RCT
Potential PURL Review Form
PURL Jam Version

PURLs Surveillance System
Family Physicians Inquiries Network

SECTION 1: Identifying Information for Nominated Potential PURL
[to be completed by PURLs Project Manager]

A. Citiation: Tita AT, Szychowski JM, Boggess K, Saade G, Longo S, Clark E, Esplin S, ClearyK, Wapner R, Letson K, Owens M, Abramovici A, Ambalavanan N, Cutter G, Andrews W;C/SOAP Trial Consortium.. Adjunctive Azithromycin Prophylaxis for CesareanDelivery. N Engl J Med. 2016 Sep 29;375(13):1231-41. doi: 10.1056/NEJMoa1602044. PubMed PMID: 27682034; PubMed Central PMCID: PMC5131636.
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E. Nominated By: Shailey Prasad
F. Institutional Affiliation of Nominator: University of Minnesota
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I. PURLs Editor Reviewing Nominated Potential PURL: Corey Lyon
J. Nomination Decision Date: 10/11/2016
K. Potential PURL Review Form (PPRF) Type: RCT
L. Assigned Potential PURL Reviewer: Gregory Castelli
M. Reviewer Affiliation: UPMC St. Margaret
N. Abstract: Background The addition of azithromycin to standard regimens for antibiotic prophylaxis before cesarean delivery may further reduce the rate of postoperative infection. We evaluated the benefits and safety of azithromycin-based extended-spectrum prophylaxis in women undergoing nonelective cesarean section. Methods In this trial conducted at 14 centers in the United States, we studied 2013 women who had a singleton pregnancy with a gestation of 24 weeks or more and who were undergoing cesarean delivery during labor or after membrane rupture. We randomly assigned 1019 to receive 500 mg of intravenous azithromycin and 994 to receive placebo. All the women were also scheduled to receive standard antibiotic prophylaxis. The primary outcome was a composite of endometritis, wound infection, or other infection occurring within 6 weeks. Results The primary outcome occurred in 62 women (6.1%) who received azithromycin and in 119 (12.0%) who received placebo (relative risk, 0.51; 95% confidence interval [CI], 0.38 to 0.68; P<0.001). There were significant differences between the azithromycin group and the placebo group in rates of endometritis (3.8% vs. 6.1%, P=0.02), wound infection (2.4% vs. 6.6%, P<0.001), and serious maternal adverse events (1.5% vs. 2.9%, P=0.03). There was no significant between-group difference in a secondary neonatal composite outcome that included neonatal death and serious neonatal complications (14.3% vs. 13.6%, P=0.63). Conclusions Among women undergoing nonelective cesarean delivery who were all receiving standard antibiotic prophylaxis, extended-spectrum prophylaxis with adjunctive azithromycin was more effective than placebo in reducing the risk of postoperative infection. (Funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development; C/SOAP ClinicalTrials.gov number, NCT01235546 .).
O. Pending PURL Review Date**:** 3/7/2017

SECTION 2: Critical Appraisal of Validity
[to be completed by the Potential PURL Reviewer]

A. Number of patients starting each arm of the study?

1019 were randomly assigned to the azithromycin group and 994 to the placebo group

B. Main characteristics of study patients (inclusions, exclusions, demographics, settings, etc.)

Women with a singleton pregnancy with a gestation of 24 weeks or more who were undergoing nonelective cesarean delivery during labor or after membrane rupture were eligible. Labor was de- fined as regular contractions with cervical dilation of 4 cm or more or with documented cervical change of at least 1 cm of dilation or at least 50% effacement. Women with membrane rupture for at least 4 hours were eligible, regardless of whether labor had started. Most women under- went the consent procedure at admission for delivery and were rescreened to confirm eligibility after the decision was made to proceed to cesarean delivery. Gestational age was estimated in accordance with the guidelines of the American College of Obstetricians and Gynecologists.[22]

Exclusion criteria were an inability to provide consent, a known allergy to azithromycin, subsequent vaginal delivery, azithromycin use within 7 days before randomization, chorioamnionitis or other infection requiring postpartum antibiotic therapy (although patients receiving antibiotics for group B streptococcus were eligible), and fetal death or known major congenital anomaly. We also excluded patients who had substantial liver disease (cirrhosis or an aminotransferase level at least three times the upper limit of the normal range), a serum creatinine level of more than 2.0 mg per deciliter (177 μmol per liter) or the need for dialysis, diarrhea at the time of planned randomization, cardiomyopathy or pulmonary edema, maternal structural heart disease, arrhythmias, use of medications known to pro- long the QT interval, or known substantial electrolyte abnormalities, such as hypokalemia, hypocalcemia, or hypomagnesemia.

C. Intervention(s) being investigated?

Patients were randomly assigned to receive either azithromycin (at a dose of 500 mg in 250 ml of saline)

D. Comparison treatment(s), placebo, or nothing?

Identical placebo

E. Length of follow-up? (Note specified end points, e.g., death, cure, etc.)

6 week post partum visit and 3 month telephone follow up.

F. What outcome measures are used? List all that assess effectiveness.

The primary outcome was a composite of endometritis, wound infection, or other infections (abdominopelvic abscess, maternal sepsis, pelvic septic thrombophlebitis, pyelonephritis, pneumonia, or meningitis) occurring up to 6 weeks after surgery.

A major secondary neonatal outcome was a composite of death, suspected or confirmed sepsis, or other complications, including the respiratory distress syndrome, necrotizing enterocolitis, periventricular leukomalacia, grade III or higher intraventricular hemorrhage, the systemic inflammatory response syndrome, and bronchopulmonary dysplasia. Other secondary out- comes that were specified in the statistical analysis plan included a neonatal safety composite (death, allergic reaction, or transfer to a long-term care facility), a maternal safety composite outcome (defined below as maternal serious adverse events), and infection with resistant organisms.

G. What is the effect of the intervention(s)? Include absolute risk, relative risk, NNT, CU, p-values, etc.
The primary outcome occurred in 6.1% of patients in the azithromycin group compared to 12% of patients in the placebo group. The RR was 0.51, 95% CI 0.38-0.68, NNT 17. Lower rates of endometritis seen (3.8% vs. 6.1%; relative risk, 0.62; 95% CI, 0.42 to 0.92; P=0.02) and wound infections (2.4% vs. 6.6%; relative risk, 0.35; 95% CI, 0.22 to 0.56; P<0.001).

H. What are the adverse effects of intervention compared with no intervention?

Maternal serious adverse events were less com- mon in the azithromycin group than in the pla- cebo group (1.5% vs. 2.9%, P=0.03)

I. The study addresses an appropriate and clearly focused question.
(select one) Well covered

Comments: Yes. One that is very important for the patient population.

J. Random allocation to comparison groups:
(select one) Well covered

Comments: Block-designed randomization was computer generated.

K. Concealed allocation to comparison groups:
(select one) Adequately addressed

Comments: Block-designed randomization was computer generated.

L. Subjects and investigators kept “blind” to comparison group allocation:
(select one) Well covered

Comments: While blinding did occur, investigational pharmacists could access the randomization algorithm. Clinical and research staff members other than the investigational pharmacist were unaware of treatment assignments.

M. Comparison groups are similar at the start of the trial:
(select one) Well covered
Comments:

N. Were there any differences between the groups/arms of the study other than the intervention under investigation? If yes, please indicate whether the differences are a potential sources of bias. (select one) Well covered
Comments: No differences were statistically significant between the groups other than the rates

of smoking during pregnancy, where more placebo patients used tobacco cigarettes.

O. Were all relevant outcomes measured in a standardized, valid, and reliable way?
(select one) Well covered
Comments:

P. Are patient oriented outcomes included? If yes, what are they?
Yes. The primary outcome of post operation infection for 6 weeks. Evaluated for harm of treatment to both mother and child.

Q. What percent dropped out, and were lost to follow up? Could this bias the results? How?
1961 of 2013 (97.4%) of patients followed up at a 6-week post-partum visit.

R. Was there an intention-to-treat analysis? If not, could this bias the results? How?
Yes, clearly stated.

S. If a multi-site study, are results comparable for all sites?
Yes. The authors state that the results did not vary significantly between clinical site. Not otherwise discussed.

T. Is the funding for the trial a potential source of bias? If yes, what measures were taken to ensure scientific integrity?
No.

Funding was provided by the Eunice Kennedy Shriver National Institute of Child Health and Human Development. Pfizer donated the azithromycin that was used in the trial but did not participate in the design, conduct, or reporting of the trial.

U. To which patients might the finding apply? Include patients in the study and other patients to whom the findings may be generalized.
Women undergoing nonelective cesarean delivery

V. In what care settings might the finding apply, or not apply?
Any clinical sites who perform cesarean deliveries.

W. To which clinicians or policy makers might the finding be relevant?
Applicable to family physicians who practice OB, OB-GYNs, national obstetrics guidelines

SECTION 3: Review of Secondary Literature
[to be completed by the Potential PURL Reviewer]
[to be revised by the Pending PURL Reviewer as needed]

Citation Instructions: For up-to-date citations, use style modified from http://www.uptodate.com/home/help/faq/using_UTD/index.html#cite & AMA style. Always use Basow DS on editor & current year as publication year.

Example: Auth I. Title of article. {insert author name if given, & search terms or title.} In: Basow DS, ed. UpToDate [database online]. Waltham, Mass: UpToDate; 2009. Available at: http://www.uptodate.com. {Insert date modified if given.} Accesses February 12, 2009. [whatever date PPRF reviewer did their search.}

For DynaMed, use the following style:
Depression: treatment {insert search terms or title}. In: DynaMed [database online]. Available at http://www.DynamicMedical.com. Last updated February 4, 2009. {Insert date modified if given.} Accessed June 5, 2009. {search date}

A. DynaMed excerpts

- **inclusion of electronic medical record reference text guiding prophylactic antibiotic selection associated with increase in recommended antibiotic use (level 2 [mid-level] evidence)**
  - based on before-and-after study
  - 2,101 women having cesarean section before or after addition of reference text to electronic medical record order set guiding physicians in selection of recommended prophylactic antibiotic use for cesarean deliveries evaluated
  - adequate antimicrobial prophylaxis defined as
    - 1 or 2 g IV cefazolin administered to women with body mass index (BMI) < 35 kg/m^2 or weight < 220 lb (100 kg)
    - 2 g IV cefazolin administered to women with BMI ≥ 35 kg/m^2 or weight ≥ 220 lb (100 kg)
    - 600 mg clindamycin and 120 mg gentamicin administered via IV to women with a penicillin allergy
    - 1 g IV vancomycin administered to women with penicillin and clindamycin allergies
  - recommended antimicrobial prophylaxis defined as above, except for women with BMI < 35 kg/m^2 or weight < 220 lb (100 kg), 1 g IV cefazolin recommended
  - comparing before vs. after addition of reference text for prophylactic antibiotic selection
    - adequate antimicrobial prophylaxis in 85.7% vs. 92.6% ($p < 0.005$)
    - recommended antimicrobial prophylaxis in 43.4% vs. 58.1% ($p < 0.05$)
  - Reference - Obstet Gynecol 2012 Dec;120(6):1382
- **perioperative antibiotic prophylaxis rate 60% in the United States between 2003 and 2010, but somewhat higher in women without initial labor (level 2 [mid-level] evidence)**
  - based on retrospective cohort study
  - 1,137,804 women with cesarean delivery in the United States between 2003 and 2010 evaluated
  - 59.5% received perioperative antibiotics
  - proportion of patients receiving antibiotics increased from 52.5% in 2003 to 63.1% in 2010 ($p < 0.001$)
  - receipt of perioperative antibiotics in 66% without initial labor vs. 44% with cesarean delivery after labor ($p < 0.001$)
  - Reference - Obstet Gynecol 2014 Aug;124(2 Pt 1):338

Efficacy:

- **prophylactic antibiotics may reduce postoperative endometritis and other infectious morbidity in women having cesarean section (level 2 [mid-level] evidence)**
  - based on Cochrane review of trials with methodologic limitation
  - systematic review of 95 randomized or quasi-randomized trials comparing prophylactic antibiotics vs. placebo or no treatment (control) in > 15,000 women having cesarean section
  - prophylactic antibiotics included ampicillin, penicillin, cefazolin, cefamandole, cefuroxime, cefoxitin, cefotetan, metronidazole, beta-lactam/beta-lactamase inhibitor combinations, and aminoglycoside-containing combinations
  - most trials had ≥ 1 methodologic limitation including
    - unclear or no allocation concealment
    - unclear or no blinding of outcome assessors
    - small sample size
  - prophylactic antibiotics associated with
    - lower risk of endometritis in analysis of 83 trials with 13,548 women
      - risk ratio (RR) 0.38 (95% CI 0.34-0.42)
      - NNT 10-11 with endometritis in 16% of control group
    - reduced wound infection in analysis of 82 trials with 14,407 women, results limited by significant heterogeneity
      - RR 0.4 (95% CI 0.35-0.46)
      - NNT 17-21 with wound infection in 9% of control group

        - reduced maternal urinary tract infection in analysis of 66 trials with 10,928 women
            - RR 0.56 (95% CI 0.49-0.65)
            - NNT 22-32 with maternal urinary tract infection in 9% of control group
        - reduced maternal febrile morbidity in analysis of 56 trials with 9,046 women, results limited by significant heterogeneity
            - RR 0.45 (95% CI 0.4-0.51)
            - NNT 6-7 with maternal febrile mortality in 29% of control group
        - lower risk of serious maternal infectious complications in analysis of 32 trials with 6,159 women
            - RR 0.31 (95% CI 0.2-0.49)
            - NNT 50-79 with serious maternal infectious complications in 2.5% of control group
        - increased risk of adverse effects (including rash and phlebitis at site of IV infusion) (RR 2.43, 95% CI 1-5.9) in analysis of 13 trials with 2,131 women
    - administration of prophylactic antibiotics before or after cord clamping gave similar results for endometritis and other infectious morbidity
    - no studies systematically collected and reported on adverse infant outcomes
    - Reference - Cochrane Database Syst Rev 2014 Oct 28;(10):CD007482
- **IV antibiotics and antibiotic irrigation associated with similar risk of endometritis in women having cesarean section (level 2 [mid-level] evidence)**
    - based on Cochrane review of trials with unclear allocation concealment
    - systematic review of 10 randomized trials comparing different routes of antibiotic prophylaxis in 1,354 women having cesareansection
    - 9 trials compared IV antibiotics to antibiotic irrigation (same antibiotic in both groups)
        - antibiotics included cefamandole (3 trials), cefazolin (2 trials), cefoxitin (2 trial), ceforanide (1 trial), cefotaxime (1 trial), and mezlocillin (1 trial)
        - IV antibiotics were administered as single dose (3 trials), multiple doses (5 trials), or continued for 2 days after cesareansection (1 trial)
        - for antibiotic irrigation, antibiotics were diluted in 500-1,000 mL normal saline
    - comparing IV antibiotics to antibiotic irrigation
        - no significant differences in
            - endometritis in analysis of 8 trials with 966 women
            - wound infection in analysis of 7 trials with 859 women
            - postpartum febrile morbidity in analysis of 3 trials with 264 women
            - urinary tract infection in analysis of 5 trials with 660 women
        - no serious infectious complications in 1 trial with 81 women
        - no maternal adverse events (allergic reactions) in 3 trials with 284 women
    - Reference - Cochrane Database Syst Rev 2016 Jun 17;(6):CD011876
- **addition of azithromycin to standard antibiotic prophylaxis reduces risk of endometritis and wound infection after nonelective cesarean section (level 1 [likely reliable] evidence) (The current study up for review)**
    - based on randomized trial
    - 2,013 women with singleton pregnancy at ≥ 24 gestational weeks having nonelective cesarean section during labor or after membrane rupture were randomized to addition of azithromycin 500 mg IV vs. placebo to standard antibiotic prophylaxis and followed for 3 months
        - standard antibiotic prophylaxis was cefazolin or clindamycin with or without gentamicin for women allergic to cephalosporin or penicillin
        - exclusion criteria included other infection requiring postpartum antibiotics (except for group B streptococcus), fetal death, congenital anomaly, maternal liver disease, elevated serum creatinine, need for dialysis, diarrhea, cardiac conditions, use of medications prolonging QT interval, pulmonary edema, or electrolyte abnormalities
    - primary outcome was composite of endometritis, wound infection, or other infection (abdominopelvic abscess, maternal sepsis, septic pelvic thrombophlebitis, pyelonephritis, pneumonia, or meningitis) at ≤ 6 weeks after surgery
    - 97.4% completed 6-week follow-up and 94.6% completed 3-month follow-up; all patients included in analyses
    - comparing azithromycin vs. placebo
        - primary outcome in 6.1% vs. 12% ($p < 0.001$, NNT 17)
        - endometritis in 3.8% vs. 6.1% ($p = 0.02$, NNT 44)
        - wound infection in 2.4% vs. 6.6% ($p < 0.001$, NNT 24)
        - serious maternal adverse events in 1.5% vs. 2.9% ($p = 0.03$, NNT 72)
        - neonatal death or complications in 14.3% vs. 13.6% (not significant)
    - no significant differences in risk of
        - other maternal infections (abdominopelvic abscess, maternal sepsis, septic pelvic thrombophlebitis, pyelonephritis, pneumonia, or meningitis)

    - other neonatal outcomes (sepsis, intensive care unit admission, or rehospitalization)
  - azithromycin associated with significantly decreased incidence of other maternal outcomes including postpartum fever, need for readmission or unscheduled visits, and antibiotic use
  - Reference - C/SOAP trial (N Engl J Med 2016 Sep 29;375(13):1231), editorial can be found in N Engl J Med 2016 Sep 29;375(13):1284
- **cefazolin reduces postoperative infections in women having elective cesarean delivery (level 1 [likely reliable] evidence)**
  - based on randomized trial
  - 1,112 women having elective cesarean delivery at term randomized to 1 of 3 groups
    - cefazolin 2 g IV 20-30 minutes before skin incision
    - cefazolin 2 g IV immediately after umbilical cord clamping
    - placebo given before skin incision
  - postoperative infectious morbidity defined as wound infection, endometritis, or urinary tract infection
  - postoperative infectious morbidity
    - in 4.9% with cefazolin before skin incision
    - in 3.8% with cefazolin after cord clamping
    - in 12.1% with placebo ($p < 0.001$ compared to both cefazolin groups, NNH 12-14)
  - no significant difference between cefazolin groups, but trial not powered for this comparison
  - Reference - Arch Surg 2011 Dec;146(12):1404 full-text, commentary can be found in Arch Surg 2011 Dec;146(12):1409

B. DynaMed citation: Cesarean Section: Periprocedural Management {prophylactic antibiotics}. Chisholm A. In: DynaMed [database online]. Available at: www.DynamicMedical.com Last Updated: January 18, 2017. Accessed February 23, 2017.

C. Bottom line recommendation orsummary of evidence from DynaMed (1-2 sentences) Prophylactic antibiotics should be used for patients undergoing cesarean section. Based off of best available evidence, cefazolin and azithromycin should be used in the absence of drug allergies.

D. UpToDate excerpts

Antibiotic prophylaxis

Choice of drug and dose — In the absence of antimicrobial prophylaxis, women undergoing cesarean delivery have a 5- to 20-fold greater risk for infection compared with women who give birth vaginally [25]. To reduce this risk, a single intravenous dose of a narrow-spectrum antibiotic, such as cefazolin or ampicillin, should be administered within 60 minutes before making the skin incision to all women undergoing cesarean delivery [25-27] (see 'Evidence of efficacy' below). Women at high risk of postoperative infection may benefit from an extended-spectrum regimen, but available data do not mandate a change in practice at this time. (See 'Extended-spectrum antibiotics' below.)

Comparative trials do not provide strong evidence on which to base a recommendation for the optimal drug and dose. We use cefazolin 2 g for women <120 kg and 3 g for women ≥120 kg (table 2), based on expert opinion from infectious disease experts [28]. These doses have an excellent safety profile. The higher dose for obese women is supported by a study in which ≥20 percent of obese (body mass index [BMI] 30 to 39.9 kg/m^2) and extremely obese women (BMI ≥40 kg/m^2) did not achieve minimal inhibitory concentrations for Gram-negative rods in adipose samples at skin incision with a 2 g dose [29]. Cefazolin has a longer half-life than ampicillin, which is an advantage in long surgeries. In a 2014 systematic review, however, cefazolin and

ampicillin appeared to be similarly effective for preventing postoperative maternal infection (endometritis, wound infection) after cesarean delivery [30]. A systematic review also noted that a single dose of antibiotics was as effective as multiple doses [31].

Evidence of efficacy — The benefit of antibiotic prophylaxis was illustrated in a 2014 systematic review of 95 randomized trials that compared infection outcomes with or without use of prophylactic antibiotics in both scheduled and in labor cesarean deliveries [25]. Antibiotic prophylaxis significantly reduced the incidence of postoperative fever, endometritis, wound infection, urinary tract infection, and serious maternal infectious complications compared with controls receiving no antibiotic treatment. The relative risk of endometritis was reduced by approximately 60 percent after scheduled cesarean delivery, in labor cesarean delivery, and for all patients (relative risk [RR] = 0.38, 0.39, and 0.37, respectively). None of the trials reported on short- and long-term adverse effects in offspring, such as bacterial resistance, oral thrush, or effects on immune system development. A subsequent analysis found no increase in neonatal sepsis (RR 0.76, 95% CI 0.51-1.13, five trials, n = 2907) or infection with antimicrobial-resilient bacteria (RR 0.70, 95% CI 0.32-4.14, one trial, n = 379), but more data are needed to confirm these findings [32].

Although the relative risk reduction in maternal infection is statistically significant and similar for both scheduled and in labor procedures, the absolute risk of maternal infection is quite low in scheduled cases: postpartum endometritis 2 percent with antibiotic prophylaxis, 2.6 percent without antibiotic prophylaxis and wound infection, 0.52 percent with antibiotic prophylaxis, and 0.96 percent without antibiotic prophylaxis [33]. Thus, 1000 women undergoing scheduled cesarean would receive antibiotics to prevent 6 cases of endometritis and 4.4 cases of abdominal wound infection. The low risk of maternal infection in these cases and uncertainty about long-term effects in offspring have prompted a call for more research on potential long-term risks of exposure to antibiotic prophylaxis and strategies for risk stratification to identify the best candidates for antibiotic prophylaxis [34]. Until these data available, we administer antibiotics before all cesarean deliveries, in accordance with ACOG guidelines [27].

Antimicrobial therapy should be administered within 60 minutes before making the skin incision to ensure adequate drug tissue levels [27]. This recommendation is supported by a 2014 meta-analysis of randomized trials that compared infection rates in women assigned to a single preincision dose of antibiotic prophylaxis versus those assigned to administration after cord clamping [32]. Preincision prophylaxis was significantly more effective than delayed administration for prevention of endometritis (RR 0.54, 95% CI 0.36-0.79) and was not associated with an increase in proven neonatal sepsis, sepsis work-ups, or admission to the neonatal intensive care unit, although the trials had limited power to detect adverse neonatal effects. (See "Antimicrobial prophylaxis for prevention of surgical site infection in adults", section on 'Timing'.)

Extended-spectrum antibiotics — Emerging data support use of extended-spectrum antibiotic combinations for women at high risk of postcesarean infection [35-38]. In a placebo-controlled multicenter randomized trial including over 2000 women, administration of azithromycin 500 mg intravenously before skin incision in addition to preoperative cefazolin resulted in a 50 percent reduction in the composite outcome of endometritis, wound infection, or other infection

(endometritis 3.8 versus 6.1 percent, wound infection 2.4 versus 6.6 percent), without affecting the frequency of adverse neonatal outcomes [38]. Of note, only women who had a cesarean delivery during labor or at least four hours after rupture of membranes where included, so these data do not apply to scheduled cesarean deliveries. Specific tests for *Ureaplasma* or *Mycoplasma* species were not routinely performed, thus it is not known whether coverage against *Ureaplasma* and *Mycoplasma* species provided by the extended antibiotic regimen accounted for the reduction in postoperative infection.

This trial provides the best evidence to date of the benefits of an extended-spectrum regimen. However, we believe a strong recommendation in favor of routine extended-spectrum prophylaxis is unwarranted at this time, given the high prevalence of obesity in at least one of the trial populations (>70 percent [38]), the lack of comparative data on the efficacy of high-dose (3 g) cefazolin in obese women, the lack of microbial data in these trials, and concern about inducing resistance to azithromycin [39]. It would also be useful to determine whether the intervention has any long-term effects on the newborn microbiome. We continue to administer narrow-spectrum antibiotic prophylaxis (eg, cefazolin) to all patients; however, others may reasonably choose to use an extended regimen (adding azithromycin) in women who are in labor or have had ruptured membranes for at least four hours, as these women are at higher risk of postoperative infection and the patient population targeted by the largest trial.

If an alternative extended regimen is chosen (eg, cefazolin plus doxycycline and azithromycin [35,36]), we recommend avoiding amoxicillin-clavulanic acid because of concerns about its safety. In a 2013 meta-analysis of placebo-controlled randomized trials of antibiotic therapy in women with preterm rupture of membranes, use of amoxicillin-clavulanic acid appeared to be associated with a significant increase in the number of babies who developed necrotizing enterocolitis (RR 4.72, 95% CI 1.57-14.23, two trials: 29/1236 [2.3 percent] versus 3/613 [0.5 percent]) [40]. The wide confidence interval shows that these findings need to be confirmed by larger studies; in the meantime, we avoid its use since safe and effective alternatives are available.

Penicillin allergy — For women with a history of serious penicillin allergy (immediate hypersensitivity reaction), we suggest combination therapy with a single dose of clindamycin (900 mg) plus gentamicin (5 mg/kg) intravenously, which provides broad coverage [27,28].

When gentamicin is used for prophylaxis in combination with a parenteral antimicrobial with activity against anaerobic agents, we advise 4.5 to 5 mg/kg of gentamicin as a single dose as many studies support the safety and efficacy of this dose when used as a single dose for prophylaxis in patients without renal insufficiency. In addition, a trial of antibiotic prophylaxis in colorectal surgery reported that this dose may be more effective than multiple standard doses of 1.5 mg/kg during prolonged surgeries [41]. However, cesarean delivery typically takes less than an hour; thus, a lower dose of gentamicin may be adequate; there are no comparative dosing trials in this population.

A cephalosporin can be given to patients at low risk of a serious IgE-mediated reaction. The risk of a penicillin-allergic patient reacting to a cephalosporin may be assessed based upon the

results of penicillin skin testing (if available), the clinical features of the penicillin reaction, and the time elapsed since the last reaction to penicillin (algorithm 1). (See "Penicillin-allergic patients: Use of cephalosporins, carbapenems, and monobactams" and "Penicillin allergy: Immediate reactions".)

E. Beghella. Cesarean delivery: Preoperative issues. In Basow DS, ed. UpToDate [database online]. Waltham, Mass: UpToDate; 2017. Available at: http://www.uptodate.com. Last updated: December 20, 2016 . Accessed: February 23, 2017.

F. Bottom line recommendation or summary of evidence from UpToDate (1-2 sentences)
Extended-spectrum antibiotic prophylaxis may reduce infectious sequelae in women at high risk of postoperative infection (eg, labor, ruptured membranes). Because of limitations in available data, we continue to use narrow-spectrum antibiotic prophylaxis for all patients; however, others may reasonably choose to use an extended regimen in high-risk patients. (See 'Extended-spectrum antibiotics' above.)

G. Other excerpts (USPSTF; other guidelines; etc.)
Recommendations from professional organizations and general considerations:
World Health Organization (WHO) recommends
   a. routine antibiotic prophylaxis for women having elective or emergency cesarean section (WHO Strong recommendation, Moderate-quality evidence)
   b. antibiotics administered prior to skin incision not intraoperatively after umbilical cord clamping (WHO Strong recommendation, Moderate-quality evidence)
   c. single dose first-generation cephalosporin or penicillin as preferred antibiotics (WHO Conditional recommendation, Very low-quality evidence)
   d. Reference - WHO recommendations for prevention and treatment of maternal peripartum infections (WHO 2015 PDF)
American College of Obstetricians and Gynecologists (ACOG) recommends
   e. antimicrobial prophylaxis for all cesarean deliveries (if patient has not already received adequate antibiotics)
   f. antibiotics administered ≤ 60 minutes prior to start of cesarean delivery
   g. Reference - ACOG Committee Opinion 465 (Obstet Gynecol 2010 Sep;116(3):791)
National Institute for Health and Clinical Excellence (NICE) recommendations(1)
   h. administer antibiotics before incision for all cesarean deliveries (reduces risk of maternal infection more than antibiotics after incision)
   i. choose antibiotics effective against endometritis, urinary tract infections, and wound infections
   j. avoid co-amoxiclav (amoxicillin/clavulanic acid) when administering antibiotics (potentially associated with increased risk for necrotizing enterocolitis) (BMJ 2011 Nov 23;343:d7108 full-text)
Royal College of Obstetricians and Gynaecologists (RCOG) recommends administration of antibiotics prior to skin incision in women having elective repeat cesarean section (RCOG Grade B) (RCOG 2015 Oct:45 PDF)

H. Citations for other excerpts

I. Bottom line recommendation or summary of evidence from Other Sources (1-2 sentences)

SECTION 4: Conclusions
[to be completed by the Potential PURL Reviewer]
[to be revised by the Pending PURL Reviewer as needed]

A. **Validity**: How well does the study minimize sources of internal bias and maximize internal validity? 2

B. If **A** was coded 4, 5, 6, or 7, please describe the potential bias and how it could affect the study results. Specifically, what is the likely direction in which potential sources of internal bias might affect the results?

C. **Relevance**: Are the results of study generalizable to and relevant to the health care needs of patients cared for by "full scope" family physicians? 1 (extremely well

D. If **C** was coded 4, 5, 6, or 7, please provide an explanation.

E. **Practice changing potential**: If the findings of the study are both valid and relevant, does the practice that would be based on these findings represent a change from current practice? 1 (definitely a change from current practice)

F. If **E** was coded as 1, 2, 3, or4, please describe the potential new practice recommendation. Please be specific about what should be done, the target patient population and the expected benefit.

G. **Applicability to a Family Medical Care Setting**:
Is the change in practice recommendation something that could be done in a medical care setting by a family physician (office, hospital, nursing home, etc.), such as a prescribing a medication, vitamin or herbal remedy; performing or ordering a diagnostic test; performing or referring for a procedure; advising, education or counseling a patient; or creating a system for implementing an intervention? 1 (definitely could be done in a medical care setting)

H. If **G** was coded as a 4, 5, 6, or 7, please explain.

I. **Immediacy of Implementation**:
Are there major barriers to immediate implementation? Would the cost or the potential for reimbursement prohibit implementation in most family medicine practices? Are there regulatory issues that prohibit implementation? Is the service, device, drug, or other essentials available on the market? 1 (definitely could be immediately applied)

J. If **I** was coded 4, 5, 6, or 7,please explain why.

K. **Clinically meaningful outcomes or patient oriented outcomes**:
Are the outcomes measured in the study clinically meaningful or patient oriented?
1 (definitely clinically meaningful or patient oriented)

L. If **K** was coded 4, 5, 6, or 7 please explain why.

M. In your opinion, is this a pending PURL? 1 (definitely a pending PURL)

1. Valid: Strong internal scientific validity; the findings appear to be true.
2. Relevant: Relevant to the practice of family medicine.
3. Practice Changing: There is a specific identifiable new practice recommendation that is applicable to what family physicians do in medical care settings and seems different than current practice.
4. Applicability in medical setting.
5. Immediacy of implementation

N. Comments on your response for question M.