pseudomonas* infection (clinical response = 83%).[41]

Globally, the majority of these studies reported an absence of serious adverse events during treatment and follow-up. However, only 23% (33/141) of neonates had been followed-up for more than 1 year after treatment. Osteoarticular complications were assessed exclusively by clinical examination. In several studies, authors explicitly monitored routine biologic parameters,[31,39,41,46] growth and neurodevelopment parameters,[25,28,38] audition,[31,32,45,50] and vision testing,[32,45] though most do not give details of patient monitoring. Only, 3 studies reported adverse events possibly related to use of ciprofloxacin. In one study, among 15 treated neonates, authors noted the presence of 1 skin rash and 1 case of transient thrombocytopenia during treatment.[46] Also, 2 cases of greenish discoloration of teeth were observed between 1 and 2 years of life, in a group of 11 neonates who had received combinations of various antibiotics together with ciprofloxacin for the treatment of severe *Klebsiella* sepsis.[47] Finally, in a case report of a neonate presenting with *Klebsiella pneumoniae* infection, an increased hearing threshold was detected at hospital discharge.[31]

DISCUSSION

To our knowledge, this is the first systematic review to summarize all available data regarding the use of ciprofloxacin in neonatal infection. Observational cohort studies, case reports and descriptions of patient series account for all medical literature reviewed. Ciprofloxacin was administered as salvage therapy in neonatal sepsis due to multidrug-resistant strains or in sepsis with signs of clinical deterioration under empirical antibiotic treatment. Initial administration was always IV with variable dosing schedule. Reported clinical response to treatment was 64% and 91% in 2 cohort studies. In case series, median clinical response was 83% and 12 of 14 case reports yielded positive clinical outcomes. Overall, no serious adverse events, particularly joint toxicity, were reported.

Ciprofloxacin has been shown to be effective for the treatment of numerous infectious conditions in adults, yet its use in children remains limited. Restrictions to pediatric use are related to concerns about (1) the potential of quinolones to induce cartilage toxicity in weight-bearing joints in juvenile animals,[52] even though it remains unclear whether cartilage toxicity in experimental animals and some tendon disorders observed in humans are related,[53,54] and (2) their potential to increase the prevalence of FQ-resistant pathogens as already described in adults.[6,55]

Despite such considerations, clinicians are confronted with situations where the use of quinolones may offer significant benefits to neonates in the context of resistance to other antibiotics.[56–59] In the presence of meningitis, adequate CSF penetration of ciprofloxacin has been established in adults and older children[6] and available data in infected neonates although limited (n = 2), showed that CSF concentrations were comparable to serum ciprofloxacin concentrations.

The use of medicinal products in neonates requires adequate pharmacokinetic data since it is well known that pharmacokinetics in neonates differ from older children,[60] and demonstration of long-term drug safety. Evaluation of efficacy, however, may be extrapolated from other age groups, if similar exposure in older children and neonates can be assumed to produce similar efficacy.[61,62] In particular, for antibiotics, it can be assumed that their antibacterial activity, related to the ratio of the area under the concentration-time curve (AUC) to the minimal inhibitory concentration (MIC), will be similar in all age groups from neonates to adults.

Unsurprisingly, data on the pharmacokinetics of ciprofloxacin in neonates are to date scarce, as the drug has primarily been evaluated in older children mainly in patients with cystic fibrosis.[63–66] The only pharmacokinetic study performed in septic preterm neonates concluded that a dose of 20 mg/kg/d in 2 divided doses would be effective for common gram-negative infections except for *Pseudomonas aeruginosa* infections and ineffective for *Staphylococcus aureus* infections. Although this study is well conducted, it does not provide sufficient data to establish the optimal dosing schedule of ciprofloxacin in neonatal sepsis.

All adverse events reported were minor and reversible including discoloration of teeth, skin reactions hematological/biochemical abnormalities (transient thrombocytopenia). Two other studies including neonates, infants and children have described such adverse events and also cases of raised transaminases,[12,14] thus close monitoring should be considered. The potential for joint toxicity and impact on growth is probably the most

TABLE 2. Summary of Single Case-reports of Neonates Treated by Ciprofloxacin

Publication (Reference)	Population	Condition Treated by Ciprofloxacin/Bacteriology	GA at Birth (wk)	Age (d)			Dosing Schedule of Ciprofloxacin Treatment; Duration (d)	No. With Clinical Response	Mean Follow-up After Hospital Discharge (mo)	Antibiotics Associated to Ciprofloxacin
				At Study Inclusion or Beginning of Infection	At Isolation of Causal Organism	At Start of Ciprofloxacin Treatment				
Bhutta et al[25]	Pakistan	*Salmonella paratyphi A* meningitis	36	5	26	26	10 mg/kg/d bid IV; 21	1	7	
Bhutta[26]	Pakistan	*Salmonella paratyphi B* meningoencephalitis	36	4	12	12	12 mg/kg/d IV; 5	0	NA	
Bingen et al[27]	France	Recurrent *Escherichia coli* meningitis	35	9	9, 34, 70	70	20 mg/kg/d; 60	1	1	Cefotaxime
Chotigeat et al[28]	Thailand	*Acinetobacter* meningitis	33	1	14	16	60 mg/kg/d bid IV; 21	1	6	Co-trimethoprim
Duran et al[29]	Turkey	Multidrug-resistant *Ochrobactrum anthropi* bacteriemia	29	2	7	7	IV; 14	0	NA	Gentamycin
Hata et al[30]	Japan	*Mycoplasma hominis* meningitis	38	25	31	31	22 mg/kg/d IV; 11	1	NS	
Khaneja et al[31]	USA	Multidrug-resistant *Klebsiella pneumoniae* infection	26	23	23	23	20 mg/kg/d bid IV; NS	1	0	Gentamycin
McPherson et al[32]	USA	*Citrobacter koseri* infection	23 1/7	19	22	22	10–20 mg/kg/d bid IV; 21	1	1	Cefotaxime
Pillay et al[33]*	South Africa	Multidrug-resistant *Klebsiella pneumoniae* infection	NS	NS	First days of life	NS	NS	1	0	
Sarkar et al[34]	India	Multidrug-resistant *Klebsiella pneumoniae* meningitis and septicemia	Full-term	11	NS	NS	10 mg/kg/d bid IV; NS	1	NS	
Van den Oever et al[35]	The Netherlands	Multiresistant *Enterobacter cloacae* invasive infection	31	9	9	12	20 mg/kg/d bid IV; 7	1	36	Trimethoprim-sulphamethoxazole
Wessalowski et al[36]	Germany	Cerebral abscesses caused by *Salmonella enteritidis*	37	2	31	33	10 mg/kg/d; 33	1	24	Cefotaxime
Wolthers et al[37]	The Netherlands	*Mycoplasma hominis* meningitis	37	8	NS	14	20 mg/kg/d bid IV; 21	1	3 wk	Amoxicillin then clindamycin
Workman et al[38]	UK	*Salmonella enteritidis* meningitis and multiple cerebral abscesses	36	28	NS	NS	5 then 15 mg/kg/d IV; 75	1	24	Ampicillin and cefotaxime

*Thirty-three neonates participated in this study but only 1 received IV ciprofloxacin.
NS indicates not stated; NA, not applicable; IV, intravenous; bid, twice a day.

TABLE 3. Summary of Series of Patients Treated by Ciprofloxacin

Publication (Reference)	Population	No. of Neonates Treated by Ciprofloxacin*/ No. of Participants	Condition Treated by Ciprofloxacin/ Bacteriology	GA at Birth (wk), Mean (±SD) or/and (Range)†	Age (d), Mean (±SD) or/and (Range)†			Dosing Schedule; Duration (d), Mean (±SD) or/ and (Range)†	No. With Clinical Response†	Mean Follow-up‡ (mo, Mean (±SD)†	Antibiotics Associated to Ciprofloxacin
					At Study Inclusion or Beginning of Infection	At Isolation of Causal Organism	At Start of IV Treatment				
Aggarwal et al[39]	India	24§/24	Neonatal sepsis (meningitis n = 4)	32 (±2.4; range: 28–36)	NS	NS	3–25	20 mg/kg/d bid IV; NS	17	0	
Bannon et al[40]	United Kingdom	6/6	*Enterobacter cloacae* septicemia (ventriculitis, n = 1)	24–29	NS	5–29	9–49	10 mg/kg/d bid IV; 14–21	3	0	
Belet et al[41]	Turkey	29/30	Multiresistant *Pseudomonas aeruginosa* nosocomial infection	31 (±3.7) (range: 25–38)	NS	21, 1 (±16.7) (range: 4–79)	NS	10 mg/kg/d to 40 mg/kg/d bid IV; 13.8 (±4.7) (range: 7–24)	24	1 wk	
Green et al[42]	Zaire	2/2	Neonatal meningitis due to resistant Gram (−) bacteria (*E. coli; Flavobacterium meningosepticum*)	Both full term	2 and 13	8 and 16	8 and 16	60 and 50 mg/d bid IV; 4 d then orally: 18 and 9 d	2	0	
Guillamat et al[43]	France	2/9	*Salmonella enteritidis* meningitis	NS	12, 17	NS	NS	30 mg/kg/d IV; 20 and 15	2	NS	Amoxicillin, cepharosporin aminoglycosid
Gungor et al[44]	Turkey	3/4	*Chryseobacterium meningosepticum* sepsis in a NICU	31, 31, 34	7, 14, 10	18, 24, 22	12, 19, 15	NS; 7, 6 and 7	0	NA	
Krcméry et al[45]	Slovakia	3/12	Nosocomial meningitis/Gram (−) bacteria sensitive to ciprofloxacin	NS	21, 27, 28	NS	NS	10–60 mg/kg/d IV; 14 to 28	3	NS	
Lahbabi et al[46]	Maroc	15/15	Nosocomial infection due to Gram (−) multidrug-resistant bacteria	38 (range: 35–39)	Range: 1 h–7 d	NS	Range: 3–16	20 mg/kg/d bid IV; 11 ± 3 (range: 7–21)	14	Range: 12–15	Amoxicillin, cefotaxime, amikacin
Lumbiganon et al[47]	Thailand	13¶/13	Severe *Klebsiella* infection	8 preterm (>26) and 3 full term	NS	NS	4–30	10–40 mg/kg/d bid IV; 10–20	10	Range: 12–23	
Mishra et al[48]	India	21/79	*Acinetobacter* sepsis	NS	First days of life	NS	NS	NS	11	NS	
PIllay et al[49]	South Africa	5/9	Multidrug-resistant *Acinetobacter infection*	<37	NS	Range: 1–23	NS	NS	5	0	Amikacin
Tanase-Derkaoui et al[50]	France	2/2	*Pseudomonas aeruginosa* meningitis	Full term and 32 4/7	6, 10	6 and 11	6 and 11	30 mg/kg/d tid; 10 and 28	2	30 and 36	Gentamycin and ceftazidime
van Ogstrop et al[51]	The Netherlands	4/5	Colonization (n = 2) and infection due to *Serratia marcescens* (n = 2)	Range: 25–29	NS	Range: 13–23	Range: 13–23	IV; NS	3	0	Gentamycin alone or with vancomycin

*Neonates with an infection appearing in the first 28 days of life and treated by ciprofloxacin in the first 3 months of life.
†Data on ciprofloxacin treated neonates.
‡After hospital discharge.
§Available data on outcome only for 22 patients (2 were lost to follow-up).
¶Data on GA at birth, age at start of ciprofloxacin treatment, dosing schedule, mean follow-up after discharge available only for 11/13 neonates.
No. indicates number; NS, not stated; NA, not applicable; bid, twice a day; tid, 3 times a day; IV, intravenous; GA, gestational age.

important limiting factor to its use in young patients and primarily neonates. The absence of reported osteoarticular toxicity in the reviewed literature is compatible with evidence from previous studies in older children and infants.[10,67] Only 1 case of femoral bone inflammation was described in a premature infant after treatment by ciprofloxacin and was regarded as a complication of sepsis by the authors.[14] Nonetheless, monitoring of joint toxicity in neonates is limited in all studies by the variability in patients' follow-up and the absence of a validated method to assess joint toxicity. Indeed, radiologic explorations to assess potential toxicity were reported in only 1 cohort.[21] As the frequency of articular side-effects of FQ is known to be greater in children than in adults,[6] it is particularly important to assess the impact of ciprofloxacin treatment in neonates in the long term. The reports summarized here do not include enough neonates to provide data on rare adverse events.

Evaluations of safety reports and global therapeutic response are hampered because septic neonates often receive various combinations of antibacterial drugs including ciprofloxacin, in association with various additional drugs (vasoactive or gastrointestinal drugs) and are often in a critical state (leading to confounding by indication).

Finally, methodological quality and level of evidence of the studies included in this review was universally low. To date, only one randomized controlled trial has evaluated the efficacy and safety of topical ciprofloxacin in bacterial conjunctivitis and this trial was of poor quality. Moreover, the cohort studies aiming to evaluate safety of ciprofloxacin use presented various limitations. Inclusion criteria for neonates both exposed and not exposed to ciprofloxacin were either very diverse or not sufficiently specified. Monitoring for adverse events during therapy and after hospital discharge was highly variable with numerous patients lost to follow-up. In addition, most studies had a limited duration of follow-up with a very small number of patients evaluated, so conclusions on long-term safety are difficult to draw. Finally, the main sources of information on ciprofloxacin efficacy and safety in neonates were case reports and patients series. These reports are very heterogeneous in terms of the severity of illness treated, the timing and schedule of ciprofloxacin administration, the existence of other coadministrated antibiotics, the duration of follow-up, and the reliability of safety outcomes measured.

Only descriptive statistics were reported in this review thus the presence of possible publication bias or statistical between-study heterogeneity was not assessed. Nevertheless, it seems unlikely that studies reporting negative outcomes after use of ciprofloxacin remain unpublished and thus excluded from the review. In fact, because of previous publications on ciprofloxacin's potential of joint toxicity in juvenile animals, the use of this antibiotic has been highly debated between neonatologists probably favoring the publication of negative outcome studies.

Data available in current literature provide some information to support the rational use of ciprofloxacin in neonatal sepsis. However, key elements of prescribing information are not supported by high quality studies. Additional well-conducted pharmacokinetic and pharmacokinetic/pharmacodynamic studies will allow appropriate dosing recommendations. Extrapolation of efficacy from adult data should be in agreement with regulatory guidelines while both short and long-term safety data are mandatory.[68] All safety studies should focus on evaluating the potential osteoarticular and neurodevelopmental toxicities by using validated criteria. We are not aware of any validated criteria for osteoarticular assessment among the survivors of neonatal intensive care. There is still a need to identify the most appropriate safety and efficacy outcomes and the ways in which they should be assessed. For all these reasons, ciprofloxacin was included in the off-patent priority list for pediatric medicines prepared by the European Medicines Agency (EMA) and a European pediatric project[69] is currently ongoing to provide missing information.

APPENDIX

Search Strategies for PUBMED (1966 to July 2009)

1. "Ciprofloxacin" [All fields] AND ("Premature Birth" [Mesh] OR "Infant, Premature" [Mesh])
2. ("ciprofloxacin" [MeSH Terms] OR "ciprofloxacin" [All Fields]) AND ("infant" [MeSH Terms] OR "infant" [All Fields] OR "infants" [All Fields])
3. ("Ciprofloxacin" [MeSH Terms] OR "Ciprofloxacin" [All Fields]) AND ("drug toxicity" [MeSH Terms] OR ("drug" [All Fields] AND "toxicity" [All Fields]) OR "drug toxicity" [All Fields] OR ("adverse" [All Fields] AND "drug" [All Fields] AND "reaction" [All Fields]) OR "adverse drug reaction" [All Fields]) AND ("infant, newborn" [MeSH Terms] OR ("infant" [All Fields] AND "newborn" [All Fields]) OR "newborn infant" [All Fields] OR "newborn" [All Fields] OR "Infant, Premature" [Mesh])
4. (("therapeutics" [MeSH Terms] OR "therapeutics" [All Fields] OR "therapeutic" [All Fields]) AND ("ciprofloxacin" [MeSH Terms] OR "ciprofloxacin" [All Fields])) AND ("infant, newborn" [MeSH Terms] OR ("infant" [All Fields] AND "newborn" [All Fields]) OR "newborn infant" [All Fields] OR "newborn" [All Fields] OR "neonatology" [All fields] OR "Infant, Premature" [Mesh] OR "preterm" [All fields]) AND ("humans" [MeSH Terms] AND (Clinical Trial[ptyp] OR Meta-Analysis[ptyp] OR Randomized Controlled Trial[ptyp] OR Review[ptyp]))
5. (("therapeutics" [MeSH Terms] OR "therapeutics" [All Fields] OR "therapeutic" [All Fields]) AND ("ciprofloxacin" [MeSH Terms] OR "ciprofloxacin" [All Fields])) AND (Clinical Trial[ptyp] OR "clinical trials as topic" [MeSH Terms] OR Clinical Trials[tw] OR Meta-Analysis[ptyp] OR Randomized Controlled Trial[ptyp] OR Review[ptyp] OR "randomized controlled trials as topic" [MeSH Terms] OR Controlled clinical trial[ptyp] OR ("Comparative Study " [ptyp] AND "Control Groups" [Mesh]) OR evaluation studies[ptyp] OR "follow-up studies" [MeSH Terms] OR "Case-Control Studies" [Mesh] OR "Cohort Studies" [Mesh] OR "Epidemiologic Studies" [Mesh] OR "Cross-Sectional Studies" [Mesh] OR "Retrospective Studies" [Mesh] OR "Intervention Studies" [Mesh] OR "Prospective Studies" [Mesh]) AND ("humans" [MeSH Terms] AND ("infant" [MeSH Terms]))
6. ("Fluoroquinolones" [All fields] OR "Fluoroquinolones" [Mesh]) AND ("Ciprofloxacin" [All fields] OR "Ciprofloxacin" [Mesh]) AND "humans" [MeSH Terms] AND "infant" [MeSH Terms]
7. ("fluoroquinolones" [MeSH Terms] OR "fluoroquinolones" [All Fields]) AND (preterm[All Fields] OR ("infant, newborn" [MeSH Terms] OR ("infant" [All Fields] AND "newborn" [All Fields]) OR "newborn infant" [All Fields] OR "neonate" [All Fields]) OR ("infant, newborn" [MeSH Terms] OR ("infant" [All Fields] AND "newborn" [All Fields]) OR "newborn infant" [All Fields] OR "neonates" [All Fields]) OR ("infant" [MeSH Terms] OR "infant" [All Fields] OR "infants" [All Fields])) AND "humans" [MeSH Terms]

Search Strategies for EMBASE (1980 to July 2009)

1. "ciprofloxacin"/exp/mj AND [newborn]/lim AND [humans]/lim
2. "ciprofloxacin"/exp/mj AND ([newborn]/lim OR [infant]/lim) AND [humans]/lim

3. fluoroquinolones'/exp/mj AND ([newborn]/lim OR [infant]/lim) AND [humans]/lim

Search Strategies for the Cochrane Database of Systematic Reviews (up to July 2009)

1. infant, newborn
2. infant*
3. newborn*
4. neonate*
5. (#1 OR #2 OR #3 OR #4)
6. Ciprofloxacin
7. #5 AND #6
8. Fluoroquinolones: ti, ab, kw
9. Ciprofloxacin: ti, ab, kw
10. (#8 OR #9)
11. (#2 AND #10)
12. (#7 OR #11)

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