Addition of Azithromycin for Pre-Operative Prophylaxis for Cesarean Delivery

Clinical Recommendations:

1. Azithromycin is recommended as pre-operative prophylaxis for cesarean delivery in patients who meet the following criteria:
    - In labor with regular contractions + cervical dilation ≥ 4 cm

    OR

    - Membrane rupture ≥ 4 hours

    AND

    - BMI ≥ 30 kg/m^2
2. A single dose of 500 mg should be administered intravenously 30-60 minutes prior to incision

Background:

Surgical site infections (SSIs) are infections that occur after surgery in the incision or organ space where the surgery took place.[1] One such patient population of concern for SSIs are mothers undergoing cesarean delivery (CD). CD accounts for approximately one-third of all deliveries and is one of the most common surgical procedures performed in the United States.[2] The current approach to minimizing the risk of developing SSIs is to give prophylactic antibiotics before surgical intervention. The rationale behind this approach is for the blood and tissues to achieve high enough levels of appropriate antibiotics based on the minimum inhibitory concentration (MIC) of commonly encountered organisms that could cause infection before surgical incision takes place.[3] Postpartum SSIs after CD include wound infection and endometritis, and are a major cause of maternal death.[4,5] Post-CD endometritis is commonly polymicrobial resulting from translocated bacteria from the lower genital tract to the upper genital tract. Gram-positive and Gram-negative aerobic and anaerobic organisms have been implicated in postpartum endometritis along with *Ureaplasma urealyticum*, a non-Gram staining, fastidious bacterium. *Ureaplasma* is part of the normal vaginal flora and has been isolated in blood cultures of women with postpartum infections.[5,6] The current standard of practice for SSI prophylaxis, intravenous (IV) cefazolin, does not cover *Ureaplasma* spp. Randomized controlled trial data from 2016 demonstrated the addition of IV azithromycin to pre-operative cefazolin reduced risk of SSI compared to cefazolin monotherapy in women undergoing non-elective CD.[4]

Clinical Data

A 2016 randomized controlled compared cefazolin + azithromycin to cefazolin + placebo for antibiotic prophylaxis before cesarean delivery in women undergoing non-elective cesarean section at 14 hospitals in the United States.[4] Among the 2013 subjects included, 6.1% of those who received cefazolin + azithromycin had a wound infection, endometritis or other infection within 6 weeks after surgery, compared to 12% of patients who received cefazolin + placebo. The result was statistically significant (Fig 1). The trial had 3 important confounding factors: patient weight, wound closure practices, and cefazolin dosing. Almost three quarters of the

subjects had a BMI greater than 30 kg/m^2 and use of staples for wound closure was common. Both are associated with increased risk of post-operative infection. Additionally, the dose of cefazolin was not controlled; the trial was conducted prior to routine recommendation of 2 – 3 grams of cefazolin pre-operatively to account for higher body weight. Adverse maternal outcomes were not significantly different between the two groups (Fig 2). Subjects were followed up to 6 weeks following CD.

Fig. 1: Primary outcome: Composite of endometritis, wound infection, or other infection[4]

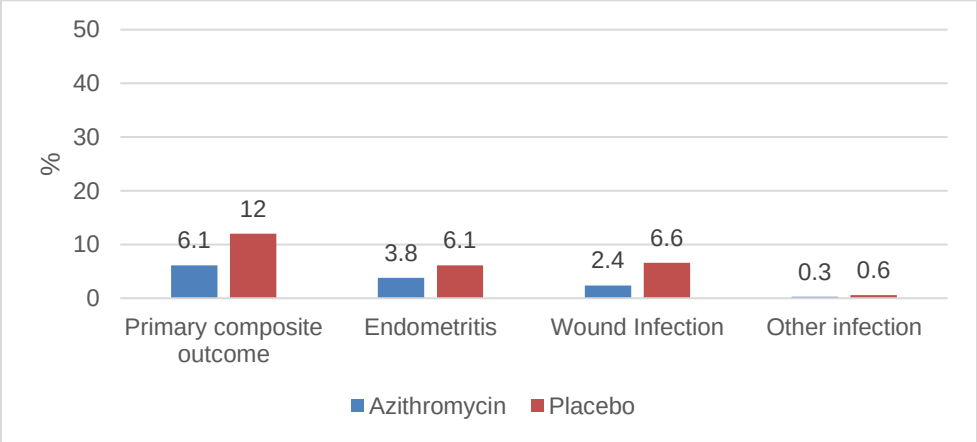
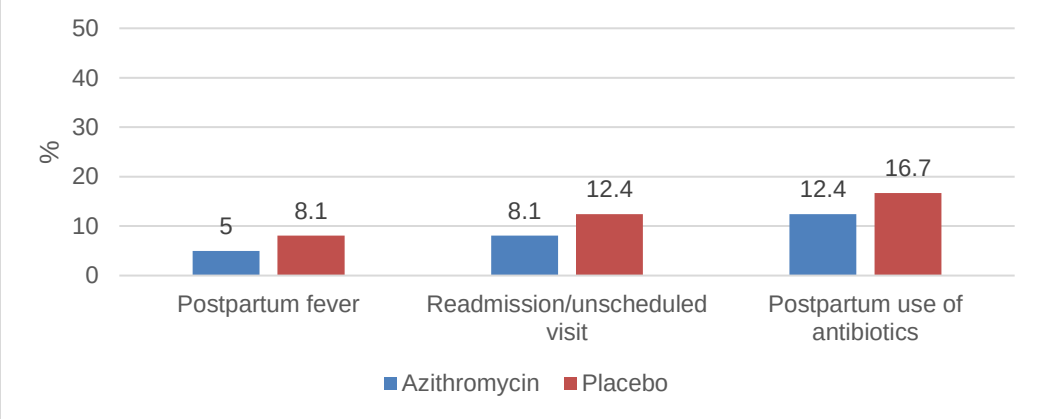


Fig. 2: Maternal safety outcomes[4]



Risk to Infant

Risk of azithromycin to infants exposed after maternal pre-operative prophylaxis is minimal. Azithromycin is categorized as Class B in pregnancy by the FDA. The drug displays placental transfer, but exposure depends on the duration of time between the dose and delivery. In one study, maximum neonatal serum concentrations of azithromycin were seen 12 to 24 hours after administration of an oral dose.[8] Azithromycin sustains concentrations in breast milk up to 48 hours after a single intravenous dose.[9] Infant exposure is anticipated but low: approximately 1% of therapeutic drug concentrations.[9] Given established safety data, it is clinically reasonable to continue breastfeeding without delay in women who receive azithromycin pre-operatively.[4,9]

In their 2016 randomized controlled trial, Tita et al evaluated neonatal outcomes up to 3 months after CD.[4] Among patients who received pre-operative prophylaxis with azithromycin, rates of adverse neonatal events including death, sepsis, or other neonatal complications were not different than those received placebo: 14.3% (146/1019) and 13.6% (134/994) respectively.

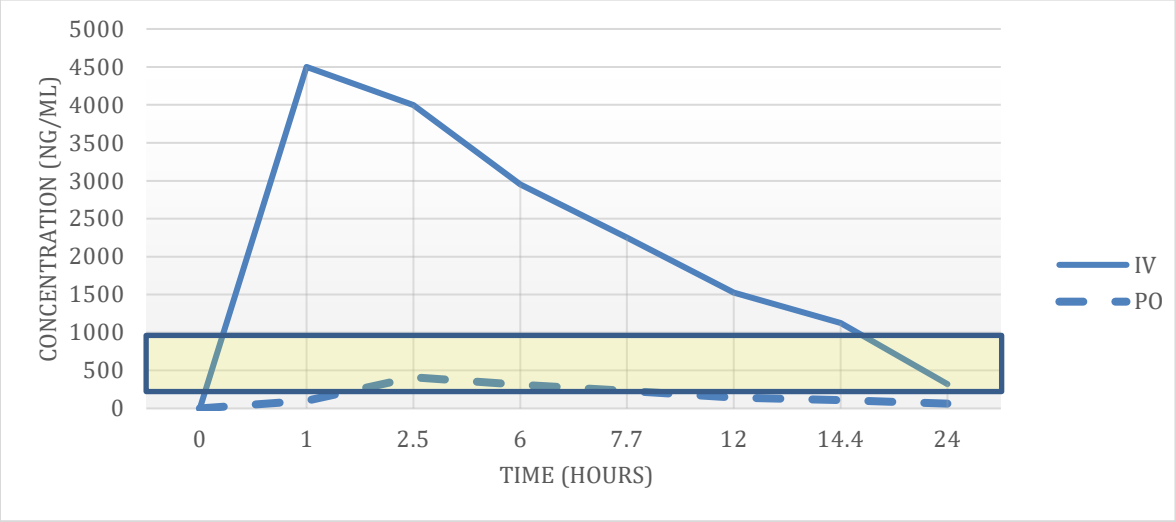
Dosage and Administration

Dosage: The recommended dose of azithromycin is 500 mg diluted in 250 ml of compatible solution (2 mg/ml).[4,9]

Administration: Intravenous dosing is preferred due to faster achievement of serum therapeutic drug concentrations compared to oral administration (Figure 3).[8,9] Azithromycin is compatible with cefazolin by Y-site administration.

Antibiotic timing: Azithromycin should be administered 30-60 minutes intravenously prior to incision for CD.[4,10]

Fig 3: Maternal serum concentrations of Azithromycin after a single 500 mg dose, IV or PO[8,9]



Serum IV concentrations exceeded the MIC_{50} for *Ureaplasma* spp, range 250 – 1000 ng/ml, (noted by the yellow box in the figure), starting within the first hour and up to 14 hours after the dose. Serum azithromycin concentrations after PO administration did not reliably exceed the MIC_{50}. Regardless of route of administration, concentrations of azithromycin in the placenta, adipose, and myometrium tissues sustained levels well-above the MIC_{50}.[8,9]

Conclusion: The addition of azithromycin as an adjunct to standard pre-operative prophylaxis for cesarean delivery is a reasonable measure to reduce risk of post-operative infection for high-risk patients: women with BMI ≥ 30 kg/m^2, undergoing a non-elective CD. Maternal and neonatal adverse events were minimal in the immediate post-operative period and up to 3 months after surgery.[4] No data are available for long term adverse effects. Based on available data, adoption of this medication as adjunctive prophylaxis should be reserved for those patients at highest risk of a post-operative infection. This practice is consistent with adoption of expanded pre-operative prophylaxis procedures at the University of Washington Medical Center.

References:

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Appendix:

Study Summary—Adjunctive Azithromycin Prophylaxis for Cesarean Delivery[4]

Study	Tita et al. 2016
Design	Double-blind, pragmatic, randomized clinical trial
Sample size	2013
Inclusion criteria	- Consent provided by study participants - Singleton pregnancy - Gestation age 24 weeks or later - Undergoing non-elective cesarean delivery during labor or after membrane rupture or membrane rupture within 4 hours regardless of labor status
Exclusion criteria	- Non-consenting - Had a known allergy to azithromycin - Had a subsequent vaginal delivery - Had used azithromycin within 7 days before randomization - Had chorioamnionitis or other infection requiring postpartum antibiotics (patients receiving antibiotics for group B streptococcus were eligible) - Fetal death or known major congenital anomaly
Primary endpoint	Composite of endometritis, wound infection, or other infection (abdominopelvic abscess, maternal sepsis, pelvic septic thrombophlebitis, pyelonephritis, pneumonia, or meningitis) occurring within 6 weeks after surgery
	62/1019 (6.1%) azithromycin vs. 119/994 (12%) placebo (95% CI: 0.38 to 0.68; P<0.001)
	• NNT all SSI=17 • NNT endometritis=43 • NNT wound infection=24
Secondary endpoints	- Composite of neonatal death, suspected or confirmed neonatal sepsis or other neonatal complications. - Neonatal safety composite (death, allergic reaction, or transfer to a long-term care facility) - Maternal safety composite (postoperative infections, maternal fever, unscheduled visits and readmissions, neonatal complications, and length of hospital stay)
	146/1019 (14.3%) azithromycin vs. 135/994 (13.6%) placebo (P=0.63)

Pharmacokinetic Data

Study Summary— Maternal and transplacental pharmacokinetics of azithromycin[8]

Study	Ramsey et al 2003
Design	Single dose PK study of oral azithromycin prior to scheduled cesarean delivery.
Sample size	N=30
Inclusion criteria	- Women ≥37 weeks of gestation - Singleton intrauterine pregnancy - Undergoing scheduled cesarean delivery
Exclusion criteria	- Recent history of: o Pregnancy induced hypertension o Preeclampsia o Diabetes mellitus o Intrauterine growth restriction

	○ Abruptio placentae
Drug and dose	Azithromycin 1 gm orally once at 6, 12, 24, 72, or 168-hour intervals prior to cesarean delivery
Sample time and fluid concentrations	- Samples prior to incision: blood and urine - Tissue samples intraoperatively: amniotic fluid, umbilical cord serum, myometrium, adipose tissue, placental tissue

Serum concentration of 311 ng/mL occurred at 6 hours post-dose, with rapid decline to 63 ng/mL at 24 hours. Amniotic fluid of 151 ng/mL occurred at 6 hours, with decline to 23 ng/mL at 72 hours. Umbilical cord serum concentrations peaked at 24 hours at 27.1 ng/mL and remain low throughout times measured. Myometrial, adipose, placental tissue levels achieved azithromycin levels of 1382, 1031, and 2130 ng/mL, respectively, and remained elevated up to 72 hours post-dose. A single oral dose of azithromycin 500 mg achieves a peak concentration of 400 ng/mL in approximately 2.5 hours exceeding the lower end of the MIC_{50} for *Ureaplasma parvum* (250 ng/mL) and *Ureaplasma urealyticum* (200 ng/mL).[8]

Study Summary— Perinatal pharmacokinetics of azithromycin for cesarean prophylaxis[9]

Study	Sutton et al 2013
Design	Single dose PK study of IV azithromycin administered pre-and perioperatively prior to cesarean delivery
Sample size	N=30
Inclusion criteria	- Women ≥37 weeks of gestation - Singleton intrauterine pregnancy - Undergoing scheduled cesarean delivery
Exclusion criteria	- Women of preterm gestation (<37 weeks) - Ruptured membranes or labor - Known fetal abnormalities - Oligi/polyhydramnios - Azithromycin exposure within two weeks - Allergy to macrolides - Significant medical or obstetric comorbidities - Hepatic or renal impairment - Concurrent use of QT prolonging medications - Cardiac defects
Drug and dose	Azithromycin 500 mg IV infused over one hour at 15, 30, or 60-minute intervals prior to planned incision
Sample time and fluid concentrations	- Serum concentration: before infusion, at end of infusion, at time of incision, and 30 minutes, 1, 3, 5, and 7 hours after conclusion of infusion - Tissues sampled intraoperatively: Amniotic fluid, umbilical cord serum, myometrial tissue, adipose tissue, placental tissue

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