Single Oral Dose of Azithromycin Versus 5 Days of Oral Erythromycin or No Antibiotic in Treatment of *Campylobacter* Enterocolitis in Children: A Prospective Randomized Assessor-Blind Study

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ABSTRACT

Objective: To evaluate efficacy of a single oral azithromycin dose versus standard oral erythromycin regimen or no antibiotic for *Campylobacter* enterocolitis in children younger than or equal to 12 years of age.

Patients and Methods: Randomized parallel group assessor-blind trial testing for inequality in efficacy between treatments was done. Patients (N = 120) were enrolled at less than or equal to 48 hours since disease onset to receive erythromycin 50 mg kg^{-1} day^{-1} for 5 days, single-dose azithromycin 20 mg/kg or 30 mg/kg, or no antibiotic (no treatment control) (1 : 1 : 1 : 1). Antibiotics were commenced 8 to 10 hours after enrollment. Patients were assessed at 24-hour intervals for 6 days.

Results: In the intent-to-treat analysis, *Campylobacter* eradication was achieved in 20 of 30 controls and in all of the patients treated with antibiotic. Incidence of clinical cure during the observed period was 15 of 30 in the control, 14 of 30 in the erythromycin, 20 of 30 in the lower, and 25 of 30 in the higher azithromycin dose group. With adjustment for age, sex, baseline disease severity, and disease duration before enrollment, only azithromycin 30 mg/kg was superior to no treatment: incidence ratio (IR) 1.76 (95% confidence interval [CI] 1.11–2.87). It was also superior to erythromycin (IR 1.80, 97.5% CI 1.13–2.84). Regarding time to clinical cure, only azithromycin 30 mg/kg was superior to no treatment (adjusted hazard ratio [HR] 4.90, 95% CI 2.44–9.84). It was also superior to erythromycin (HR 4.17, 97.5% CI 1.91–9.09). All treatments were well tolerated.

Conclusions: The administration of single oral dose of azithromycin 30 mg/kg early after disease onset effectively eradicates the pathogen and accelerates clinical cure in childhood *Campylobacter* enterocolitis. It is clinically superior to an early commenced 5-day erythromycin regimen, which apparently conveys no clinically relevant benefit over no antibiotic treatment.

Key Words: azithromycin, *campylobacter* enterocolitis, children, erythromycin

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Campylobacter enterocolitis is the most frequent form of acute bacterial diarrhea affecting humans, particularly children and young adults (1). Although several *Campylobacter* spp. cause diarrhea, *C jejuni* accounts for more than 90% of the infections, whereas *C coli* accounts for most of the remaining cases (1). Typically, *C jejuni/coli* enterocolitis is characterized by diarrhea, fever, and abdominal cramps, but symptoms are not so distinctive as to allow for a straightforward differentiation from enterocolitis caused by other organisms (2). Generally, it has a good prognosis, although postinfectious sequels are possible and Guillain-Barré syndrome is the most serious secondary complication (3,4).

In most cases, *Campylobacter* enterocolitis does not require antimicrobial treatment because it is a self-limiting and mild disease of short duration. However, antibiotic therapy is indicated in children presenting with persistent fever, bloody diarrhea, more than 8 bowel movements per day or with a significant volume loss, or, when history of diarrhea exceeds 7 days (1). HIV-positive or immunocompromised children should also receive antimicrobial treatment (5–7). In such cases, antibiotics could reduce disease duration, enable a faster recovery, and shorten the period of germ carrying. The spectrum of antibiotic agents that can be used for treatment of *C jejuni/coli* enterocolitis in childhood is limited and erythromycin is usually a drug of choice (8). Erythromycin has a good safety profile, although gastric distress occurs in a significant proportion of patients (9). The use of erythromycin also carries a risk of drug interactions due to its cytochrome P450 inhibitory activity (9), and frequent daily dosing makes it less popular for use in children. In addition, increasing emergence of erythromycin resistance among isolates of *C jejuni*/*coli* has prompted a search for alternative macrolide derivatives effective against *Campylobacter* spp. (10). Azithromycin is active in vitro against *Campylobacter* spp. and seems to be better tolerated than erythromycin (9,11,12). Its specific pharmacokinetic profile enables single-dose treatment and it appears devoid of major drug interactions at the cytochrome P450 level (9,13–15). To our knowledge, clinical experience with azithromycin in the treatment of *Campylobacter* enterocolitis has been scarce and related primarily to adults, in whom it appears comparable or superior to ciprofloxacin or levofloxacin in bacteriological and clinical terms (16,17). Therefore, the present trial specifically aimed to evaluate efficacy and tolerability of a single oral azithromycin administration early in the course of the disease through a comparison with a standard 5-day erythromycin regimen or no antibiotic in treatment of *Campylobacter* enterocolitis in children younger than or equal to 12 years of age.

PATIENTS AND METHODS

General Design

This was a single-center, randomized no treatment-controlled, parallel group, assessor-blind trial with a primary objective to test for inequality in efficacy between treatments (null hypothesis = no difference). Secondary objective was to assess safety of the administered treatments. Children with a proven *C jejuni/coli* enterocolitis were randomized to 1 of the 4 treatment arms (1:1:1:1; permutated block randomization, recruiter blinded to the randomization list): no antibiotic (no treatment-control); erythromycin 50 mg kg^{-1} day^{-1} orally (p.o. [per os]) for 5 days, divided in 3 daily doses (erythromycin syrup 400 mg/5 mL, Genericon Pharma, Austria); azithromycin 20 mg/kg p.o. as a single dose; and azithromycin 30 mg/kg p.o. as a single dose (Sumamed syrup forte 200 mg/mL or 250-mg capsules [Pliva, Zagreb, Croatia]). Supportive measures (parenteral rehydration, electrolyte imbalance correction, and oral paracetamol if body temperature was more than 38.5°C) were provided as needed to all patients. For the no treatment-control patients, rescue antibiotic treatment was anticipated in the case of disease deterioration; however, no such cases occurred. The study was approved by the institutional ethics committee.

Inclusion/Exclusion Criteria

Candidates for inclusion were children younger than or equal to 12 years of age presenting with symptoms of acute enterocolitis suspected to be of bacterial origin and referring to our outpatient department within 48 hours since symptom onset. Inclusion criteria were informed consent (parents/guardians); bacteriologically confirmed *C jejuni/coli* infection (enzyme immunoassay [EIA], in agreement with a standard stool culture; see below). Exclusion criteria were antibiotic treatment within 15 days before enrollment; known hypersensitivity to macrolides/azalides; any form of immunodeficiency; and concomitant treatment with drugs known for their potential for clinically relevant interactions with erythromycin/azithromycin.

Study Flow

At the screening visit (time 0, day 1) (Fig. 1), a detailed medical history, physical examination, and blood, urine and stool samples were taken. Patients were hospitalized and supportive measures were commenced. Symptoms relevant for *Campylobacter* enterocolitis (2,18)—body temperature, number of loose/watery stools within 24 hours, presence of blood and/or mucus in the stool, colicky pain, vomiting and food intake within 24 hours, and dehydration—were assessed using a scoring system modified after Leibovitz et al (19) that assigned points to discrete variables (eg, mucus in stool: no [0] or yes [1]; vomiting within 24 hours: no [0], 1–2 times [1], more than or equal to 3 times [2]; blood in stool: no [0], traces microscopically, [1], and macroscopically visible blood (3), etc [Table 1]) to produce a symptom score as an overall measure of "baseline disease severity." This value was used as a covariate in the adjusted analysis of efficacy outcomes (see below).

Approximately 8 hours later (time +8 hours, day 1) (Fig. 1), when the laboratory tests were completed and based on a positive EIA result (ProSpecT *Campylobacter* enzyme immunoassay [Alexon-Trend Inc, Ramsey, MN]) patients were randomized and the assigned treatment was commenced. ProSpecT *Campylobacter* assay has excellent diagnostic properties with high sensitivity and specificity but false-positive results are possible (20–23). Therefore, the final inclusion/exclusion decision was made after obtaining the stool culture results (48–72 hours after the screening visit). Although a positive EIA test and a negative culture can be found in *Campylobacter* infections, in the case of a negative culture the EIA result was considered false-positive (20–23). Such patients continued treatment but were withdrawn from the study. Because proportion of false-positive results with ProSpecT can amount to

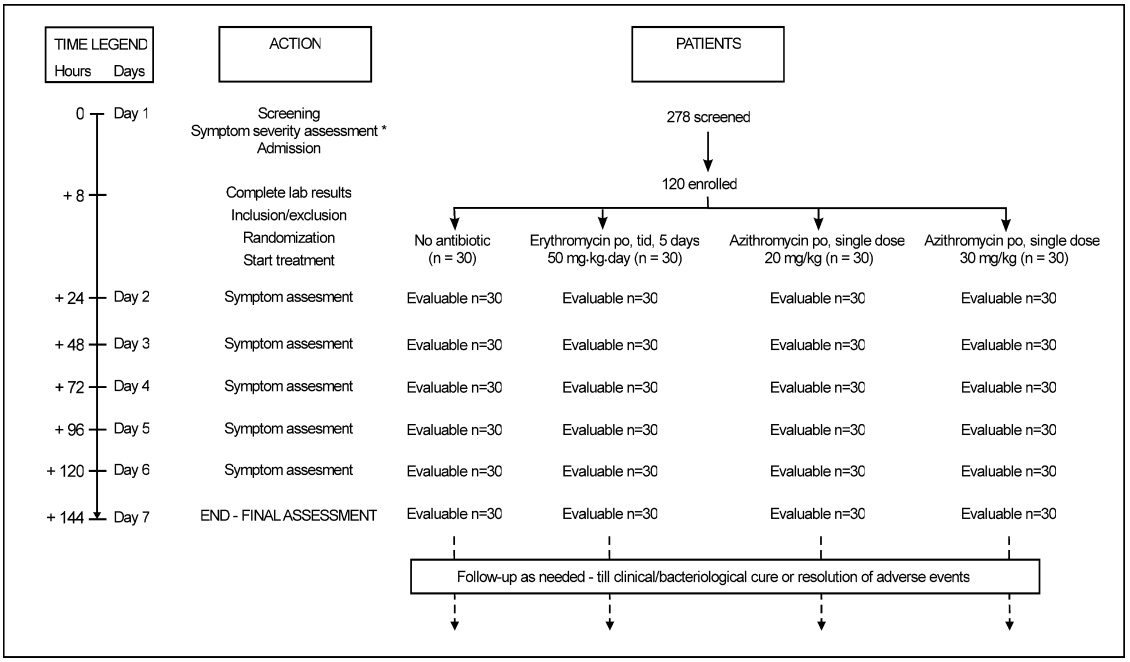

FIGURE 1. Study outline and patient flow. p.o = per os; t.i.d = thrice daily. *Symptom severity assessment was based on a scoring system modified after Leibovitz et al (19) and focused on symptoms listed in Table 1 (see Patients and Methods).

TABLE 1. Baseline patient characteristics (counts, median [quartiles] or mean ± SD)

	No antibiotic (control)	Erythromycin $5 \times 50\,mg\,kg^{-1}\,day^{-1}$	Azithromycin $1 \times 20\,mg/kg$	Azithromycin $1 \times 30\,mg/kg$
No. (male/female)	30 (18/12)	30 (18/12)	30 (17/13)	30 (17/13)
Age, y	2.1 (1.3–4.3)	1.5 (1.0–3.8)	1.1 (0.8–3.6)	1.2 (0.7–2.3)
Time lag onset–screening, h: ≤24 or 25–48	13/17	11/19	13/17	12/18
C-reactive protein, mg/L	12.0 (9.5–16.0)	14.0 (7.8–17.0)	12.0 (8.0–10.0)	10.0 (6.0–12.5)
Erythrocyte sedimentation rate, 1st h	15 (11–20)	14 (8–18)	16 (13.5–18.5)	18 (13.5–22)
Hemoglobin, g/dL	11.56 ± 1.14	11.71 ± 1.20	11.73 ± 1.03	11.45 ± 1.12
WBC count, $\times 10^9$	11.3 ± 3.5	11.9 ± 3.4	11.7 ± 2.9	11.4 ± 3.8
AST, U/L	18.0 (15.8–22.0)	16.5 (14.0–18.3)	16.5 (14.0–18.3)	18.0 (16.0–22.5)
Bilirubin, μmol/L	10.63 ± 2.40	9.20 ± 1.56	9.43 ± 1.38	8.97 ± 2.24
Urea, mmol/L	4.9 (4.6–5.6)	5.4 (5.1–6.3)	5.4 (4.3–6.4)	5.3 (4.7–5.9)
Distribution of patients by symptoms*				
Rectal temperature, °C: <38.0 or ≥38.0	22/8	23/7	21/9	24/6
No. of watery stools within 24 h: 1–3/4–5/≥6	5/24/1	1/28/1	3/26/1	5/24/1
Blood in stool: no/trace/visible	16/11/3	13/15/2	10/18/2	16/11/3
Mucus in stool: no/yes	2/28	1/29	0/30	2/28
No. of regurgitations within 24 h: 0/1–2/≥3	27/3/0	19/11/0	21/9/0	23/7/0
Food intake within 24 h: normal/low/none	0/14/16	0/15/15	0/20/10	0/9/21
Colicky pain within 24 h: no/yes	0/30	5/25	3/27	3/27
Dehydration: no/moderate/severe	0/30/0	0/30/0	0/30/0	0/30/0
Total symptom score*	7 (7–8)	7.5 (7–8)	7.5 (7–8)	7.5 (7–8)

* Symptoms relevant for *Campylobacter* enterocolitis (2,18) were assessed using scoring modified after Leibovitz et al (19) (see Patients and Methods) to produce a total symptom score as a measure of "baseline disease severity" (minimum score = 0, maximum = 15). AST = asparagine amino-transferase; SD = standard deviation; WBC = white blood cell.

up to around 10% (20–23) randomization list contained 136 codes. The enrollment continued until 30 subjects per group were randomized. A total of 7 subjects with discordant EIA culture results were observed (3 initially randomized to no treatment-control, 2 to lower azithromycin dose, and 1 to the higher azithromycin dose and erythromycin group each). Patients were assessed for clinical symptoms in regular 24-hour intervals until 144 hours after the screening visit (day 7). After that, they were followed up on an as needed basis (Fig. 1).

Patient Assessment

All patient assessments were done by a physician unaware of the assigned treatment. Standard laboratory tests (hematology, blood, and urine chemistry) were performed at the screening visit and on days 4 and 7. Stool was analyzed for the presence of blood and mucus daily. For bacteriological analysis, fresh samples (no transport media) were sent to the microbiology laboratory within 2 hours and were analyzed using ProSpecT EIA (according to manufacturer's instructions) (day 1) and were also plated on a standard *Campylobacter* medium (MacConkey, XLD, SS agar, selenite enrichment broth) (day 1 and end of study).

Endpoints

Two primary endpoints were bacteriological and clinical cure rates achieved during the 144-hour study period. A patient was considered clinically cured when the following was established at a regular visit: no loose/watery stools, mucus or blood in stool, colicky abdominal pain or vomiting within the previous 24 hours, afebrile, or hydrated with normal food intake; "low" food intake was the only symptom on 2 consecutive assessments 24 hours apart. Secondary endpoints were time (in hours) since symptom onset until the clinical cure (symptom onset-to-screening visit + screen-screening-to-cure; patients still not attaining clinical cure by the end of the study were considered to be "censored data") and safety outcomes (adverse events and safety laboratory parameters).

Sample Size and Power Considerations

Sample size considerations were based on the assumed χ^2 statistics for clinical cure rate in a 2 (cure yes/no) × 4 (treatments) contingency table. We expected around 45% of the patients to attain clinical cure without antibiotic treatment during the observed period. We considered that a meaningful antibiotic treatment would need to increase the cure rate by at least 30%, that is, to 75%, an effect size of 0.306. In a contingency table with 3 degrees of freedom, 116 patients are needed to obtain more than 80% power to detect this effect size at a 2-sided 0.05 α level. Therefore, 120 patients were enrolled, 30 to each treatment arm.

Data Analysis

A blinded data review was performed by a person not involved in the clinical part of the study. Because all of the enrolled patients completed the study with regular treatment delivery and assessments (Fig. 1), the intent-to-treat and per-protocol datasets were identical. Incidence of clinically cured patients was analyzed using a modified Poisson regression with robust error variance (24,25) to obtain unadjusted or adjusted (age, sex, time elapsed between disease onset and the screening visit, and baseline disease severity) IRs. Data on time to clinical cure were summarized by a Kaplan-Meier cumulative hazard curve and were analyzed by proportional hazard regression to obtain HRs, unadjusted or

adjusted for the same covariates as in the case of clinical cure rates. We used Statistical Analysis System (SAS) for Windows 9.1 software (SAS Inc, Cary, NC).

RESULTS

Patient Characteristics

All of the infections were sporadic and individual, not related to outbreaks. Overall, 66 patients (55%) came from a rural environment, 12 (10%) had eaten home-bred poultry, 6 (5%) had drunk raw milk, and 7 (6%) had contacts with pets (mostly dogs, none of which seemed ill). All initial *Campylobacter* isolates (106 [88.3%] *C jejuni*, 14 *C coli*) were sensitive to azithromycin and erythromycin in vitro (12 resistant to ciprofloxacin). In respect to demographics and baseline disease severity (individual symptoms and total symptom score), the enrolled patients were essentially similar across the 4 groups (Table 1). Parenteral rehydration was commenced after admission to all patients, whereas only a few patients overall (within the first 48 hours) received oral paracetamol.

Efficacy

By the end of the study, bacteriological cure was achieved in 20 of 30 (66.6%) controls and in all of the patients treated with antibiotic. Incidence of clinically cured patients during the 144-hour study period was 15 of 30 (50%) in the control and 14 of 30 (46.6%), 20 of 30 (66.6%) and 25 of 30 (83.3%) in the erythromycin, azithromycin 20 mg/kg, and azithromycin 30 mg/kg groups, respectively. Only azithromycin 30 mg/kg was in this respect superior to no treatment: unadjusted IR 1.67 ($P = 0.011$), adjusted IR 1.76 ($P = 0.004$) (Fig. 2). Azithromycin 30 mg/kg was also superior to erythromycin: unadjusted IR 1.79 ($P = 0.006$), adjusted IR 1.80 ($P = 0.004$) (Fig. 2). Attainment of clinical cure appeared considerably accelerated for the azithromycin 30 mg/kg group (Fig. 3). Analysis indicated no difference between the erythromycin and the control groups and a markedly higher hazard of clinical cure attainment for the azithromycin 30 mg/kg group versus control (unadjusted HR 3.80, adjusted HR 4.90, both $P < 0.001$) and versus erythromycin (unadjusted HR 3.72, adjusted HR 4.17, both $P < 0.001$) (Fig. 3).

Safety

The treatments were comparably well tolerated. Only 2 adverse events were assessed as ''possibly treatment related'': 1 patient in the erythromycin group experienced moderate upper abdominal pain and vomited on the fifth day of treatment, which resolved within the next 36 hours; 1 patient treated with 30 mg/kg azithromycin was leukopenic at study end (leukocyte count 4.6×10^9 with 8% neutrophils), but the leukocyte count was normal 7 days later. No statistically significant differences among treatments were detected regarding the hematological and chemistry laboratory test results over time.

Poststudy Period

For the control patients who were not bacteriologically cured during the study (n = 10), stool tested microbiologically negative on day 7 (n = 4) or day 15 (n = 6) after the end of the study. Patients who were not clinically cured during the study were discharged as ''cured'' as follows: in the control (n = 15) and erythromycin (n = 16) groups, during 1 to 7 days after the formal study end; in the azithromycin 20 mg/kg group (n = 10) during 1 to 5 days after the study end, and in the azithromycin 30 mg/kg group (n = 5) within 48 hours after the study.

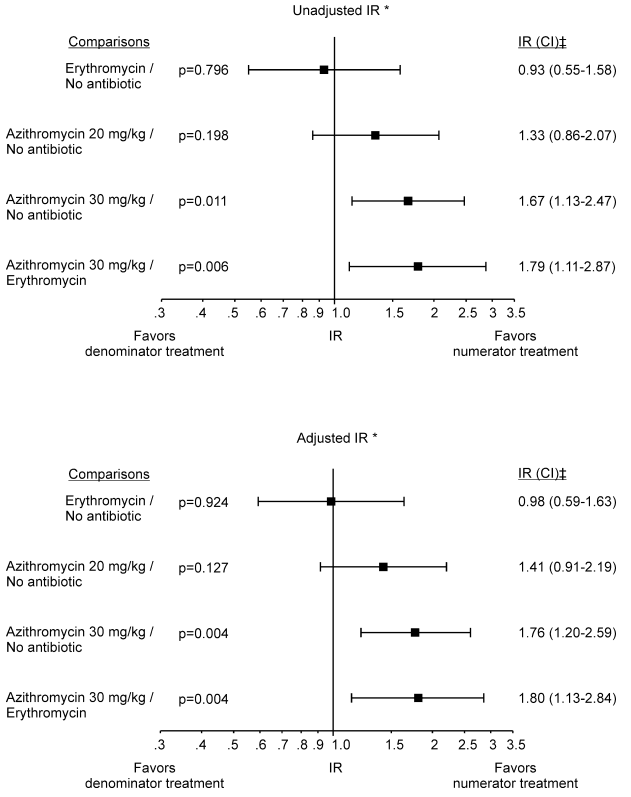

FIGURE 2. Analysis of incidence of clinical cures during the study. Data are presented as IR (incidence ratios [squares]) with CI (confidence intervals [horizontal bars]). *IRs were obtained without (unadjusted) or with adjustment for age, sex, baseline symptom score (disease severity), and time elapsed since disease onset and enrollment. ‡No antibiotic control was the reference group in the regression analysis, hence IRs for antibiotic treatments vs no antibiotic are given with 95% CI, whereas an additional estimate for azythromycin 30 mg/kg vs erythromycin is given with a 97.5% CI.

DISCUSSION

Campylobacter enterocolitis does not routinely require antimicrobial treatment, but antibiotics are indicated in immunocompromised and other high-risk patients or in severe forms of the disease (1,5–7). A recent meta-analysis concluded that antibiotics, especially when started within the first 3 days after disease onset, could shorten the duration of intestinal symptoms (26). In children, erythromycin (for 5 days) is considered a standard treatment, although there are certain limitations to its use (eg, emerging microbial resistance, potential drug interactions) (9,10) and although evidence of its efficacy has not been overwhelming. In the first-ever randomized controlled trial of erythromycin for *Campylobacter* enterocolitis (adults and children, erythromycin n = 15, placebo n = 14), 5-day erythromycin treatment introduced at 5 to 6 days since symptom onset eradicated *C jejuni* from the stool, but it did not alter the natural course of the disease (8). Three subsequent trials restricted to children (overall 42 on erythromycin,

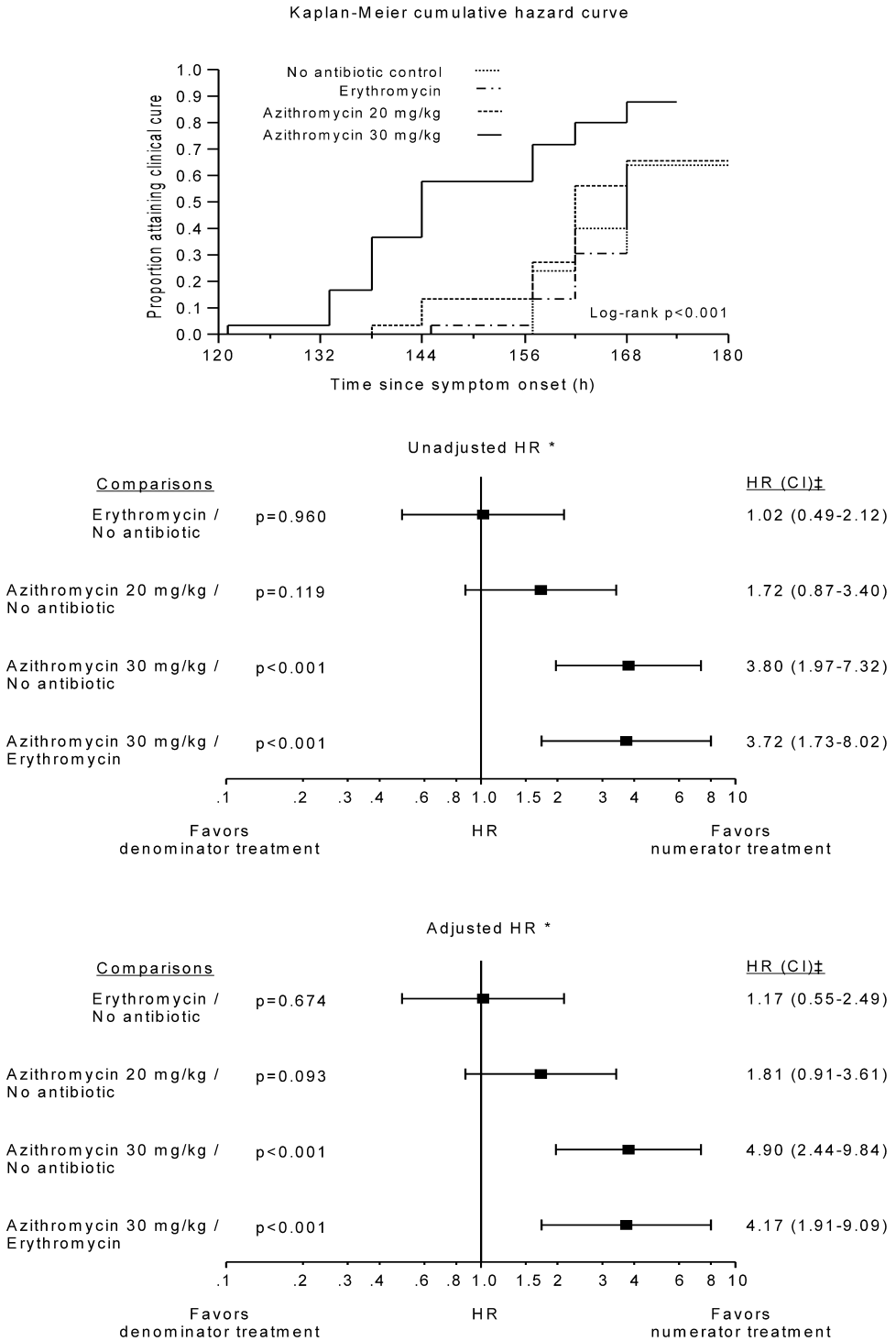

FIGURE 3. Summary and analysis of ''time-to-clinical cure'' data. Data are summarized as a Kaplan-Meier cumulative hazard curve. Analysis results are presented as HR (hazard ratio [squares]) with CI (confidence interval [horizontal bars]). *HRs were obtained without (unadjusted) or with adjustment for age, sex, baseline symptom score (disease severity), and time elapsed since disease onset and enrollment. ‡No antibiotic control was the reference group in the regression analysis, hence HRs for antibiotic treatments vs no antibiotic are given with 95% CI, whereas an additional estimate for azythromycin 30 mg/kg vs erythromycin is given with a 97.5% CI.

38 on placebo or no treatment) (27–29) consistently showed shorter bacterial shedding with erythromycin. Two studies failed to demonstrate any clinical benefit of erythromycin when introduced 4 days after disease onset or later (27,28), whereas the third study with earlier treatment commencement indicated a benefit of earlier stool normalization: after 5 days, stool was normalized in 15 of 16 patients in the erythromycin group and in 6 of 12 in the placebo group; time since treatment start to stool normalization was on average 1.8 days shorter with erythromycin (29). Our objective was to evaluate the efficacy of azithromycin delivered as a single oral dose (20 or 30 mg/kg) early in the course of the disease (within the first 60 hours) through a comparison with no antibiotic and an early commenced standard 5-day erythromycin regimen. Distinct from earlier studies (27–29), we defined clinical cure, that is, lack of any disease symptoms (2,18) and not only stool normalization as an outcome of interest. We reasoned that a meaningful treatment would have to accelerate the disease resolution and have ''early'' effects. For this reason and to preserve ''assay sensitivity,'' study duration was limited to 144 hours after treatment commencement (corresponds to 5 days of erythromycin + 24 hours to the final assessment). Under these conditions, all antibiotic treatments (expectedly) resulted in a prompt *Campyolobacter* eradication, but differed considerably in clinical terms. Considering either the attained clinical cure rates during the observed period or time needed to attain clinical cure, erythromycin apparently conveyed no relevant benefit over no (antibiotic) treatment. As with any trial testing for inequality, a failure to reject a null hypothesis may be difficult to interpret because it could be simply due to inadequate power. Indeed, the present study was powered to detect a rather large treatment effect (an absolute difference in clinical cure rate of 30%). However, it is not simply the lack of statistically significant difference between the 2 groups that suggests a true lack of relevant clinical difference between erythromycin and no treatment, rather it is a practically nonexisting erythromycin treatment effect (IR and HR point estimates consistently close to 1.0). Even if, as suggested by other studies (29), early commenced erythromycin accelerated stool normalization for 1 or 2 days, the benefit is rather modest and of questionable practical relevance. On the other hand, a single dose of 30 mg/kg azithromycin was clearly statistically superior to no treatment or to erythromycin regarding efficacy with, at the same time, comparable tolerability. In our opinion, the observed differences should be considered practically relevant. Due to a relatively small sample size (although this is, to our knowledge, the largest single trial specifically evaluating antibiotic treatments for *Campylobacter* enterocolitis in children so far), the effect estimates have relatively wide confidence intervals, but point estimates suggest an absolute difference in proportion of clinical cures of around 33% and 36% versus no treatment or versus erythromycin during the 6 days after administration (ie, during the first 7–8 days of the disease). With adjustment for covariates, this ''translates'' into around 80% higher probability of attaining clinical cure within the short period of time since disease onset. Analysis of ''time-to-event'' data specifically points out superiority of azithromycin 30 mg/kg versus no treatment or versus erythromycin in terms of acceleration of clinical symptoms resolution, suggesting a 4 to 5 times greater probability of attaining clinical cure during any subsequent 24-hour period within the first 6 days since treatment commencement. Because the trial was conducted at a single center with a limited number of otherwise healthy children (ie, no immune-suppressed patients were included), present observations are of limited generalizability. On the other hand, we believe that the methodology used has ascertained a fair level of internal validity despite a lack of a placebo control and double blinding and that the present estimates are reasonably accurate and unbiased.

In practice, the use of antibiotics for childhood *Campylobacter* enterocolitis is determined by several factors: the disease is typically benign and spontaneously resolving, both clinically and microbiologically; due to the time needed for standard microbiological diagnostics, specific treatment cannot start before 3 to 4 or more days after disease onset; under such conditions, antibiotics are unlikely to convey a clinical benefit and shorter microbial shedding may not be particularly relevant, except in the case of outbreaks (eg, in day care centers or schools); uncritical use of antibiotics is likely to result in increased microbial resistance; and antimicrobial therapy is most effective when started shortly after disease onset (1,5–7,26). Therefore, the key practical problem is a quick identification of patients in whom benefits of antibiotic treatment are likely to outweigh the risks. The present data suggest that a single oral dose of azithromycin 30 mg/kg delivered early in the disease course is likely to provide a considerable clinical benefit and that it is clinically superior to an early commenced 5-day erythromycin regimen.

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