EVOLUTION OF ANTIBIOTIC PROPHYLAXIS IN CESAREAN DELIVERY

Diantha Gonzales, Pharm. D.
Pharmacy Practice Resident
St. David’s North Austin Medical Center
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Objectives
- Discuss background and current guidelines regarding prophylactic antibiotic use associated with Cesarean delivery
- Evaluate available literature to explore current recommendations for practicing evidence-based medicine
- Draw a conclusion about appropriate therapy using literature presented

Abbreviations
Abx: Antibiotics
BMI: Body Mass Index
CD: Cesarean Delivery
G1P0: Gravida 1 Parity 0
GBS: Group B Strep
GFR: Glomerular Filtration Rate
kg: Kilogram
LOS: Length of Stay
mg: Milligram
mL: Milliliter
NNT: Number Needed to Treat
OR: Operating Room

Statistics
- CD most common major surgical OR procedure performed in U.S
- 1.3 million CD performed yearly in U.S., which is almost 1/3 of all births
- 1.7 million hospital acquired infections and 99,000 associated deaths annually. 22% are SSI
- U.S. cesarean delivery rates have increased— from 20.7% in 1996 to 31.9% in 2016

Assessment Question #1
When considering CD, which antibiotic approach is best?

a) narrow-spectrum started before delivery
b) narrow-spectrum started after delivery
c) broad-spectrum started before delivery
d) broad-spectrum started after delivery

Assessment Question #2
33 y/o G1P0 at 40w1d presents in spontaneous labor and is dilated to 4.5 cm. Reached complete cervical dilation after artificial rupture of membranes and oxytocin augmentation. After 6 hours of pushing, minimal descent of the fetal vertex beyond +1 station with significant fetal distress. Physician decides to proceed with CD. What antibiotics should be administered prior to incision to reduce postoperative infection?
BACKGROUND

History

1860: Lister introduced principles of anti-sepsis. Post-op death went from 50% to 15%.

1960s: Burke showed giving abx prior to wound contamination decreased rate of infection.

1992: SSIs increase hospital stay by 10+ days and add $3152 per case.

2005-2010: Studies supporting abx prophylaxis timed prior to incision are safer and more beneficial than after cord clamping.

Today: CD rates at all-time high. Abx prophylaxis continually evolving.

Lamont RF, et al. BJOG 2011;118:193–201

Background

• CD indicated:
  • Failure to progress during labor (35%)
  • Unstable fetal status (24%)
  • Fetal malpresentation (19%)
  • Other medical concerns

• Frequent complications include:
  • SSI
  • Endometritis
  • UTI

• 8.9% SSI occur post-CD
  • Before hospital discharge: 1.8%
  • Rate of infection peaks after POD 4 or 5
  • >75% of SSI occur after discharge

Lamont RF, et al. BJOG 2011;118:193–201

Coverage

Polymicrobial

• Aerobes
• Anaerobes
• Ureaplasma

Endometritis

• Ureaplasma
• Aerobic gram-negative rods
• Enterococci

SSI/Wound Infections

• Ureaplasma
• Staphylococci
• Enterococci


Ideal Agent

• Low incidence of adverse effects
• Long-acting
• Inexpensive
• Narrow-spectrum for pathogens

Lamont RF, et al. BJOG 2011;118:193–201

Considerations

Variables of CD prophylactic antibiotic

• Agent(s)
• Timing
• Number of doses
• Emergent vs. planned
• Infant vs. mother

Prophylactic antibiotics reduce

• Feverile morbidity
• Endometritis
• Wound infections
• Urinary tract infections

Development of infection after CD can increase

• Hospital stay
• Patient costs
• Social complications

Other considerations

• Adverse abx effect (mother and infant)
• Development of antimicrobial resistance
• Multiple sources

Lamont RF, et al. BJOG 2011;118:193–201
**Abx Dosing in Pregnancy**

**Challenges**
- Increased GFR decreases $t_{1/2}$
- Increased $V_d$
- Hormone-mediated increase in protein binding
- Decrease in gastric emptying time
- Alteration in gastric acidity

**CURRENT GUIDELINES**

**Vaginal Antimicrobials**

- CDC recommends
  - Preoperative cleansing
  - Alcohol skin preparation
  - Chlorhexidine
  - Povidone-iodine may be considered

**Standard Regimen Agents**

- Cefazolin
- Cefotetan
- Cefuroxime
- Ampicillin
- Piperacillin-tazobactam
- Cefoxitin
- Ampicillin–sulbactam

**Dosing**

- 1 g IV cefazolin
  - Patients <80kg
  - Low cost
  - Favorable safety profile
  - Single-dose therapy

**Timing**

**Administration**

Recommended *prior* to surgical incision or potential exposure

- 60 minutes before CD
- ASAP for emergency

**Duration**

Less than 24 hours
Extended Spectrum Agent

- Add 500mg IV Azithromycin if
  - In labor
  - Ruptured membrane
  - Non-elective CD

Specific Patient Populations

PCN Allergy
Clindamycin 900mg + aminoglycoside 5 mg/kg

Known MRSA colonization
One dose of Vancomycin appropriate

Specific Patient Populations

Obese patients (weight > 80 kg or BMI >30)
- 2g Cefazolin dose recommended
- Cephalosporins have
  - Increased Vd
  - Increased drug clearance
  - OR-
  - Clindamycin 900 mg + aminoglycoside 5 mg/kg

Specific Patient Populations

Woman receiving GBS prophylaxis
- Labor or with ruptured membranes already receiving penicillin G
  - Do not add cephalosporin or switch to ampicillin
  - Do give dose of azithromycin

Specific Patient Populations

Women with chorioamnionitis
- Generally treated with ampicillin + gentamicin
  - Do give one dose of
    - clindamycin 900 mg –OR–
    - metronidazole 500 mg
  - Do not give azithromycin

Specific Patient Populations

Prolonged surgery or excessive blood loss
- Antibiotic levels fall over time and with blood loss (>1500 mL)
- A second dose of cefazolin is appropriate
LITERATURE REVIEW

ANTIBIOTIC PROPHYLAXIS VERSUS NO PROPHYLAXIS FOR PREVENTING INFECTION AFTER CESAREAN SECTION
Smaill FM et al. (2014)

Study Methods

Objective
- Determine efficacy of prophylactic abx compared with placebo or no treatment in women undergoing CD

Trial Design
- Meta analysis including 95 RCT
- Over 15,000 women
- 1980s-2011

Endpoints
- Primary: Febrile morbidity, SSI, endometritis, and serious complication due to infection

Population
- Women undergoing CD elective or non-elective/emergency

Intervention
Any prophylactic antibiotic regimen compared to placebo or no treatment

Timing
- 40 studies gave abx pre-operatively
- 51 studies gave abx after cord clamping

Agent
- Ampicillin
- 1st generation cephalosporin
- 2nd generation cephalosporin
- Cotrimoxazole
- Metronidazole
- Extended spectrum of activity
- Penicillins
- β-lactam/β-lactamase inhibitor combination
- Aminoglycoside-containing combination

Duration
- Varied from one dose up to one week

Results

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>NNT</th>
<th>41.7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal wound infection</td>
<td>38.5</td>
<td></td>
</tr>
<tr>
<td>Maternal endometritis</td>
<td>31.2</td>
<td>17 studies</td>
</tr>
<tr>
<td>Maternal post operative infection</td>
<td>25.0</td>
<td>4 (studies)</td>
</tr>
</tbody>
</table>

Conclusions

- Reductions in febrile morbidity and UTI
- Similar effects seen in dosing timed pre-operatively and after cord clamp
- Reduction in infection is clinically important
- Results are generalizable
Study Limitations and Critique

- Variable amount of bias in studies
  - Several studies classified as quasi-RCTs judged at high risk of selection bias
- 33% of studies had no blinding and control group received no treatment
- Even studies classified as blinded could not be confidently confirmed
- Some studies provided insufficient data for dropouts to be used in an intention-to-treat analysis

Study Methods

Objective
- Compare efficacy of single dose ceftriaxone with multiple doses of triple drug regimen for infection prevention for CD

Trial Design
- RCT
  - 200 women undergoing CD in Nigeria

Intervention
- Single 1g IV ceftriaxone dose after cord clamp
- Multi-dose IV ampiclox, gentamicin and metronidazole for initial 48 hours followed by oral regimen for 5 more days

Patient Population

Inclusion
- No risk factors for infection
- Consented
- Scheduled for CD

Exclusion
- Abx in prior 2 weeks
- Visible infection
- Elevated temperature
- Ruptured membranes
- Allergy to regimen medication
- Anemic
- HIV+

Endpoints
- Endometritis
- SSI
- Febrile morbidity
- UTI

Baseline Characteristics

<table>
<thead>
<tr>
<th>Variables</th>
<th>Ceftriaxone ± SD</th>
<th>Triple therapy ± SD</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>33.53 ± 3.313</td>
<td>32.98 ± 4.453</td>
<td>0.102</td>
</tr>
<tr>
<td>Parity</td>
<td>1.69 ± 1.107</td>
<td>1.46 ± 1.109</td>
<td>0.128</td>
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<tr>
<td>Gestational age (weeks)</td>
<td>38.60 ± 1.022</td>
<td>38.60 ± 0.921</td>
<td>0.404</td>
</tr>
<tr>
<td>PCV (%)</td>
<td>34.16 ± 1.412</td>
<td>34.23 ± 1.45</td>
<td>0.730</td>
</tr>
<tr>
<td>Duration (min)</td>
<td>75.30 ± 17.16</td>
<td>76.55 ± 18.05</td>
<td>0.616</td>
</tr>
</tbody>
</table>

Results

<table>
<thead>
<tr>
<th></th>
<th>Ceftriaxone</th>
<th>Triple therapy</th>
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<tbody>
<tr>
<td>Endometritis, n (%)</td>
<td>14 (14%)</td>
<td>15 (15%)</td>
<td>0.841</td>
</tr>
<tr>
<td>SSI, n (%)</td>
<td>7 (7%)</td>
<td>8 (8%)</td>
<td>0.788</td>
</tr>
<tr>
<td>Febrile morbidity, n (%)</td>
<td>7 (7%)</td>
<td>6 (6%)</td>
<td>0.400</td>
</tr>
<tr>
<td>UTI, n (%)</td>
<td>11 (11%)</td>
<td>15 (15%)</td>
<td>0.774</td>
</tr>
<tr>
<td>Total, n (%)</td>
<td>39 (39%)</td>
<td>44 (44%)</td>
<td></td>
</tr>
</tbody>
</table>
Conclusions

• No statistically significant difference in any type of infection between treatments
• Ceftriaxone holds advantage
  • Lower cost
  • More convenient administration
  • Saves nursing time
  • Lower incidence of adverse effects
  • Less chances for drug-drug interaction
  • Lower incidence of resistance

Study Limitations and Critique

• May not be generalizable
• Relatively small study population
• No discussion of blinding
• Dosing differences
  • Single vs. multidose comparison
  • Extended duration vs. one time
• Used physical examination of wound infection as qualifier for study, not culture results
• Overall outcomes matched many similar studies
• Elective CD only

ADJUNCTIVE AZITHROMYCIN PROPHYLAXIS FOR CESAREAN DELIVERY (C/SOAP TRIAL)

Tita, ATN et al. (2016)

Study Methods

Objective
• Compare efficacy of azithromycin versus placebo when added to standard prophylaxis in women undergoing non-elective CD

Trial Design
• Double-blinded RCT
• 2013 women from 14 centers in U.S.

Intervention
• 500 mg azithromycin IV bag
• Identical placebo IV bag
• Added to standard CD prophylaxis
• Given prior to incision

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<td>• First pregnancy with gestation of 24+ weeks</td>
<td>• Allergy to azithromycin</td>
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<td>• Undergoing non-elective CD during labor or after membrane rupture</td>
<td>• Vaginal delivery</td>
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<td>• Chorioamnionitis or other postpartum infection (not GBS)</td>
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Endpoints

• Composite
• Endometritis
• SSI
• Other infections

Study Methods

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Results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Azithromycin (n=1564)</th>
<th>Placebo (n=1306)</th>
<th>Relative Risk (95% CI)</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite outcome</td>
<td>42 (2.7)</td>
<td>51 (3.9)</td>
<td>0.83 (0.63-1.10)</td>
<td>17</td>
</tr>
<tr>
<td>Endometritis</td>
<td>35 (2.2)</td>
<td>51 (3.9)</td>
<td>0.82 (0.42-1.62)</td>
<td>56</td>
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<tr>
<td>Wound infection</td>
<td>24 (1.5)</td>
<td>66 (4.5)</td>
<td>0.35 (0.22-0.58)</td>
<td>100</td>
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<tr>
<td>Necrotizing fasciitis</td>
<td>0</td>
<td>4 (0.4)</td>
<td>NA</td>
<td>0.90</td>
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<td>Deep wound infection</td>
<td>6 (0.3)</td>
<td>8 (0.6)</td>
<td>0.97 (0.57-1.68)</td>
<td>9.60</td>
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<tr>
<td>Other infection</td>
<td>7 (0.4)</td>
<td>6 (0.4)</td>
<td>1.12 (0.59-2.14)</td>
<td>9.00</td>
</tr>
<tr>
<td>Abdominal surgical abcess</td>
<td>3 (0.2)</td>
<td>5 (0.4)</td>
<td>NA</td>
<td>0.30</td>
</tr>
<tr>
<td>Septic pelvic thrombophlebitis</td>
<td>0</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Maternal sepsis</td>
<td>1 (0.1)</td>
<td>1 (0.1)</td>
<td>1.25 (0.18-9.2)</td>
<td>&gt;120.0</td>
</tr>
<tr>
<td>Myometritis</td>
<td>1 (0.1)</td>
<td>0</td>
<td>NA</td>
<td>1.00</td>
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<tr>
<td>Pneumonia</td>
<td>1 (0.1)</td>
<td>2 (0.2)</td>
<td>0.46 (0.05-4.31)</td>
<td>6.20</td>
</tr>
<tr>
<td>Metritis</td>
<td>0</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
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Conclusions

• Addition of azithromycin to standard prophylaxis significantly reduced frequency of infection in non-elective CD

• Serious adverse maternal events and readmissions were lower in azithromycin group

• Exact mechanism of action of azithromycin unclear. Culture results and other research suggest effect extends beyond coverage of Ureaplasma

• Long-term outcomes pending for future study

Study Limitations and Critique

• Azithromycin covers Ureaplasma
• Non-elective CD only
• Excluded chorioamnionitis
• Resistance patterns
• Need further studies on treatment for elective CD

Literature Comparison

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<tr>
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<tr>
<td>Meta analysis n= 15,000+ women</td>
<td>RCT n= 200 women</td>
<td>Double-blinded RCT n= 2013 women</td>
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<tr>
<td>Both emergent and non-emergent CD</td>
<td>Non-emergent CD only</td>
<td>Emergent CD only</td>
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<tr>
<td>Ax vs. placebo</td>
<td>Ceftriaxone vs. triple therapy</td>
<td>Azithromycin v. placebo, both combined with standard prophylaxis regimen</td>
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<tr>
<td>Pre-incision and post cord clamp</td>
<td>After cord clamp</td>
<td>Pre-incision</td>
<td></td>
</tr>
<tr>
<td>60% reduction in SSI</td>
<td>No statistical differences between treatment groups</td>
<td>RR 0.35 for SSI</td>
<td></td>
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<tr>
<td>70% reduction in endometritis with abx</td>
<td></td>
<td>RR 0.62 for endometritis with azithromycin</td>
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</table>

Antibiotic Selection

Azithromycin is leading option for extended-spectrum regimen for CD.

• t1/2: 68 hours
• Higher tissue concentration than other choices
• Low potential for fetal transfer
• Both aerobic and some weakly anaerobic coverage
• Uniquely covers Ureaplasma
• Only choice associated with significantly reduced incidence in both endometritis and wound infection

Proposed mechanism of action for prophylaxis:
• Likely origin of observed benefits extends to suppression of other susceptible organisms
• Prolongs the time from membrane rupture to delivery

Assessment Question #1

When considering CD, which antibiotic approach is best?

a) narrow-spectrum started before delivery
b) narrow-spectrum started after delivery
c) broad-spectrum started before delivery
d) broad-spectrum started after delivery
Considerations

• In 1998, 18% of pneumococcal isolates resistant to macrolides
• By 2013, macrolide resistance rates average ~30% in U.S.
• 68 hour $t_{1/2}$ contributes to increased resistance
• One dose of azithromycin stays in the body for over a week

Assessment Question #2

33 y/o G1P0 at 40w1d presents in spontaneous labor and is dilated to 4.5 cm. Reached complete cervical dilation after artificial rupture of membranes and oxytocin augmentation. After 6 hours of pushing, minimal descent of the fetal vertex beyond +1 station with significant fetal distress. Physician decides to proceed with CD. What antibiotics should be administered prior to incision to reduce postoperative infection?

Conclusion

• Prophylactic antibiotic treatment shown to be necessary for safe and healthy maternal outcome.
• Most appropriate treatment regimens shown to be equally efficacious in previous studies. Choice of treatment comes down to other factors.
• Further research to elucidate mechanism of action for efficacy of azithromycin in protection from infection may open doors in other areas.
• Examined just one side of the prophylactic equation. Must also consider fetal health and safety outcomes.

References


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