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An Update on Antibiotics for Chorioamnionitis and Obstetric Sepsis

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Topics for Today's Webinar

- Antibiotics for Patients with Chorioamnionitis
- Prophylactic Antibiotics in OB
  - Cesarean, 3rd/4th Lacerations, PPROM latency
- Antibiotic Considerations for Sepsis in Obstetric Patients

Disclosures and Conflicts: All speakers report none

Supported by: NICHD UG3-HD108053: Large-scale Implementation of Community Co-led Maternal Sepsis Care Practices to Reduce Morbidity and Mortality from Maternal Infection

Special Acknowledgements

Topics for Today's Webinar

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PROM latency

sis in Obstetric

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Special Acknowledgements

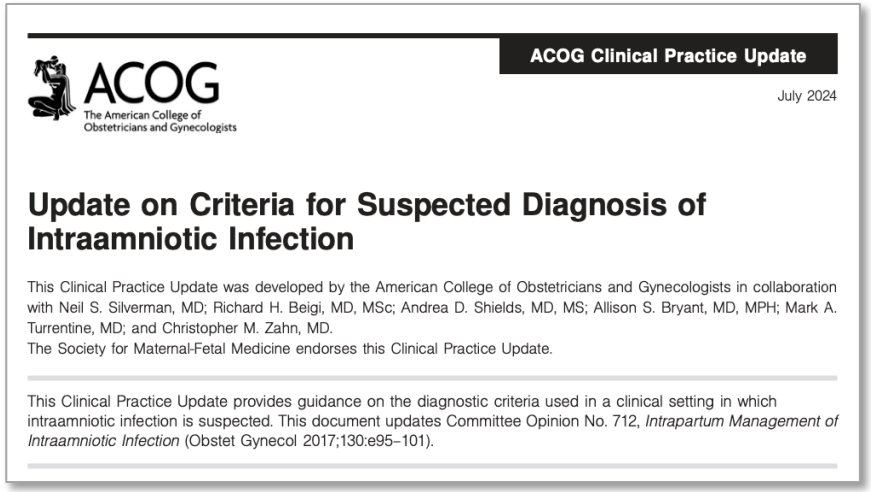
Todays' Presentation is a Preview of Chapters in the Upcoming CMQCC Toolkit: Diagnosis and Treatment of Obstetric Sepsis

Chorioamnionitis / Intraamniotic Infection (IAI)

- Incidence (approximate)
  - Term labor: 3-4%;Term PROM >24hr: 40%; PTL or PPROM: 40-70%
- Definition of “fever”
  - Fever with clinical signs? Fever alone? Signs alone?
- Laboratory testing (including histopathology) has limited diagnostic utility
- Worse outcomes with higher temperatures and longer course before delivery. Cesarean delivery may increase maternal risk.
- Vaginal delivery (source control) is an effective treatment
- Maternal antibiotic treatment reduces sepsis in the newborn

Key ACOG (2017) Treatment Recommendations

- Administration of intrapartum antibiotics is recommended whenever an intraamniotic infection is suspected or confirmed.
- Antibiotics should be considered in the setting of isolated maternal fever unless a source other than intraamniotic infection is identified and documented.
- Intraamniotic infection alone is rarely, if ever, an indication for cesarean delivery.



ACOG Clinical Practice Update

July 2024

ACOG
The American College of Obstetricians and Gynecologists

Update on Criteria for Suspected Diagnosis of Intraamniotic Infection

This Clinical Practice Update was developed by the American College of Obstetricians and Gynecologists in collaboration with Neil S. Silverman, MD; Richard H. Beigi, MD, MSc; Andrea D. Shields, MD, MS; Allison S. Bryant, MD, MPH; Mark A. Turrentine, MD; and Christopher M. Zahn, MD.
The Society for Maternal-Fetal Medicine endorses this Clinical Practice Update.

This Clinical Practice Update provides guidance on the diagnostic criteria used in a clinical setting in which intraamniotic infection is suspected. This document updates Committee Opinion No. 712, *Intrapartum Management of Intraamniotic Infection* (Obstet Gynecol 2017;130:e95–101).

What bacteria do we need to cover with Chorioamnionitis?

- **Primary pathogens:** Group A and B *Streptococci* (GAS and GBS), *Escherichia coli* and other enteric gram negatives.
- **Anaerobic coverage** is necessary for cesarean delivery or more serious infections.
- ***Enterococcus* spp**. is less common in routine chorioamnionitis; however, empiric coverage should be added if the patient is failing to respond adequately to the initial antibiotic regimen and should be considered for endomyometritis readmissions.
- **Choice of optimal hospital antibiotic regimen** is driven by the local antibiogram and in consultation with Infectious Disease, Maternal-Fetal Medicine specialists, and pharmacists trained in antibiotic stewardship.

Antibiotic Considerations for Chorioamnionitis-1

Antibiotic	Discussion
Aminoglycosides (gentamicin, tobramycin)	Difficult pharmacokinetics in pregnancy (i.e., challenging to achieve adequate blood levels); weight-based dosing requires pharmacy preparation with potential delays; rising resistance of gram-negative bacteria; risks for nephrotoxicity and ototoxicity; needs to be part of the "Triple Drug Regimen" to be most effective for chorioamnionitis followed by cesarean. Not ideal in sepsis and septic shock and may be associated with worse outcomes.
Ampicillin	Narrow in spectrum, covers *Streptococcus* spp. well, but little else; must be part of the "Triple Drug Regimen" to be most effective for chorioamnionitis followed by cesarean.
Ampicillin-Sulbactam	Covers gram-positive bacteria and anaerobes (due to addition of sulbactam); typically needs the addition of an aminoglycoside based on local antibiogram gram-negative bacteria susceptibility patterns.

Antibiotic Considerations for Chorioamnionitis-2

Antibiotic	Discussion
Cefoxitin	Growing resistance among gram-negative bacteria; facilities should review local antibiogram to guide use. Not so good for Group B *Streptococcus* and no *Enterococcus* spp. coverage.
Ceftriaxone	Similar coverage for gram-negative bacteria as aminoglycosides without the safety and monitoring concerns; good gram-positive coverage, needs second drug for anaerobes (often metronidazole); does not cover *Enterococcus* spp. nor *Pseudomonas aeruginosa.* Daily dosing (2g) is advantageous.
Clindamycin	Substantial resistance is developing among pelvic anaerobes (esp. *Bacteroides* spp.). May have beneficial anti-inflammatory and anti-exotoxin effects when used for a serious infection due to *Streptococcus* spp. and *Staphylococcus* spp. (i.e., necrotizing fasciitis or streptococcal toxic shock syndrome).

Antibiotic Considerations for Chorioamnionitis-3

Antibiotic	Discussion
Metronidazole	Excellent anaerobic coverage; inexpensive; oral is equivalent to IV. Opinions vary among clinicians on its use in lactating women; concerns have been related to infant feeding intolerance (metallic taste) and diarrhea. However, current literature demonstrates that breastfed infants receive metronidazole in doses that are less than those used to treat infections in infants.
Piperacillin-tazobactam	Broad spectrum; excellent anaerobic coverage and likely sufficient coverage of gram-positive and gram-negative GU pathogens depending on local antibiogram. Can replace ampicillin/ aminoglycoside/ clindamycin triple regimen with a single drug and may present cost savings. When given as an extended infusion, the first dose is infused over 30 min and then 4 hours later start a 4-hour infusion (extended infusion may be beneficial for patients with sepsis). Concerns: IV-line access and compatibility during extended infusions.
Vancomycin	Added to a chorioamnionitis regimen to provide coverage for MRSA, if needed due to colonization, historical infection, or risks factors (i.e., IV drug use, incarceration, multiple dental carries, health-care worker within a facility with high MRSA rates). Can cover *Enterococcus* spp.

Empiric Management of Chorioamnionitis/Endomyometritis-1

Setting	Preferred Regimens	Type I Allergy to Penicillin (immediate hypersensitivity)	Type I Allergy to cephalosporins or type II-IV Penicillin Allergy
Uncomplicated Chorioamnionitis and Endomyometritis	Ampicillin 2g IV q6h **AND** Aminoglycoside **IF having a cesarean, ADD** Clindamycin 900mg IV q8h **OR** Metronidazole 500mg PO/IV q8h **OR** Piperacillin-tazobactam 4.5g IV q8h, 4-h infusion **OR** Ceftriaxone 2g IV q24h **AND** Metronidazole 500mg PO/IV q8h **OR** Ampicillin-Sulbactam 3g IV q6h **AND** Aminoglycoside	Ceftriaxone 2g IV q24h **AND** Metronidazole 500mg PO/IV q8h	Ertapenem 1g IV q24 hours **OR** Meropenem 1g IV q8 hours

Empiric Management of Chorioamnionitis/Endomyometritis-1

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Empiric Management of Chorioamnionitis/Endomyometritis-2

Setting	Preferred Regimens	Type I Allergy to Penicillin (immediate hypersensitivity)	Type I Allergy to cephalosporins or type II-IV Penicillin Allergy
Serious Illness (signs of end organ injury) (If different from the routine chorioamnionitis regimen above, replace with one of these regimens)	Piperacillin-tazobactam 4.5g IV q8h, 4-h infusion **OR** Ceftriaxone 2g IV q24h **AND** Metronidazole 500mg PO/IV q8h	Ceftriaxone 2g IV q24h **AND** Metronidazole 500mg PO/IV q8h	Meropenem 1g IV q8 hours
Critical Illness (requiring broad spectrum coverage)	Refer to antibiotics for Sepsis of Unknown Source OR Septic Shock		

Empiric Management of Chorioamnionitis/Endomyometritis-2

Setting	Preferred Regimens	Type I Allergy to Penicillin (immediate hypersensitivity)	Type I Allergy to cephalosporins or type II-IV Penicillin Allergy
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Critical Illness (requiring broad spectrum coverage)	Refer to antibiotics for Sepsis of Unknown Source OR Septic Shock		

What about settings with high rates of drug resistance?

- Local and regional antibiograms need to track rates of multi-drug resistant organisms (MDRO) and Extended Spectrum Beta-Lactamase producing organisms (ESBL)
- Once antimicrobial resistance trends show 30% of gram negative isolates (e.g., *E. coli*) as ESBL, the facility should consider moving to meropenem (or the like).
- Judicious use of meropenem is vital in maintaining their effectiveness in the treatment of MDRO infections
- In most hospitals, meropenem is a “protected” antibiotic that requires ID physician approval

How can we administer aminoglycosides within 60 minutes?

Use "Grab-n-Go" Bags

- Tobramycin (Sharp Mary Birch)
  - Premixed and batched tobramycin 440 mg IVPB bags for when a STAT order for tobramycin 7mg/kg is received: Calculated using a dosing window that was within 0.5 mg/kg of the target and within 2 standard deviations of the population.
- Gentamicin (Lucille Packard/Stanford) (for cesarean prophylaxis)
  - The optimal doses for the most common patient weights were calculated based on two weight stratified categories (<120 kg and ≥120 kg) to make approximately 2 mg/kg dosing. Premixed 120 mg bags are stored refrigerated on the Labor unit. Patients with weights <120 kg receive 240 mg (2 bags), patients with weights ≥120 kg receive 360 mg (3 bags).

Postpartum Antibiotics in Chorioamnionitis

- Postdelivery continuation of antibiotics depends on the type of delivery and seriousness of the infection.
- With a vaginal birth either none or one additional dose of antibiotics is recommended.
- For women undergoing cesarean deliveries, most California centers continue the antibiotic regimen until afebrile (<38°C) for 24-48hrs post-op.
- The current (2017) ACOG guidance recommend to give at least one additional dose unless higher risk factors are present (e.g., continued fever, unstable vital signs, bacteremia).
- This recommendation has been made more complicated by the widespread use of continuous ketorolac (Toradol®), acetaminophen, and/or ibuprofen as part of an Enhanced Recovery After Surgery (ERAS) program. This regimen may blunt the development of fever so that an assessment would need to be based on other signs and symptoms.

Chorioamnionitis Recommendations

1) Obstetric unit leadership should collaborate with the antibiotic stewardship team to review their local antibiogram and update standard chorioamnionitis treatment regimens as needed.
2) Given the generally low cost of the recommended antibiotics and the growing concern for bacterial resistance, priority should be placed on selecting antibiotic regimens that provide appropriate aerobic and anaerobic bacterial coverage, while also considering nursing administration efficiency (e.g. frequency of individual doses to administer).
3) A standardized unit approach to chorioamnionitis treatment is strongly recommended, including development of EHR order sets. This will streamline antibiotic selection, facilitate faster pharmacy response times, and ensure clear options for patients with beta-lactam allergies.

Prophylactic Antibiotics on Labor and Delivery

- Pre-op cesarean delivery
  - Cefazolin optimal dose?
  - Azithromycin?
  - What if on antibiotics for chorioamnionitis? For GBS?
  - Penicillin allergic patient
- 3rd/4th laceration repair
- PPROM latency (revised regimen)

Pre-Cesarean Antibiotic Prophylaxis

- Prophylactic antibiotics, prior to incision, is now standard of care
- Cefazolin is the drug of choice
  - Low cost, ease of use, comparable efficacy to other cephalosporins
  - Best when weight adjusted and administered WITHIN 1-hour prior to skin incision
  - Current ACOG recommendation is 1g if <80kg and 2g if >80kg
  - National consensus surgical guidelines in non-obstetric patients* recommend 2g if <120kg and 3g if >120kg
  - Application of this dosing strategy for pre-cesarean cefazolin makes sense for consistency and simplicity

*Bratzler DW, Dellinger EP, Olsen KM, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. Am J Health Syst Pharm. 2013;70:195–283.

What is the role of Azithromycin?

- Azithromycin is an important addition as adjunctive prophylaxis for unscheduled cesarean in the absence of chorioamnionitis.
  - In a large multi-center trial in non-elective cesarean deliveries, women treated with 500mg azithromycin (also receiving cefazolin) had a 50% reduction in the composite rate of wound infections, endometritis and other infections.*
  - No evidence to demonstrate the benefit of azithromycin use for elective cesarean delivery
  - Azithromycin is usually administered over 1-hour, so at times, the infusion may be completed beyond the surgery end time

*Tita AT, Szychowski JM, Boggess K, Saade G, Longo S, et al. Adjunctive azithromycin prophylaxis for cesarean delivery. N Engl J Med 2016;375:1231–41.

What if already on antibiotics for chorioamnionitis?

- Penicillin and ampicillin do not provide adequate coverage of skin flora (such as *Staphylococcus aureus*)
- Therefore, weight-adjusted, pre-surgical cefazolin is required to be administered within 1-hour prior to initial incision. Remember that patients with chorioamnionitis undergoing cesarean delivery need anaerobic coverage and clindamycin may no longer provide adequate coverage (see earlier discussion)
- In patients receiving antibiotics for chorioamnionitis the value of additional azithromycin is limited, if any

What if already on antibiotics for GBS prophylaxis?

- In most circumstances, GBS prophylaxis cannot replace pre-cesarean surgical prophylaxis
- Therefore, weight-adjusted, pre-surgical cefazolin is required to be administered within 1-hour prior to initial incision
- Azithromycin adjunctive surgical prophylaxis should follow pre-surgical cefazolin administration for non-elective cesareans, in the absence of chorioamnionitis

Prophylaxis for the Penicillin Allergic Patient

- The first step is to obtain a thorough allergy history. If the history identifies a strong current (Type I-IV) allergy:
  - ACOG 2018 guidelines recommend clindamycin 900mg IV and gentamicin 5mg/kg IV given prior to surgical incision
  - Per local antibiogram, tobramycin 5-7mg/kg may replace gentamicin
- It should be noted that the above regimen is inferior to cefazolin for *Streptococcus* spp. coverage
- Cefazolin may be considered for patients with history of mild urticaria especially if not recent

Prenatal Evaluation of Penicillin Allergies-1

- Approximately 10% of patients will report having a penicillin class antibiotic allergy, but fewer than 1% of the population is truly allergic to penicillins.
- Furthermore, up to 80% of patients with a true IgE allergic reaction earlier in life lose their sensitivity over time, so even patients with a remote history of true allergy may be able to currently receive antibiotics safely.
- Therefore, a very important task during prenatal care is to evaluate and potentially “de-label” persons with a reported penicillin allergy.

Prenatal Evaluation of Penicillin Allergies-2

- If a reported allergy is suspected to be high risk for a severe reaction such as recent history of anaphylaxis, symptoms consistent with a type I IgE–mediated allergic reaction after recent penicillin exposure (such as respiratory compromise), or a prior reaction history consistent with Type II-IV Hypersensitivity, it is acceptable to accept the label.
- For all others, skin testing is very valuable and recommended by ACOG. A recent study of 46 medium risk pregnant patients found 43 (93%) to be penicillin tolerant on testing consistent with two other studies.

Antibiotic Prophylaxis for 3rd/4th laceration repair

- Several cohort studies and a multicenter RCT in California have demonstrated a 60% reduction in perineal wound complications with a single dose of cefoxitin or cefotetan
- Recent literature suggests cefotetan is inferior to cefoxitin in respects to coverage of *Bacteroides* spp.
- This taskforce recommends a single dose of cefoxitin 2g IV at the time of 3rd/4th degree perineal laceration repair (cefoxitin 1g was used in the OB RCT but cefoxitin 2g is recommended by surgical consensus bodies for bowel surgery)*

*Berríos-Torres SI, Umscheid CA, Bratzler DW, et al; Healthcare Infection Control Practices Advisory Committee. Centers for Disease Control and Prevention guideline for the prevention of surgical site infection, 2017. *JAMA Surg*. 2017;152(8):784-791.

Revised Regimen for PPROM Latency

- In the setting of ruptured membranes without labor prior to 34 weeks gestation prophylactic antibiotics are indicated for latency
- Classic regimen: ampicillin (2g IV q6h) with erythromycin (250mg IV q6h) for 48 hours, followed by amoxicillin (250mg PO q8h) and erythromycin-base (333mg PO q8h) for a total of 7 days
- Unfortunately, erythromycin has notable GI tolerability issues, is costly, and has experienced intermittent shortages
- Recent studies have found that azithromycin was non-inferior for latency, better to prevent chorioamnionitis and about 95% cheaper!
- The current modified regimen at Stanford is azithromycin 1g PO x1 (which replaces the 7 days of erythromycin), ampicillin 2g IV q6h for 48h followed by amoxicillin 250mg po q8h for an additional 5 days.
- Based on local antibiograms, some institutions report concerns for a lack sufficient empiric *E.coli* coverage with ampicillin/ amoxicillin

OB Prophylactic Antibiotics Recommendations

1) Obstetric unit should review and update their OB prophylactic antibiotic standard orders for cesarean delivery and ensure that all drugs are rapidly available on L&D unit
2) We recommend use of Cefoxitin 2g IV x1 for patients with 3rd /4th lacerations
3) We recommend using the revised protocol using azithromycin for PPROM without labor prior to 34 weeks gestation. It should be noted that based on local antibiograms, both protocols may lack adequate empiric coverage of *E. coli*.
4) Prenatal evaluation of reported penicillin allergies is an important part of prenatal care. Hospitals can help by establishing a protocol for allergy evaluation, de-labeling, and staff education.

Antibiotic Considerations for Sepsis in Obstetric Patients

- Antibiotics for sepsis from known/suspected cause
- Source control
- Group A *Streptococcus* (GAS)
- Antibiotics for sepsis from unknown cause

Antibiotics for sepsis from known/suspected cause

Source of Infection	Preferred Regimen	Type I Penicillin Allergy
Septic Abortion or Retained Products of Conception or Pelvic Abscess	Piperacillin-tazobactam 4.5g IV q8h, 4-h infusion **May add** Doxycycline 100mg IV/PO q12h	Cefepime 2g IV q8h **AND** Metronidazole 500mg IV/PO q8h **May add** Doxycycline 100mg IV/PO q12h
Urosepsis	Ceftriaxone 2g IV q24h **May add** Aminoglycoside	

Refer to the CMQCC Sepsis Toolkit for extensive notes, other conditions, and discussion of options for Type II-IV allergies

Importance of Source Control

- Any locus of infection within the body can be difficult to treat with antibiotics alone. This is especially the case if the infection has progressed to an abscess, a soft tissue infection, or is within a body cavity such as the uterus
- In OB, this is of particular importance for patients with Septic Abortion, Retained Products of Conception, or Pelvic Abscess
- It is of life-saving importance for severe Group A *Streptococcus* infections (including Streptococcal Toxic Shock Syndrome) and Necrotizing Fasciitis

Group A *Streptococcus* (GAS)

- The importance of Group A *Streptococcus* (GAS) (*Streptococcus pyogenes*) cannot be overemphasized. It is perhaps the organism most commonly responsible for fatal maternal sepsis.
- GAS can cause a range of infections, including endomyometritis, fulminant endomyonecrosis, necrotizing fasciitis, and Streptococcal toxic shock syndrome (STSS)
- It is also a common organism associated with missed abortions/fetal demise cases and vaginal deliveries with retained products of conception (POC), underscoring the critical need to evacuate the uterus for source control

Clinical criteria for strep toxic shock syndrome (STSS)

- Hypotension
- Multiorgan involvement characterized by two or more of:
  - Renal impairment
  - Coagulopathy
  - Liver dysfunction
  - Acute respiratory distress syndrome
  - Erythematous macular rash (may desquamate)
  - Soft tissue necrosis (e.g., necrotizing fasciitis, myositis, or gangrene)

Treatment of GAS

- Antibiotic therapy for severe GAS infections and STSS includes combination therapy with high dose β-lactam* and clindamycin.
- Clindamycin can be considered to decrease the production of exotoxin and other virulence factors. Linezolid is another option.
- Early surgical intervention (wound debridement, vulvar debridement, evacuating the uterus, or hysterectomy or a combination of these interventions) for source control is critically important for necrotizing fasciitis.

*β-lactam: penicillin or cephalosporin

Necrotizing Fasciitis

- Diagnose necrotizing fasciitis clinically in the presence of fever, pain out of proportion to exam, crepitus, bullae, erythema, and rapid progression of findings
- Prompt surgical management (with tissue pathology and cultures) is critical and confirms the diagnosis
- Empiric Antibiotic Considerations: [piperacillin-tazobactam + vancomycin + clindamycin] or [meropenem + vancomycin + clindamycin]
  - Clindamycin is used for exotoxin reduction for 48-72d hour during hemodynamic instability

Antibiotic Considerations for Sepsis of Unknown Source

- Empiric antibiotic choices should be guided by the local antibiogram
- Empiric coverage for sepsis of unknown source or for septic shock should include coverage for gram-negative bacteria, gram-positive bacteria (including MRSA), and anaerobic bacteria.
- Additional clindamycin can be considered if *Streptococcus* or *Staphylococcus* toxic shock syndrome is a possibility to reduce exotoxin production during hemodynamic instability

Empiric Antibiotic Considerations for Sepsis of Unknown Source or Septic Shock

Piperacillin/tazobactam 4.5g IV q8h **AND** Vancomycin – per institutional protocol (target AUC_{24} 400-600)
For Type I Penicillin Allergy (immediate hypersensitivity-hives, wheezing, anaphylaxis): Cefepime 2g IV q8h **AND** Metronidazole 500mg IV/PO q8h **AND** Vancomycin – per institutional protocol (target AUC_{24} 400-600)

Add Clindamycin 900mg IV q8h; continue for 48-72 hours after hemodynamically stability is achieved

Refer to the CMQCC Sepsis Toolkit for extensive notes and discussion of options for Type II-IV allergies

Sepsis of Unknown Source Further Comments

- Patients who have recently been hospitalized or who have been recently exposed to antibiotics are at risk of being infected with multi-drug-resistant organisms (MDRO), such as methicillin-resistant *Staphylococcus aureus* (MRSA) or extended spectrum beta-lactamase producing (ESBL) organisms
- In these settings, meropenem offers the widest spectrum coverage and thus may be the best empiric option
- Meropenem 1g IV q 8h extended infusion or 500 mg IV q 6h + Vancomycin per institutional sepsis protocol

Antibiotic Recommendations for OB Sepsis

- Every hospital should have a standard Sepsis Antibiotic Order set
- Severe GAS Sepsis Infections and Necrotizing Fasciitis are devastating diagnoses; early recognition is critically important—patient and staff education should emphasize the dangerous nature of severe perineal and/or incisional pain
- Patients who are mislabeled to have true beta-lactam allergies may consequently receive less optimal antibiotic regimens. It is important to fully evaluate all patients with a history of penicillin and other beta-lactam allergies during prenatal care.

Antibiotic Topics Not Covered in the Webinar but Can be Found in the CMQCC OB Sepsis Toolkit

- Detailed medication notes for each antibiotic choice table
- Definitions of allergic reactions and cross reactivities
- Discussion of antibiotic options for Type II-IV PCN allergies for sepsis of known and unknown origin
- Management of allergy-related reactions
- Antibiotic compatibility chart for intravenous administration
- Full set of citations

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