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Original article

Combination therapy with ciprofloxacin and third-generation cephalosporin versus third-generation cephalosporin monotherapy in *Escherichia coli* meningitis in infants: a multicentre propensity score–matched observational study

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ABSTRACT

Objectives: *Escherichia coli* is the second cause of bacterial meningitis in neonates. Despite the use for 35 years of third-generation cephalosporins (3GCs), high morbidity and mortality rates with *E. coli* meningitis continue to occur. Because ciprofloxacin has good microbiologic activity against *E. coli* and good penetration in cerebrospinal fluid and brain, some authors have suggested adding ciprofloxacin to a 3GC regimen. The objective of this study was to assess combining 3GCs with ciprofloxacin versus 3GCs alone in a cohort of infants with *E. coli* meningitis.

Methods: We included all cases of *E. coli* meningitis diagnosed in infants <12 months of age that were prospectively collected through the French paediatric meningitis surveillance network between 2001 and 2016. The main outcome was the proportion of short-term neurologic complications with versus without ciprofloxacin. The analysis was conducted retrospectively by multivariable regression and propensity score (PS) analysis.

Results: Among the 367 infants enrolled, 201 (54.8%) of 367 had ciprofloxacin and 3GC cotreatment and 166 (45.2%) of 367 only a 3GC. Median age and weight were 15 days (range, 1–318 days) and 3.42 kg (range, 0.66–9.4 kg). A total of 86 (23.4%) of 367 infants presented neurologic complications (seizures, strokes, empyema, abscesses, hydrocephalus, arachnoiditis); 57 received ciprofloxacin cotreatment. Complications were associated with ciprofloxacin cotreatment on multivariable analysis (odds ratio (OR) = 1.9; 95% confidence interval (CI), 1.1–3.4) and PS analysis (OR = 1.9; 95% CI, 1.1–3.3). Mortality rate did not differ with and without ciprofloxacin: 22 (10.9%) of 201 versus 16 (9.6%) of 166 deaths (OR = 0.7; 95% CI, 0.3–1.6; PS analysis).

Conclusions: Ciprofloxacin added to 3GCs at least offers no advantage for neurologic outcome and mortality in infants with *E. coli* meningitis. **M. Tauzin, Clin Microbiol Infect 2019;25:1006**

Introduction

The burden of bacterial meningitis remains heavy in neonates and young infants, with high rates of morbidity and mortality [1]. The most common pathogens in neonatal meningitis are *Streptococcus agalactiae*, followed by *Escherichia coli*. Furthermore, *E. coli* is the first causative agent in preterm

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neonates (sevenfold more frequent than for term neonates) [1–3].

Despite the use for 35 years of third-generation cephalosporins (3GCs), high morbidity and mortality rates with *E. coli* meningitis continue to occur, with approximately 10% of mortality and 25% to 50% of severe complications in survivors [1,3].

Antibiotic therapy recommended for meningitis due to *E. coli* is a 3GC, usually cefotaxime [4]. 3GCs have very low MIC for *E. coli* and adequate cerebrospinal fluid (CSF) levels, which allows the achievement of good pharmacokinetic/pharmacodynamic properties [5]. However, drawbacks are low tissue penetration and reduced bactericidal activity on microorganisms in the stationary phase [6]. Corticosteroids are not currently recommended in the treatment of neonatal meningitis [7].

Adjunct ciprofloxacin treatment has been proposed by some experts for more than 20 years in France [6,8,9], even if such treatment is not recommended in European and US guidelines [10,11]. Ciprofloxacin has been used in infants to treat severe multidrug-resistant, Gram-negative infections in children [4,12,13]. The rationale for its use in *E. coli* meningitis is based on its antibacterial activity, its pharmacokinetics and pharmacodynamics, and its anti-inflammatory properties. Ciprofloxacin has bactericidal activity on Gram-negative rods, with low MIC for *E. coli* (modal MIC = 0.016 mg/L) (http://mic.eucast.org/). Furthermore, it has good tissue, intracellular and CSF penetration [6,9,13,14]. Indeed, intracellular ciprofloxacin levels are 4 to 5 times higher than serum levels, and CSF ciprofloxacin levels in inflamed meninges reach concentrations far above MIC values for *E. coli* [14–16]. Moreover, some studies suggest an intrinsic anti-inflammatory effect for ciprofloxacin. This neuroprotective effect of ciprofloxacin compared to cefotaxime has been shown in an *E. coli* sepsis model of rat pups [17].

For safety reasons, quinolones are rarely provided to paediatric patients. However, ciprofloxacin has been prescribed for several years in children with severe bacterial infections. A review of adverse events linked to ciprofloxacin use in paediatric patients reported a risk of 7% (95% confidence interval (CI), 3.2–14) [18]. However, the concern was mainly for arthropathy, and the events occurred only in children >7 months of age, which is not the population concerned by *E. coli* meningitis. For meningitis, and regarding the burden of its complications, the benefits could outweigh the risks.

A French prospective study of a small number of neonates ($n = 36$) suggested that adjunct ciprofloxacin therapy could reduce short-term neurologic complications [8]. To assess the use of ciprofloxacin for *E. coli* meningitis, these data needed to be confirmed in a larger cohort. The aim of this study was to compare the proportion of short-term neurologic complications in a cohort of infants with *E. coli* meningitis receiving a 3GC with or without adjunct ciprofloxacin.

Methods

Population and data collection

We conducted a multicentre observational study with cases prospectively collected through the French paediatric meningitis surveillance network between 2001 and 2016. This network included data from 227 paediatric wards working with 168 microbiology departments. We used the capture–recapture method previously published in 2006, which estimated the completeness of the system at 61% (95% CI, 58–65) [19]. For this hospital-based active surveillance, three times a year, a clinical investigator in each participating ward was contacted for information on new cases or to confirm the lack of such cases [2]. The data collection was approved by the French National Data Protection Commission (CNIL, no. 913006). Data were prospectively collected. The reporting of the study results complies with the STROBE guidelines.

All neonates (<1 month of age) and infants (<12 months of age) with a confirmed diagnosis of *E. coli* meningitis were included. The diagnosis of meningitis was based on at least one of the following: positive CSF culture, presence of positive soluble antigens in CSF, positive PCR results for CSF and/or positive blood culture associated with pleocytosis (≥30 cells/μL) in CSF.

The following patient characteristics were collected: sex, gestational age at birth (<32 weeks, very preterm; 32 to 36 weeks + 6 days, moderate to late preterm; ≥37 weeks, term), birth weight, postnatal age and weight at diagnosis and underlying conditions. Early-onset, late-onset and very late-onset diseases were defined as ≤6, 7–89 and ≥90 days of age, respectively. The results of lumbar puncture (LP) were recorded (cell count, CSF glucose/blood glucose ratio and CSF protein value), along with microbiologic data (presence of K1 antigen, amoxicillin, ciprofloxacin and nalidixic acid susceptibility of *E. coli* strains). Concerning ciprofloxacin treatment, we recorded the doses used, duration of treatment and delay between diagnosis and adjunct ciprofloxacin therapy. Early treatment with ciprofloxacin was defined as starting ≤2 days after LP and late treatment as ciprofloxacin added >2 days after LP. Ciprofloxacin was the only fluoroquinolone provided.

Infants were divided into two groups by disease severity at diagnosis: a severe group, defined by the presence of at least one of the following signs before treatment: seizures, coma, mechanical ventilation, shock and/or extensive purpura; and a nonsevere group, with none of these signs present at diagnosis.

Patients with missing data for disease severity at diagnosis, outcome or treatment were excluded from the analysis, as were patients who did not receive antimicrobial therapy with a 3GC and patients infected with *E. coli* producing an extended-spectrum β-lactamase.

Variables collected are listed in Supplementary Table S1. There was no standardized definition for neurologic complications, which the clinician filled in a questionnaire in an open section.

Outcome assessment

The primary outcome was the proportion of short-term neurologic complications with versus without ciprofloxacin. Short-term neurologic complications included seizures (considered as a complication by the clinician), strokes and thrombophlebitis, empyema, abscesses, intracranial hypertension or intraventricular bleeding or hydrocephalus and pachymeningitis or arachnoiditis.

Secondary outcomes were mortality rate with and without ciprofloxacin; proportion of CSF sterilization failure with and without ciprofloxacin; and proportion of short-term neurologic complications for patients with ciprofloxacin treatment during the first 2 days after LP (early treatment group) versus without ciprofloxacin.

Statistical analysis

Categorical variables were compared by chi-square test or the Fisher exact test, and continuous variables by the Student *t* test. To follow the reporting guidelines on propensity score (PS) analysis [20], for each outcome, we conducted two different methods to adjust for imbalance between the treatment groups. First, we presented results from a multivariate logistic regression, where all variables which were potentially associated to the outcome on univariate analysis ($p < 0.2$) were added as covariates in the model. Second, we performed a PS matched analysis. Variables considered

in the univariate analysis were gestational age at birth, postnatal age at diagnosis, birth weight, weight at diagnosis, sex, severity at diagnosis, CSF/blood glucose ratio <0.1, CSF cell count and CSF protein value. The PS method attempts to balance treated and nontreated groups in order to reduce confounding by indication in observational designs, thereby creating a quasirandomized experiment [20]. The PS were calculated with a multivariable logistic regression model to establish each patient's probability of receiving combination therapy with ciprofloxacin according to baseline characteristics. Covariates that could be associated with outcome or allocation to ciprofloxacin treatment group (clinically relevant or chosen through univariable analysis) were used to generate the PS: gestational age at birth, postnatal age at diagnosis, birth weight, weight at diagnosis, sex, seizures before treatment, coma, mechanical ventilation, shock, CSF/blood glucose ratio <0.1, CSF cell count and CSF protein value. Patients receiving 3GC monotherapy were then matched to those receiving combination therapy with a 3GC and ciprofloxacin by their PS by using 1:1 nearest-neighbour matching without replacement, with a minimum caliper of 0.25. Finally, we performed a conditional logistic regression analysis with the matched cohort to test the association between adjunct ciprofloxacin therapy and each outcome and reported the results as odds ratios (OR) and 95% CIs [21]. To handle missing data, we used a multiple imputation with chained equations in PS analysis [22] by calculating the mean propensity score (PS) averaged over 15 imputed datasets [23]. Multivariate regression analysis was computed with raw data and no imputation; indeed, because a bias with multiple imputation is possible, we chose to perform multivariate analysis on subjects without missing data in order to compare the results of both analysis. In order to limit the number of subjects excluded from the regression analysis and to avoid reducing the study's power, we created a 'missing value' class for variables with a substantial number of missing data.

Statistical analysis was conducted by Stata 13 (StataCorp, College Station, TX, USA) and R 3.3.1 (R Foundation for Statistical Computing, Vienna, Austria; http://www.r-project.org/). Two-sided $p < 0.05$ was considered statistically significant.

Results

Characteristics of study population

Between 2001 and 2016, a total of 6102 paediatric meningitis cases were reported. In this cohort of children, 418 (6.9%) of 6102 had a diagnosis of *E. coli* meningitis and 414 (99%) of 418 were <12 months of age. We excluded 37 patients due to missing data, two that did not receive a 3GC and eight infected with extended-spectrum β-lactamase–producing *E. coli,* which resulted in a cohort of 367 patients (Fig. 1). The median postnatal age and weight at diagnosis were 15 days (range, 1–318 days) and 3.42 kg (range, 0.66–9.4 kg). Most cases, 241 (65.7%) of 367, involved late-onset meningitis; 92 (25.1%) of 367 were early-onset meningitis; and 34 (9.2%) of 367 were very late-onset meningitis. In the cohort, 224 (63.1%) of 355 were term neonates, 85 (23.9%) of 355 moderate to late preterm and 46 (13%) of 355 very preterm. Concerning initial severity, 170 (46.3%) of 367 infants presented at least one sign of initial disease severity. Diagnosis data, results of LP, and clinical and microbiologic characteristics of the cohort are summarized in Table 1.

Among the 367 infants analysed, 201 (54.8%) of 367 received cotreatment with ciprofloxacin. For 158, ciprofloxacin was added less than 2 days after LP, whereas for 20 ciprofloxacin was added later (Table 1). The median dose was 30 mg/kg per day (range, 10–60 mg/kg per day) by intravenous route in two or three divided doses. The median duration of ciprofloxacin treatment was 6 days (range, 2–95 days). All infants received antimicrobial therapy with

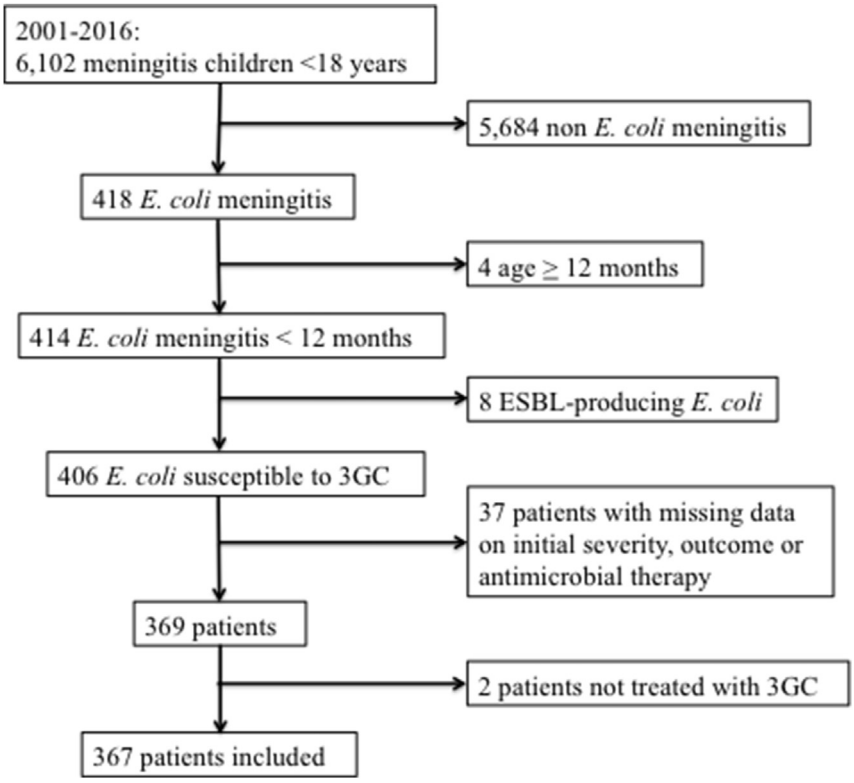

Fig. 1. Flowchart of study infants. ESBL, extended-spectrum β-lactamase; 3GC, third-generation cephalosporin.

Table 1
Demographic, microbiologic and treatment characteristics without and with adjunct ciprofloxacin

Demographic characteristics	No ciprofloxacin (n = 166, 45.2%)	Ciprofloxacin (n = 201, 54.8%)	Total (N = 367)	p
Age at diagnosis (days) (NA = 0)	14.5 (1–318)	15 (2–304)	15 (1–318)	
Early-onset disease	50/166 (30.1)	42/201 (20.9)	92/367 (25.1)	
Late-onset disease	102/166 (61.5)	139/201 (69.1)	241/367 (65.7)	0.1
Very late-onset disease	14/166 (8.4)	20/201 (10)	34/367 (9.2)	
Birth weight (kg) (NA = 12)	2.92 (0.66–5.01)	2.95 (0.86–5.28)	2.94 (0.66–5.28)	
Weight at diagnosis (kg) (NA = 99)	3.4 (0.66–8)	3.43 (0.86–9.4)	3.42 (0.66–9.4)	
Sex (NA = 9)				0.2
Male	87/161 (54)	119/197 (60.4)	206/358 (57.5)	
Female	74/161 (46)	78/197 (39.6)	152/358 (42.5)	
Gestational age (NA = 12)				0.9
≥37 weeks	102/164 (62.2)	122/191 (63.9)	224/355 (63.1)	
32–36 + 6 weeks	41/164 (25)	44/191 (23)	85/355 (23.9)	
<32 weeks	21/164 (12.8)	25/191 (13.1)	46/355 (13)	
Diagnosis (NA = 0)				
Positive CSF culture	132/166 (79.5)	168/201 (83.6)	300/367 (81.7)	
Positive soluble antigen	18/166 (11)	26/201 (12.9)	44/367 (12)	
Blood culture with pleocytosis	13/166 (3.5)	10/201 (5)	23/367 (6.3)	
Positive CSF PCR results	7/166 (4.2)	5/201 (2.5)	12/367 (3.3)	
Initial severity (NA = 0)				
Nonsevere disease	93/166 (56)	104/201 (51.7)	197/367 (53.7)	0.4
Severe disease	73/166 (44)	97/201 (48.3)	170/367 (46.3)	
Assisted ventilation	45/166 (27.1)	63/201 (31.3)	108/367 (29.4)	0.4
Shock	37/166 (22.3)	35/201 (17.4)	72/367 (19.6)	0.2
Coma	13/166 (7.8)	29/201 (14.4)	42/367 (11.4)	0.04*
Seizures before treatment	14/166 (8.4)	21/201 (10.4)	35/367 (9.5)	0.5
Extensive purpura	2/166 (1.2)	0/201 (0)	2/367 (0.5)	
Lumbar puncture results				
CSF white blood count (NA = 34)	1490 (3–52000)	2300 (0–250000)	2000 (0–250000)	.1
CSF protein level (g/L) (NA = 73)	1.98 (0–17.4)	2.36 (0.44–20.5)	2.1 (0–20.5)	0.4
CSF/blood glucose ratio <0.1/total (NA = 153)	35/99 (35.4)	50/115 (43.5)	85/214 (39.7)	0.4
Microbiologic data				
Escherichia coli K1/total (NA = 115)	91/106 (85.8)	120/146 (82.2)	211/252 (83.7)	0.5
Ciprofloxacin susceptibility: R/total (NA = 232)	0/60 (0)	4/75 (5.3)	4/135 (3)	0.1
Nalidixic acid susceptibility: R/total (NA = 252)	2/51 (3.9)	12/64 (18.7)	14/115 (12.2)	0.02*
Ciprofloxacin treatment				
Daily dose (mg/kg per day) (NA = 80)		30 (10–60)		
Delay of adjunct therapy (NA = 23)				
≤2 days after lumbar puncture		158/178 (88.8)		
>2 days after lumbar puncture		20/178 (11.2)		
Duration of treatment (NA = 21)		6 (2–95)		

Data are presented as n/N (%) or median (range). CSF, cerebrospinal fluid; R, resistant; NA, number of missing data.
*Statistically significant difference between ciprofloxacin and no-ciprofloxacin groups.

the 3GC: cefotaxime in 251 (68.4%) of 367, ceftriaxone in 38 (10.4%) of 367, cefotaxime switched to ceftriaxone in 76 (20.7%) of 367 and ceftazidime in two (0.5%) of 367. An aminoglycoside was prescribed for 329 (89.7%) of 367 infants, including 177 (88%) of 201 in the ciprofloxacin group versus 152 (91.6%) of 166 in the non-ciprofloxacin group (p 0.4). In the ciprofloxacin group, 97 (48.3%) of 201 infants presented a sign of initial disease severity versus 73 (44%) of 166 in the nonciprofloxacin group (p 0.4).

In our cohort, 211 (83.7%) of 252 infants had *E. coli* infection with K1 antigen (Table 1). Half of the *E. coli* strains were susceptible to amoxicillin (146/274, 53.3%). Four (3%) of 135 strains tested were resistant to ciprofloxacin.

Ciprofloxacin and neurologic complications

In our cohort, 86 (23.4%) of 367 infants had at least one short-term neurologic complication. The most frequent complications were empyema or pericerebral collection (34/367, 9.3%), hydrocephalus, intraventricular haemorrhage or intracranial hypertension (27/367, 7.4%), and seizures (22/367, 6%), followed by stroke or thrombophlebitis (11/367, 3%), cerebral abscess (5/367, 1.4%) and pachymeningitis or arachnoiditis (4/367, 1.1%) (Fig. 2). Overall, 57 (28.4%) of 201 infants in the ciprofloxacin group had complications versus 29 (17.5%) of 166 without ciprofloxacin.

The following variables were included in the multivariable analysis: CSF/blood glucose ratio <0.1, gestational age at birth, postnatal age at diagnosis and initial severity. In the classic multivariable logistic regression without PS analysis, neurologic complications were associated with treatment with ciprofloxacin (OR = 1.9; 95% CI, 1.1–3.4; p 0.03) (Table 2), initial severity (OR = 7.2; 95% CI, 4.0–12.9; p < 0.001), very late onset disease (OR = 5.5; 95% CI, 1.9–15.7; p 0.001) and CSF/blood glucose ratio <0.1 (OR = 2.4; 95% CI, 1.2–5.1; p 0.018). With PS matching also, ciprofloxacin was associated with neurologic complications (OR = 1.9; 95% CI, 1.1–3.3; p 0.02). The two groups matched by PS were well balanced on all included variables (Supplementary Fig. S1), with standardized differences between −0.1 and 0.1 and all p > 0.05 (Supplementary Table S2).

This association remained significant when considering the impact of the delay of adjunct ciprofloxacin therapy on short-term neurologic outcome. Indeed, 29 (17.5%) of 166 infants without ciprofloxacin treatment presented complications versus 44 (27.8%) of 158 with ciprofloxacin treatment ≤2 days after LP (OR = 2.0; 95% CI, 1.1–3.7 with PS analysis) and versus 33 (26.8%) of 123 with ciprofloxacin treatment ≤1 day after LP (OR = 3.1; 95% CI, 1.4–6.9). The association was not significant when considering infants with ciprofloxacin treatment added at day 0 versus infants without ciprofloxacin treatment (OR = 1.9; 95% CI, 0.7–5.0; p 0.17 with PS analysis on a matched cohort of 102 infants).

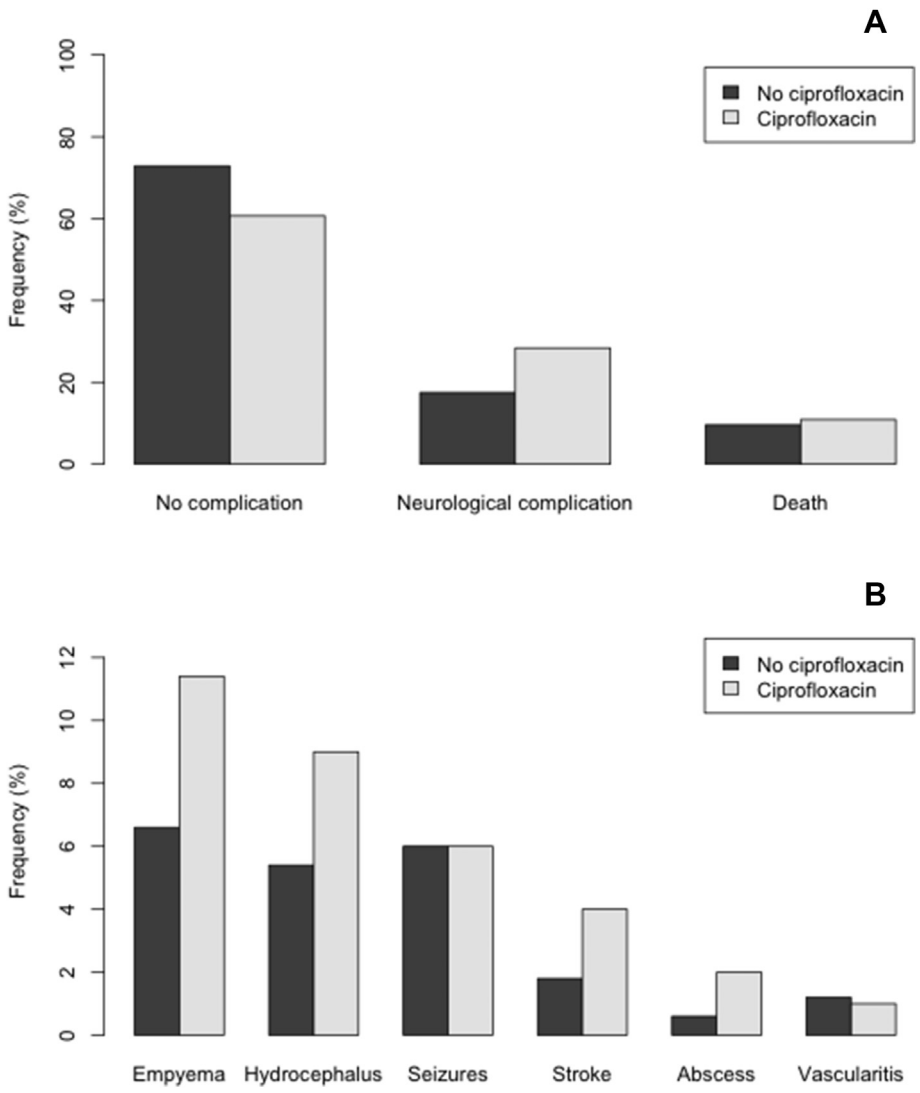

Fig. 2. (A) Percentage of neurologic complications and death and (B) types of neurologic complications in ciprofloxacin and no-ciprofloxacin groups.

Ciprofloxacin and mortality

We recorded 38 (10.4%) of 367 deaths in our cohort, 22 (10.9%) of 201 with ciprofloxacin cotreatment and 16 (9.6%) of 166 without. According to classic multivariable logistic regression, only initial severity was significantly associated with death (OR = 42.5; 95% CI, 5.7–318.4; p < 0.001), along with gestational age at birth <32 weeks (OR = 2.6; 95% CI, 1.0–6.6; p 0.05). The results of PS matching analysis for mortality were consistent with the classic analysis, showing no significant association between ciprofloxacin and mortality (OR = 0.7; 95% CI, 0.3–1.6) (Table 2).

Ciprofloxacin and CSF sterilization

Results of a second LP were available for 255 infants; second LP was performed at a median of 49.5 hours (interquartile range, 48–85.5 hours) after starting antibiotic therapy. Findings for 32 (12.5%) of 255 remained positive despite antimicrobial treatment. Ciprofloxacin and nonciprofloxacin groups did not differ in CSF sterilization failure (11.3% vs 14.3%, OR = 0.5; 95% CI, 0.2–1.4 with PS analysis) (Table 2).

Discussion

This study represents a large cohort of infants with *E. coli* meningitis and assesses the effect of cotreatment with ciprofloxacin on neurologic outcome. Our results suggest that adjunct ciprofloxacin therapy at least does not prevent short-term neurologic complications. Indeed, we found a significant increase in neurologic complications in the ciprofloxacin group (28.4%) versus the non-ciprofloxacin group (17.5%).

Contrary to our results, a previous prospective study including 36 neonates reported better results when ciprofloxacin was added to a 3GC for *E. coli* meningitis. Indeed, 93% of the 15 infants cotreated with ciprofloxacin did not present any short-term complications compared to 43% of the 21 patients without adjunct ciprofloxacin therapy [6,8,24]. This study was not randomized and did not adjust results for gestational age at birth or microbiologic data. Other studies reported on the efficacy of ciprofloxacin for treating meningitis, abscesses and ventriculitis due to *Enterobacteriaceae* in infants and neonates [12,13,25,26], but these studies are case reports or case series.

Despite the theoretical advantages of ciprofloxacin, it did not reduce neurologic complications in our cohort. One explanation

Table 2
Association between ciprofloxacin treatment and outcomes

Outcome	No ciprofloxacin ($n = 166$), n (%)	Ciprofloxacin ($n = 201$), n (%)	Multivariable analysis, OR (95% CI)	PS analysis,[a] OR (95% CI)	p value for PS analysis[a]
Neurologic complications	29 (17.5)	57 (28.4)	1.9 (1.1–3.4)[b]	1.9 (1.1–3.3)	0.02
Death	16 (9.6)	22 (10.9)	1.1 (0.6–2.3)[c]	0.7 (0.3–1.6)	0.4
CSF sterilization failure	15/105 (14.3)	17/150 (11.3)	0.8 (0.4–1.6)[d]	0.5 (0.2–1.4)	0.2
Outcome	No ciprofloxacin ($n = 166$)	Early ciprofloxacin ($n = 158$)	Multivariable analysis, OR (95% CI)	PS analysis,[a] OR (95% CI)	p value for PS analysis[a]
Neurologic complications	29 (17.5)	44 (27.8)	1.9 (1.1–3.5)[e]	2.0 (1.1–3.7)	0.02

Reference group for analysis is nonciprofloxacin group. CI, confidence interval; CSF, cerebrospinal fluid; OR, odds ratio; PS, propensity score.
[a] Matched cohort of 302 patients (151 in each group).
[b] Adjusted for postnatal age, CSF/blood glucose ratio <0.1 and initial severity (329 patients).
[c] Adjusted for gestational age and initial severity (355 patients).
[d] Adjusted for CSF/blood glucose ratio <0.1 (255 patients).
[e] Adjusted on postnatal age, CSF/blood glucose ratio <0.1 and initial severity (294 patients).

might be that neurologic complications occur during the initial invasion phase of the disease, with cell and tissue lesions showing at the very beginning of the disease [6]. In a cohort of adults with suspected meningitis, 24% already had abnormal head computed tomographic scan results before LP, and thus before antimicrobial therapy [27]. Even with early treatment, neurologic complications such as abscesses, empyema or vascular complications might occur in the early hours of the disease. There is no clear explanation for how ciprofloxacin could lead to more neurologic complications. Indeed, a risk of neurotoxicity has been reported with ciprofloxacin but leading to seizures or behavioural disorders, which does not explain the higher number of cases of empyema or hydrocephaly [18,28]. Our study suggests a clear absence of superiority of a combination therapy with ciprofloxacin, but the apparent higher risk might come from residual confounding by indication.

Combination therapies are currently questioned in the literature; in particular aminoglycosides are increasingly being discouraged to treat Gram-negative bacteraemia and sepsis because of the lack of benefit on morbidity and mortality as well as increased rates of nephrotoxicity. Recent studies suggest the lack of superiority of combination therapies for Gram-negative bacteraemia in children. Retrospective studies concluded an absence of advantage of empirical and definitive therapy with β-lactam and aminoglycoside therapy versus β-lactam monotherapy (except to treat multidrug-resistant organisms); they even suggested a decrease in nephrotoxicity with monotherapy [29–31]. These results match those of a meta-analysis of adult patients that discouraged combination therapies (mostly with aminoglycosides) to treat bacteraemia and sepsis [32,33].

The strengths of this study are a large multicentre cohort with population-based data and consistent results from two different methods of analysis (multivariable logistic regression and PS). The findings were consistent for each outcome: short-term neurologic complications, mortality, short-term complications for infants with early ciprofloxacin treatment and rate of CSF sterilization failure, which highlights the lack of benefit of ciprofloxacin for *E. coli* meningitis.

This study has several limitations. First, given the observational design of our study, we cannot prove a causal relation. However, the use of PS analysis, specifically developed to reduce indication bias in therapeutic studies without randomization, mimics randomized studies by matching patients by baseline characteristics [21]. Thus, this statistical method strongly limited the risk of confounding by indication for observational designs. However, despite the large number of cofactors included in the PS analysis, we cannot completely exclude the existence of other hidden factors that could play a role in the confusion. An indication bias cannot be excluded for several reasons. Firstly, data on clinical features of patients such as shock were reported according to clinicians' expertise and not standardized on biomarkers such as blood lactate, leading to subjectivity in the reported data. Secondly, concerning ciprofloxacin susceptibility, probably partly because of the long duration of the study (16 years), we only have data for a third of the cohort, and only four (3%) of 135 of *E. coli* strains were resistant to ciprofloxacin. However, because quinolones are rarely prescribed for paediatric patients, the rate of *E. coli* resistant to ciprofloxacin is generally low. In 2016, according to the European Antimicrobial Resistance Surveillance Network, in the age group of 0 to 4 years, the proportion is 6.5% (https://ecdc.europa.eu/en/about-us/partnerships-and-networks/disease-and-laboratory-networks/ears-net). The third limitation is the missing data on the timeline between adjunct ciprofloxacin therapy and the appearance of neurologic complications, which can bring confusion to the results (there were more infants with complications in the ciprofloxacin group). Among the infants receiving ciprofloxacin, 88.8% received treatment initially and 11.2% secondarily, possibly after the complications had occurred, which increases the number of infants with complications in the ciprofloxacin group. However, when looking at early-treated versus nontreated infants, the association between ciprofloxacin and complications remains. Another limitation is the absence of standardization of neurologic complications' assessment and the absence of data on the timing of onset of complications. Because of the absence of guidelines on this aspect of follow-up, type (head ultrasound, head computed tomography or magnetic resonance imaging) and timing of neuroimaging were performed according to the clinician's decision and to the protocol used at each hospital. We did not have data either on the number of patients who underwent brain imaging or on the type of imaging conducted. Finally, results were not adjusted by centre, which can be a possible confounding factor. However, patients from the same centre did not necessarily receive the same treatment, with a median proportion of ciprofloxacin use per centre of 50% (interquartile range, 33–83%) arguing against a centre effect.

For all these reasons, and because ciprofloxacin treatment was initiated by clinician decision and not by following specific guidelines, we cannot exclude the notion that patients treated with additional ciprofloxacin had more severe features, thus explaining the worse outcome in those patients and explaining why our study did not capture these differences. Nevertheless, these limitations would probably not change the conclusion that adjunctive ciprofloxacin treatment does not appear to be beneficial. Data on long-term outcome and on ciprofloxacin treatment tolerance were not available for our cohort.

Conclusions

This study of a large cohort of infants with *E. coli* meningitis suggests that ciprofloxacin added to a 3GC at least offers no advantage in terms of improving short-term neurologic outcomes and mortality.

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Transparency Declaration

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2018.12.026.

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