OBSTETRICS

Azithromycin vs erythromycin for the management of preterm premature rupture of membranes

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BACKGROUND: Preterm premature rupture of membranes complicates 2−3% of pregnancies. Many institutions have advocated for the use of azithromycin instead of erythromycin. This is secondary to national shortages of erythromycin, ease of administration, better side effect profile, and decreased cost of azithromycin as compared with erythromycin.

OBJECTIVE: The objective of the study was to evaluate whether there are differences in the latency from preterm premature rupture of membranes to delivery in patients treated with different dosing regimens of azithromycin vs erythromycin.

STUDY DESIGN: This is a multicenter, retrospective cohort of women with singleton pregnancies with confirmed rupture of membranes between 23^0 and 33^6 weeks from January 2010 to June 2015. Patients were excluded if there was a contraindication to expectant management of preterm premature rupture of membranes. Patients received 1 of 4 antibiotic regimens: (1) azithromycin 1000 mg per os once (azithromycin 1 day group); (2) azithromycin 500 mg per os once, followed by azithromycin 250 mg per os daily for 4 days (azithromycin 5 day group); (3) azithromycin 500 mg intravenously for 2 days, followed by azithromycin 500 mg per os daily for 5 days (azithromycin 7 day group); or (4) erythromycin intravenously for 2 days followed by erythromycin per os for 5 days (erythromycin group). The choice of macrolide was based on institutional policy and/or availability of antibiotics at the time of admission. In addition, all patients received ampicillin intravenously for 2 days followed by amoxicillin per os for 5 days. Primary outcome was latency from diagnosis of rupture of membranes to delivery. Secondary outcomes included clinical and histopathological chorioamnionitis and neonatal outcomes.

RESULTS: Four hundred fifty-three patients who met inclusion criteria were identified. Seventy-eight patients received azithromycin for 1 day, 191 patients received azithromycin for 5 days, 52 patients received azithromycin for 7 days, and 132 patients received erythromycin. Women who received the 5 day regimen were younger and less likely to be non-African American, have hypertension, have sexually transmitted infection, or experienced substance abuse. There was no statistical difference in median latency time of azithromycin 1 day (4.9 days, 95% confidence interval, 3.3−6.4), azithromycin 5 days (5.0, 95% confidence interval, 3.9−6.1), or azithromycin 7 days (4.9 days, 95% confidence interval, 2.8−7.0) when compared with erythromycin (5.1 days, 95% confidence interval, 3.9−6.4) after adjusting for demographic variables ($P = .99$). Clinical chorioamnionitis was not different between groups in the adjusted model. Respiratory distress syndrome was increased in the azithromycin 5 day group vs azithromycin 1 day vs erythromycin (44% vs. 29% and 29%, $P = .005$, respectively).

CONCLUSION: There was no difference in latency to delivery, incidence of chorioamnionitis, or neonatal outcomes when comparing different dosing regimens of the azithromycin with erythromycin, with the exception of respiratory distress syndrome being more common in the 5 day azithromycin group. Azithromycin could be considered as an alternative to erythromycin in the expectant management of preterm premature rupture of membranes if erythromycin is unavailable or contraindicated. There appears to be no additional benefit to an extended course of azithromycin beyond the single-day dosing, but final recommendations on dosing strategies should rely on clinical trials.

Key words: antibiotic, azithromycin, erythromycin, latency, preterm, rupture of membranes

Preterm premature rupture of membranes (PPROM) complicates 2−3% of pregnancies and accounts for 30% of neonatal morbidity and mortality among premature gestations.[1,2] Much of the morbidity is due to imminent delivery and inherent prematurity but is also attributable to the presence of intrauterine infection and inflammation.[3−5]

Current standard of care practice between 24 and 34 weeks is expectant management with inpatient hospital admission, frequent fetal monitoring, assessment for signs of infection, antenatal corticosteroid administration, and administration of antibiotics to prolong latency between PPROM to delivery. Given the wide range of possible causative organisms and the often polymicrobial nature of infectious PPROM, the American College of Obstetricians and Gynecologists recommends broad-spectrum antibiotics.[6]

Many antibiotic regimens have been evaluated in prolonging latency to delivery.[7,8] The most commonly used regimen, supported by the American College of Obstetricians and Gynecologists, comes from the *Eunice Kennedy Shriver* National Institutes of Child Health and Human Development Maternal-Fetal Medicine Units Network trial using intravenous erythromycin and ampicillin for 2 days followed by an oral regimen of erythromycin base and amoxicillin for 5 days.

This regimen showed prolonged latency to delivery and a decrease in the incidence of chorioamnionitis and fetal and neonatal complications because of prematurity compared with placebo.[9] The ORACLE trial showed that the macrolide component of treatment

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AJOG at a Glance

Why was this study conducted?

aThis multicentered retrospective study addressed the limited information regarding pregnancy outcomes when azithromycin in varying dosages is used for latency antibiotics in the setting of preterm rupture of membranes.

Key findings

There was no difference in latency to delivery, incidence of chorioamnionitis, or neonatal outcomes when comparing different dosing regimens of azithromycin with erythromycin.

What does this add to what is known?

Several commonly used doses of azithromycin were studied, which was not detailed in prior publications.

improved neonatal outcomes not just by increasing latency but also by specifically reducing the fetal exposure to intrauterine infection and inflammation.[8]

Recently many institutions have advocated for the use of azithromycin instead of erythromycin. This is secondary to national shortages of erythromycin, ease of administration, better side effect profile, and decreased cost of azithromycin compared with erythromycin. However, there are scant data comparing these 2 antibiotics.[10–12] To our knowledge there are no randomized studies comparing azithromycin vs erythromycin or different dosing regimens of azithromycin in the management of PPROM.

The objective of this study was to evaluate differences in latency to delivery and delivery and neonatal outcomes when using different dosing strategies of azithromycin when compared with erythromycin.

Materials and Methods

This study was approved by the institutional review boards at Thomas Jefferson University Hospitals, Christiana Care Health System, Baystate Medical Center, and Abington Hospital. We performed a retrospective chart review of all women admitted with a diagnosis of PPROM from Jan. 1, 2010, to June 2015, to these 4 institutions.

Patients were identified using ICD-9 codes as well as hospital delivery records in an effort to capture all possible PPROM diagnoses. Women who were between 18 and 50 years of age, with a confirmed diagnosis of PPROM between 23 0/7 and 33 6/7 weeks of gestation were included.

Patients with previable rupture of membranes (<23 0/7 weeks of gestation), multiple gestation, or macrolide allergy were excluded. Patients with a contraindication to expectant management of PPROM at the time of diagnosis, such as concurrent preterm labor, placental abruption, chorioamnionitis, or nonreassuring fetal testing were excluded. Patients who received combination macrolide therapy were also excluded.

Demographic information was recorded for each patient as well as maternal comorbidities and risk factors for PPROM and preterm birth. The diagnosis of PPROM was made via sterile speculum examination and presence of pooling, positive nitrazine, and ferning. Latency was defined as the time measured in hours and days from the diagnosis of PPROM to the time of delivery.

The antenatal course was reviewed for date and time of delivery, route of delivery, indication for delivery, and presence or absence of chorioamnionitis. The diagnosis of clinical chorioamnionitis was assigned based on documentation in the medical record and was based on the presence of maternal fever (>100.4°F) in addition to fetal tachycardia (>160 bpm in more than 10 minutes), elevated maternal serum white blood cell count (>14,000 c/mm), or purulent fluid from the cervical os.[13] Histopathological chorioamnionitis was diagnosed based on the placental pathology report.

The choice of antibiotic regimen administered was made by the provider based on availability of antibiotics at the time of admission and the current institutional policies. All patients received ampicillin 2 g intravenously (IV) every 6 hours for 2 days followed by amoxicillin 250 mg orally every 8 hours for 5 days.

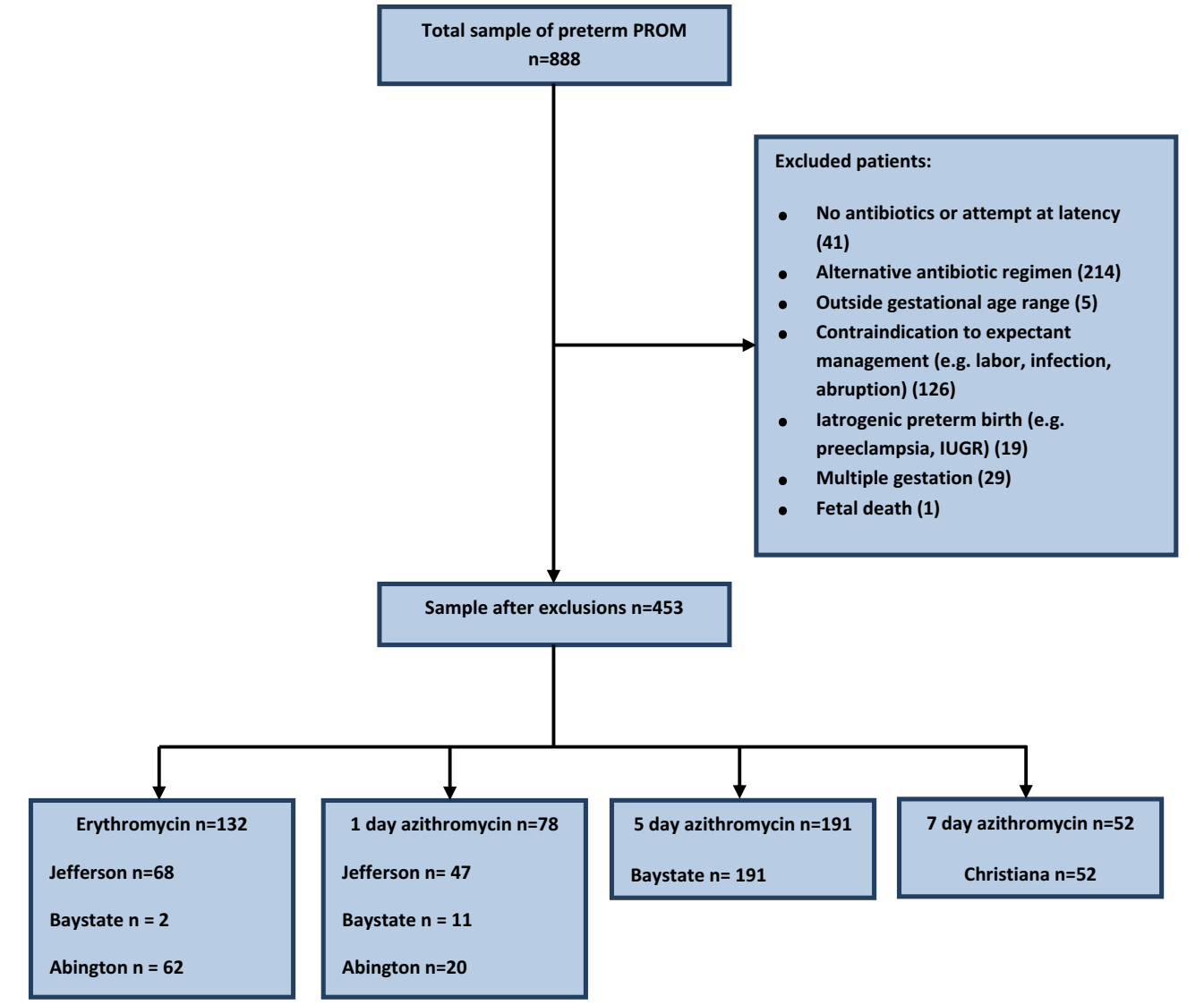
Patients received 1 of the following 4 antibiotic regimens: (1) azithromycin 1000 mg per os (PO) once (azithromycin 1 day group), (2) azithromycin 500 mg PO once, followed by azithromycin 250 mg PO daily for 4 days (azithromycin 5 day group), (3) azithromycin 500 mg IV for 2 days, followed by azithromycin 500 mg PO daily for 5 days (azithromycin 7 day group), or (4) erythromycin 250 mg every 6 hours IV for 2 days followed by erythromycin 333 mg PO every 8 hours for 5 days (erythromycin group).

The specific antibiotic regimen, including which macrolide was used and the duration, timing, and route of administration, was recorded. Thomas Jefferson Hospital used both erythromycin and the 1 day course of azithromycin. Christiana Care Health System used only a 7 day azithromycin regimen. Abington Hospital used both erythromycin and the 1 day azithromycin regimen. Baystate Medical Center used erythromycin and 1 day and 5 day courses of azithromycin because institutional guidelines changed during the study period.

Matching neonatal records were reviewed for birthweight, 5 minute Apgar score, neonatal intensive care unit length of stay (LOS), and intrauterine fetal demise. Additionally, neonatal outcomes of respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), early sepsis, and death were recorded.

The primary outcome of this study was the latency from diagnosis of PPROM to delivery. Secondary outcomes included gestational age at delivery in weeks, clinical and histological chorioamnionitis, vaginal delivery, stillbirth, and neonatal outcomes (LOS,

FIGURE 1
Inclusion and exclusion criteria flow diagram



PROM, premature rupture of membranes; IUGR, intrauterine growth restriction

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RDS, NEC, IVH, early sepsis, 5 minute Apgar score <7, and neonatal death).

Statistical methods

For univariable statistics, the 4 treatments were compared using a Fisher exact test for categorical variables and a 1-way analysis of variance for normally distributed continuous variables. Because the distributions of latency, gestational age at delivery, and LOS were skewed, the Kruskal-Wallis test was used to compare the treatment regimens.

For all univariable comparisons, if the omnibus test was significant, pairwise post hoc testing of treatment regimens was conducted using Bonferroni's adjustment to the *P* value. For multivariable analyses of latency to delivery, gestational age at delivery, and LOS, we used quantile regression to accommodate the skewed distributions.[14] We estimated the median of each distribution as a function of the covariates in the model.

Multivariable analysis of clinical chorioamnionitis was accomplished using logistic regression. For all multivariable models, the 4 treatment regimens were represented with 3 indicator variables, using erythromycin as the reference group. Estimates of treatment effect were adjusted for demographic and neonatal characteristics.

Differences in outcomes by treatment approach were first evaluated using a Wald test of the overall contribution of treatment to the adjusted regression model. If this test was not significant (ie, the global test of treatment effect was not

TABLE 1
Maternal demographics

Characteristic	Erythromycin (n = 132)	Azithromycin 1 day (n = 78)	Azithromycin 5 days (n = 191)	Azithromycin 7 days (n = 52)	*P* value
Age, y	29.8 ± 5.3	29.8 ± 5.8	27.6 ± 6.6	31.2 ± 5.5	< .001
African-American race	57 (43.5)	32 (41.0)	26 (14.9)	17 (32.7)	< .001
Nulliparous	48 (36.4)	28 (35.9)	77 (40.3)	21 (40.4)	.85
Obesity (BMI >30 kg/m^2)	30 (22.7)	20 (26.0)	52 (32.7)	14 (26.9)	.30
Chronic HTN	11 (8.3)	8 (10.3)	3 (1.6)	4 (7.7)	.004
Pregestational DM	8 (6.1)	8 (10.3)	5 (2.6)	2 (3.8)	.07
Prior PTB	36 (27.3)	26 (33.3)	45 (23.6)	16 (30.8)	.36
Tobacco use	33 (25.0)	20 (25.6)	36 (18.8)	12 (23.1)	.48
Chlamydia, gonorrhea, or trichomonas infection	16 (12.1)	10 (12.8)	9 (4.7)	3 (5.8)	.04
Substance abuse	18 (13.6)	11 (14.1)	13 (6.8)	2 (3.8)	.04
GBS positive	25 (24.5)	21 (34.4)	53 (29.9)	16 (30.8)	.57
Steroids for fetal lung maturity	130 (98.5)	75 (96.2)	187 (97.9)	52 (100.0)	.46
Gestational age at rupture, wks	29.1 ± 3.4	29.6 ± 3.2	30.6 ± 2.8	29.4 ± 2.6	< .001

Data are represented as means ± SD or number (percentage) as appropriate.

BMI, body mass index; *DM*, diabetes; *GBS*, group B streptococcus; *HTN*, hypertension; *PTB*, preterm birth.

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significant), then no pairwise comparisons among treatments were conducted. If the global test was significant, pairwise comparisons of the adjusted treatment effects were conducted using Bonferroni's correction for multiple comparisons.

Multivariable models were developed on those patients with nonmissing values for all variables included in the models (n = 436). To facilitate interpretation, results from the multivariable models are presented as adjusted medians (or proportions) with 95% confidence intervals. A Kaplan-Meier curve is presented as a visual aid in interpreting the median latency by treatment group. Comparison of treatment groups on time-to-event curves was accomplished using the Mantel-Cox test. Analyses were performed in Stata (version 15.1; StataCorp, College Station, TX). Significance testing was conducted at a critical level of 5%.

Results

Four hundred fifty-three patients with PPROM between 23 0/7 and 33 6/7 weeks who met inclusion criteria were identified (Figure 1). A majority of the patients had PPROM occur prior to 33 weeks (85%), therefore giving the patient a chance to extend latency for more than a few days. Only 14 women (3%) ruptured after 33 5/7 weeks, and this was evenly distributed between the groups ($P = .58$).

Seventy-eight patients received azithromycin for 1 day, 191 patients received azithromycin for 5 days, 52 patients received azithromycin for 7 days, and 132 patients received erythromycin. Baseline characteristics and demographics for treatment groups are detailed in Table 1. Women who received the 5 day regimen were younger and less likely to be African American, have hypertension, have sexually transmitted infection, or experienced substance abuse. They also had a later gestational age at rupture by approximately 1 week compared with the other treatment groups ($P < .001$). Gestational age at rupture was similar for the other 3 treatment groups ($P = .48$).

There was no statistical difference in the primary outcome of latency to delivery (Table 2). Unadjusted median time from PPROM to delivery was 5.0 days for the azithromycin 1 day group, 4.4 days for the azithromycin 5 day group, 4.7 days for the azithromycin 7 day group, and 4.7 days for erythromycin ($P = .98$). To account for differences in the demographic variables, multivariate logistic regression was used to assess the primary outcome.

Latency to delivery remained unaffected in the model adjusted for age, race, gestational age at rupture, sexually transmitted infection, and hypertension (Table 3). The adjusted median time of latency to delivery for azithromycin 1 day was 4.9 days, 5.0 days for azithromycin 5 day, 4.9 days for the azithromycin 7 day group, and 5.1 days for erythromycin ($P = .99$).

A Mantel-Cox test did not show a statistically significant difference in the Kaplan-Meier survival curves between the groups (Figure 2). Gestational age at delivery was significantly later for the azithromycin 5 day group compared with erythromycin in the unadjusted model ($P < .001$, Table 2). Once adjusted for confounders, this was no longer statistically significant, and median gestational age of delivery was in the 30th week for all regimens ($P = .87$).

Delivery outcomes, including clinical and histological chorioamnionitis, were

TABLE 2
Delivery data

Variables	Erythromycin (n = 132)	Azithromycin 1 day (n = 78)	Azithromycin 5 days (n = 191)	Azithromycin 7 days (n = 52)	*P* value
Latency, d	4.7 (2.4, 9.8)	5 (1.9, 12.0)	4.4 (2.3, 10.4)	4.7 (2.6, 10.5)	.98
Gestational age at delivery, wks	30.2 ± 3.3	30.6 ± 3.1	32.0 ± 2.5	30.5 ± 2.4	< .001
Vaginal delivery	76 (57.6)	47 (60.3)	123 (64.4)	28 (53.8)	.45
Clinical chorioamnionitis	34 (25.8)	13 (16.7)	25 (13.1)	8 (15.4)	.04
Histological chorioamnionitis	90 (68.2)	47 (60.3)	114 (59.7)	35 (67.3)	.38
Birthweight, g	1523 ± 577	1571 ± 531	1811 ± 511	1521 ± 459	< .001
Fetal death	3 (2.5)	1 (1.3)	0 (0.0)	0 (0.0)	.11
Neonatal outcomes					
RDS	49 (37.1)	25 (32.1)	66 (34.6)	20 (38.5)	.84
NEC	13 (9.8)	8 (10.3)	4 (2.1)	5 (9.6)	.004
IVH	20 (15.2)	10 (12.8)	8 (4.2)	7 (13.5)	.003
Early sepsis	5 (3.8)	2 (2.6)	10 (5.2)	1 (1.9)	.73
5-minutes Apgar <7	53 (40.2)	24 (31.2)	24 (12.6)	15 (28.8)	< .001
Neonatal LOS (days)	46.3 ± 31.9	40.7 ± 32.2	27.2 ± 21.2	43.7 ± 25.2	< .001
Neonatal death	4 (3.0)	1 (1.3)	7 (3.7)	1 (1.9)	.85

Data are represented as means ± SD, number (percentage), or median (interquartile range) as appropriate.

IVH, intraventricular hemorrhage; *LOS*, length of stay; *NEC*, necrotizing enterocolitis; *RDS*, respiratory distress syndrome.

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not different when comparing the different dosing regimens of azithromycin with erythromycin after multivariate regression with Bonferroni's correction ($P = .14$, Table 3). There was a much lower rate of clinical chorioamnionitis than histological chorioamnionitis seen in the 4 treatment groups. Vaginal delivery was similar among the 3 groups (Table 2).

Neonatal outcomes were significant for less NEC, IVH, and 5 minute Apgar score <7 for the women who received 5 days of azithromycin compared with the erythromycin group in the unadjusted model (Table 2). There was no difference in neonatal outcomes for the 1 day or 7 day azithromycin groups compared with erythromycin. In multivariable analyses, differences among treatment remained significant for RDS and 5 minute Apgar <7 (the global test values of $P \leq .005$).

Bonferroni-adjusted post hoc comparisons among treatments for RDS indicated a higher proportion among the azithromycin 5 day treatment compared with erythromycin (44% vs 29%, $P = .007$) and azithromycin 1 day treatments (44% vs. 29%, $P = .033$) (Table 3). Post hoc comparison showed a lower proportion of neonates with 5 minute Apgar score <7 in the azithromycin 5 day treatment compared with erythromycin (0.16 vs 0.35, $P = .001$).

Post hoc analyses of neonatal intensive care unit LOS indicated that the median number of days for azithromycin 5 days was significantly shorter than the median number of days for erythromycin treatment (35.7 days vs 41.5 days, $P = .001$).

There were 4 intrauterine fetal demises documented in the study population. All intrauterine fetal demises were in women whose fetuses were less than 24 weeks' estimated gestational age at the time of diagnosis. These women declined intervention for fetal indication. There were 13 neonatal deaths in the study population. The average gestational age at rupture for these neonates was 25 weeks, and 30% had early sepsis, 62% had IVH, and 46% had NEC. There was no difference in neonatal death between the 4 groups ($P = .85$) (Table 2).

Comment

In this retrospective study of 4 different antibiotic regimens for the management of PPROM, there was no difference in the primary outcome of latency to delivery in women receiving either azithromycin 1000 mg orally once, azithromycin for 5 days, azithromycin for 7 days, or erythromycin. All 4 groups had a median latency of approximately 5 days and median gestational age at delivery of 30 weeks.

There are no randomized controlled trials comparing azithromycin with erythromycin to evaluate the duration of latency period from PPROM to delivery in women with singleton pregnancy. Our retrospective data are in agreement with the other 3 published retrospective studies comparing the macrolide component of latency antibiotics (azithromycin vs erythromycin).[10–12]

In 2013, Gelber et al[10] reported no difference in latency or maternal and

TABLE 3
Adjusted estimates of outcome measures by treatment approach

Outcomes	Treatment regimen (n=436)				Global test	Significant pairwise comparisons
	Erythromycin	Azithromycin 1 day	Azithromycin 5 days	Azithromycin 7 days		
	Median (95% CI)					
Latency[a]	5.1 (3.9–6.4)	4.9 (3.3–6.4)	5.0 (3.9–6.1)	4.9 (2.8–7.0)	0.99	NA
Gestational age at delivery, wks[a]	30.6 (30.4–30.8)	30.5 (30.3–30.7)	30.6 (30.4–30.8)	30.5 (30.3–30.8)	0.87	NA
Neonatal LOS[b]	41.5 (39.0–44.0)	38.0 (35.5–40.5)	35.7 (33.8–37.7)	38.6 (32.8–44.3)	< 0.001	[b]
	Adjusted proportion (95% CI)					
Clinical chorioamnionitis[a]	0.24 (0.17–0.32)	0.16 (0.08–0.25)	0.14 (0.08–0.19)	0.16 (0.06–0.26)	0.14	NA
NEC[c]	0.06 (0.03–0.09)	0.09 (0.04–0.13)	0.05 (0.01–0.08)	0.12 (0.05–0.19)	0.20	NA
RDS[c]	0.29 (0.23–0.35)	0.29 (0.22–0.37)	0.44 (0.38–0.50)	0.35 (0.26–0.43)	0.005	[b,d]
IVH[c]	0.10 (0.06–0.13)	0.11 (0.06–0.17)	0.09 (0.04–0.13)	0.15 (0.08–0.22)	0.46	NA
5 minute Apgar <7[c]	0.35 (0.28–0.43)	0.30 (0.20–0.39)	0.16 (0.10–0.21)	0.28 (0.17–0.39)	0.002	[b]

Pairwise comparisons are as follows: [a] erythromycin vs azithromycin 1 day; [b] erythromycin vs azithromycin 5 days; [c] erythromycin vs azithromycin 7 days; [d] azithromycin 1 day vs azithromycin 5 days; [e] azithromycin 1 day vs azithromycin 7 days; [f] azithromycin 5 days vs azithromycin 7 days.

IVH, intraventricular hemorrhage; *LOS*, length of stay; *NA*, pairwise testing not conducted because global test is not significant; *NEC*, necrotizing enterocolitis; *RDS*, respiratory distress syndrome.

[a] Model adjusted for hypertension, infection, maternal age, gestational age at preterm premature rupture of membranes, and race; [b] Model adjusted for factors in model 1 plus clinical chorioamnionitis and gestational age at delivery; [c] Model adjusted for factors in model 1 plus clinical chorioamnionitis.

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neonatal outcomes between women with PPROM at 24–34 weeks given either azithromycin (n = 29) or erythromycin (n = 67) (doses and duration were not specified). In 2014 Pierson et al[12] compared 93 women with PPROM at 24–34 weeks who received ampicillin and single-dose azithromycin (doses not specified) with 75 similar women who received ampicillin and erythromycin. They found no difference in latency from rupture of membranes to delivery. There were similar rates of chorioamnionitis, similar birthweight, Apgar scores, and neonatal complications between the 2 groups. They determined that with equivalent outcomes between the 2 groups, azithromycin may be a favorable substitution for the original 7 day erythromycin. Of note, the chorioamnionitis rate in this study population of 49% was significantly higher than in the Maternal Fetal Medicine Units Network trial (18–23%)[9] and compared with our own institutions' chorioamnionitis rate (13–25%).

In 2017, Finneran et al[10] compared 78 women who received azithromycin 1 g once orally with 84 women who received erythromycin for 7 days, all with PPROM at 23–33 6/7 weeks. Median latency from PPROM to delivery was also similar, with the only differences in maternal and neonatal outcomes being higher incidences of cesarean delivery and positive neonatal blood cultures in the erythromycin group.[11]

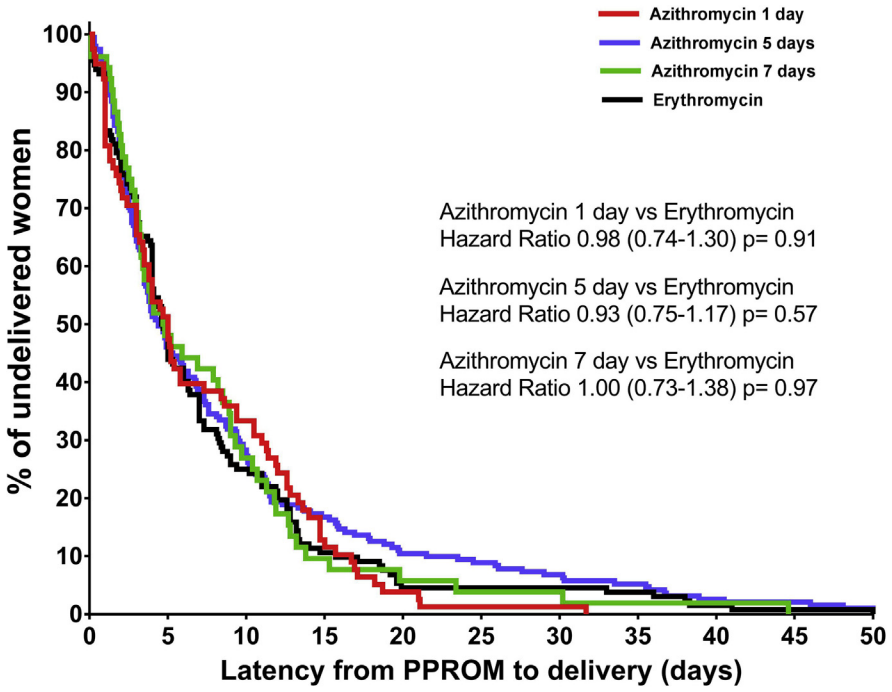
The spectrum of microbial coverage of azithromycin is similar to erythromycin, but the pharmacokinetic properties are different. Azithromycin has a significantly longer half-life of approximately 3 days compared with 1.6 for erythromycin and may be more than 70 hours in myometrium.[15–17] Azithromycin has also been shown to have a better gastrointestinal side effect profile.[18] Additionally, because of nationwide shortages of IV erythromycin, many institutions have advocated for the use of azithromycin instead of erythromycin. This may represent an opportunity for health system cost savings because of lower cost of azithromycin compared with erythromycin.[19]

In a cost analysis performed by Finneran et al,[19] the authors estimated a cost of $357,169 for standard erythromycin dosing, $15,669 for a multidose oral azithromycin regimen, and $9574 for a single-dose oral azithromycin regimen in a cohort of 981 PPROM patients. This represented a 95% cost savings for either azithromycin regimen over erythromycin.

Lastly, the dosing regimens for azithromycin vary widely, largely because there is no standard dosing regimen of azithromycin that has been studied prospectively. This study was designed to compare different dosing regimens of azithromycin with the erythromycin regimen most commonly used in the management of PPROM.

To our knowledge, there has been no study comparing different dosing regimens of azithromycin with erythromycin in the management of PPROM. However, there are several limitations to this study. Because of the retrospective nature, there was an imbalance in the study groups that may influence outcomes, even though accounted for in regression modeling. Additionally, even though all centers were tertiary referral centers, there may be subtle practice

FIGURE 2
Survival curve of latency time from PPROM to delivery, days



Survival curve of latency time from preterm premature rupture of membranes to delivery in days comparing the 4 antibiotic regimens.

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differences that may have affected the findings.

Small numbers limit the power of comparison between the different azithromycin regimens, and collinearity in the sites limit the ability to adjust for site in the multivariate regression. Ideally, recommendations for treatment would be based on findings from superiority or noninferiority randomized controlled trials. There is an ongoing superiority trial, Treatment of ppROM with Erythromycin vs Azithromycin (TREAT) (NCT 03060473) that is currently in recruitment. Results from that trial should aid in more definitive recommendations on treatment alternatives.

This study also does not address efficacy of different antibiotic regimens. There are studies that suggest clarithromycin has increased placental transfer compared to either erythromycin or azithromycin[20] and that intrauterine inflammation may be reduced.[21,22] However, the smaller retrospective studies used cephalosporins and/or metronidazole in addition to clarithromycin, so definitely identifying which agent would be optimal to add to any potential new regimen is still forthcoming.[21,22]

This study excluded pregnancies less than 23 weeks, which the authors considered to be previable. Management for PPROM less than 23 weeks has been inconsistent, and worse perinatal outcomes are expected, which may preclude expectant management.[23–25] Since the study period, the definition of viability continues to change, with institutions more commonly resuscitating neonates at an earlier gestational age, and the current standard of viability should be considered in prospective studies on PPROM management.

Our study shows no difference in the primary outcome of latency until delivery when comparing single-dose azithromycin with erythromycin or in secondary outcomes of chorioamnionitis and neonatal outcomes. A 5 day azithromycin course was associated with higher RDS but a lower rate of Apgar score <7 compared with erythromycin. Azithromycin could be considered as a safe alternative to erythromycin in the management of PPROM if erythromycin is unavailable or contraindicated. Final recommendations on dosing strategies will require data from future clinical trials. ■

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