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Peripartum Uterine Infection

Background
Intraamniotic infection, also referred to as chorioamnionitis, is an infection with resultant inflammation of any combination of the amniotic fluid, placenta, fetus, fetal membranes, or decidua.

Intraamniotic infection often is polymicrobial in origin, commonly involves aerobic and anaerobic bacteria, and frequently originates from the vaginal flora. It predominantly occurs by ascending bacterial invasion from the lower genital tract to the typically sterile amniotic cavity. Intraamniotic infection also can occur, although rarely, after invasive procedures (eg, amniocentesis or chorionic villus sampling) or by a hematogenous route secondary to maternal systemic infection (eg, Listeria monocytogenes).

Intraamniotic infection can be associated with acute neonatal morbidity, including neonatal pneumonia, meningitis, sepsis, and death, as well as long-term infant complications such as bronchopulmonary dysplasia and cerebral palsy.

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.

Obstetric care providers diagnose an intraamniotic infection, or when other risk factors for early-onset neonatal sepsis are present in labor (eg, maternal fever, prolonged rupture of the membranes, or preterm birth), communication with the neonatal care team is essential to optimize neonatal evaluation and management.

A. Intrapartum definitions
The diagnosis of intraamniotic infection can be established objectively by amniotic fluid culture, or gram stain, or both and biochemical analysis, but for most women at term who are in labor the diagnosis is primarily made using clinical criteria.

In clinical practice, confirmed intraamniotic infection among women in labor at term will most commonly be made after delivery, based on histopathologic study of the placenta. Therefore, until better and less invasive intrapartum diagnostic tools become available, any practical distinction between suspected and confirmed intraamniotic infection will remain meaningful only in research settings and not for the obstetrician–gynecologist or other obstetric care provider managing a patient in labor. Diagnosis of confirmed histologic intraamniotic infection in the postpartum period does not alter postdelivery maternal treatment

Suspected intraamniotic infection:
-maternal temperature is greater than or equal to 39.0°C (102.2 F)
or
-maternal temperature is 38.0–38.9°C (100.4 – 102.1 F) and one additional clinical risk factor is present. (maternal leukocytosis, purulent cervical drainage, or fetal tachycardia)

Isolated maternal fever:
-maternal temperature between 38.0°C and 38.9°C (100.4 – 102.1 F) with no additional risk factors present, and with or without persistent temperature elevation.

Intrapartum Management
Multivariate models of neonatal sepsis risk demonstrate the positive effect of intrapartum antibiotics on the risk of culture-confirmed neonatal infection. Intrapartum antibiotics also have been shown to decrease maternal febrile morbidity and length of hospital stay. Therefore, in the absence of any clearly documented overriding risks, administration of intrapartum antibiotics is recommended whenever intraamniotic infection is suspected or confirmed. (See Table 1)

Antipyretics can be considered in addition to antibiotics. Proper labor progression should be ensured, given the association between intraamniotic infection and dysfunctional labor progression.

In the absence of contraindications, augmentation of protracted labor in women with intraamniotic infection appears prudent. However, intraamniotic infection alone is not an indication for immediate delivery, and the route of delivery in most situations should be based on standard obstetric indications. Intraamniotic infection alone is rarely, if ever, an indication for cesarean delivery.

In addition, given the potential benefits for the woman and newborn, antibiotics should be considered in the setting of isolated maternal fever unless a source other than intraamniotic infection is identified and documented. (See Table 1)

If planning a cesarean delivery…

<u>Antibiotic Prevention</u> (also see Surgical Preparation)

Single dose
A meta-analysis of 51 antibiotic trials demonstrated no differences in efficacy when first-generation cephalosporins were compared with broader-spectrum second-generation cephalosporins or third-generation cephalosporins for the purpose of surgical prophylaxis in general. After a single 1-g intravenous dose of cefazolin, a therapeutic level is maintained for approximately 3–4 hours.
Regimen:

Cefazolin	< 80 kg	one gram	IV 15 to 60 minutes before skin incision
Cefazolin	> 80 kg	two grams	IV 15 to 60 minutes before skin incision
Cefazolin	> 40 BMI	three grams	IV 15 to 60 minutes before skin incision

If anaphylaxis to penicillin or cephalosporin
Gentamicin 5 mg / kg IV
and
Clindamycin 900 mg IV

Give a second dose of	any antibiotic if > 1500 cc EBL
”	Cefazolin if > 4 hr procedure
“	Clindamycin if > 6 hr procedure

Extended coverage
Due to the rate of post op wound complications and endometritis, we suggest extended coverage against ureaplasma for patients with Cesarean delivery performed:
-during labor
-greater than or equal to 4 hrs of ruptured membranes

Treat with:
Azithromycin 500 mg IV 15 to 60 minutes before skin incision

Local antibiotic resistance
Due to local bacterial resistance patterns, in consultation with the ANMC Antimicrobial Stewardship Program, we suggest adding metronidazole 500 mg IV q 8 hrs in addition to surgical prophylaxis. (Table 1)

Table 1 Treatment of Intraamniotic infection

Primary Regimen	
Ampicillin	2 mg IV q 6
and	
Gentamicin	5 mg/ kg IV per pharmacy
PCN allergy, no anaphylaxis	
Ceftriaxone	2 gm IV q 24 hrs
and	
Gentamicin	5 mg/ kg IV per pharmacy
PCN allergy - anaphylaxis	
Vancomycin	1 gm IV q 12 hrs < 80 kg*
and	
Gentamicin	5 mg/ kg IV per pharmacy
	***** Consult pharmacy 1.5-2.0 g
Planning a cesarean	**Add to surgical prophylaxis**
Metronidazole	500 mg IV q 8 hr
Post vaginal delivery	No additional doses
Post cesarean delivery	One additional dose of antimicrobial agents

Post-delivery with Intraamniotic infection
Data suggest that women who have vaginal deliveries are less likely to have endometritis and may not require postpartum antibiotics.

For women undergoing cesarean deliveries, at least one additional dose of antimicrobial agents after delivery is recommended.

However, the presence of other maternal risk factors such as bacteremia or persistent fever in the postpartum period may be used to guide continuation of antimicrobial therapy, duration of antimicrobial therapy, or both in vaginal and cesarean deliveries.

Isolated maternal fever and suspected or confirmed intraamniotic infection should be communicated to neonatal caregivers at birth. Regardless of evolving national recommendations and local variations in approach, such infants will require enhanced clinical surveillance for signs of developing infection.

B. Endomyometritis
A patient may also develop a fever after delivery. In terms of infectious morbidity, the first 24 hours are often excluded because isolated low grade fever during this period is common and often resolves spontaneously, especially after vaginal birth.

The infection begins in the decidua, and then may extend into the myometrial and parametrial tissues. As above the infection is polymicrobial, usually involving a mixture of two to three aerobes and anaerobes from the lower genital tract.

There are no characteristic sonographic findings associated with postpartum endometritis.

The time of onset of signs and symptoms depends upon several factors, including whether intrauterine infection developed antepartum, intrapartum, or postpartum and the bacterium or bacteria causing the infection. For example, group A streptococcus (GAS) infection should be suspected in patients with early onset, high fever.

An elevated lactic acid concentration is a marker for serious infection.

Definition
Postpartum endomyometritis is defined as a persistent oral temperature of ≥38.0 degrees Celsius (≥100.4 degrees Fahrenheit) with one of the following:
-tachycardia
-midline lower abdominal pain
-uterine tenderness

Other non-specific supporting factors may be:
-Foul lochia, chills, and lower abdominal pain.
-Uterus may be soft and subinvoluted, which can lead to excessive uterine bleeding.
-Initial sepsis is an unusual presentation

Laboratory
-Leukocytosis is present, but this can be a normal finding in postpartum women secondary to the physiologic leukocytosis of pregnancy and the effects of labor
-Vaginal, cervical, endometrial or uterine cultures are not helpful.
-Blood cultures can be useful in guiding the choice of antimicrobial treatment if the patient fails to respond to empiric therapy, if the patient is immunocompromised, or if the patient is septic

Differential diagnoses include:
-Surgical site infection (cesarean delivery incision, episiotomy incision, perineal lacerations)
-Mastitis or breast abscess
-Pyelonephritis
-Aspiration pneumonia
-Unexplained fever with significant back pain after a neuraxial anesthetic, especially when accompanied by neurologic symptoms, may be due to infection or inflammation of the spinal cord.
-Pseudomembranous colitis due to Clostridium difficile is a rare, but potentially serious, cause of postpartum fever. It should be considered in postpartum women who have low-grade fever, abdominal and gastrointestinal symptoms, and recent antibiotic exposure
-Any disorder associated with fever, such as appendicitis or viral syndrome

Management
Treatment is indicated for relief of symptoms and to prevent sequelae, such as peritonitis, salpingitis, oophoritis, phlegmon or abscess, and septic pelvic thrombophlebitis. Prompt administration of appropriate antibiotics is critical in septic patients. Treatment is the same, regardless of mode of delivery. (See Table 2)

Table 2: Treatment of Endomyometritis

First line	
Ceftriaxone	2 gm IV q 24 hrs
and	
Metronidazole	500 mg PO q 8rs
PCN/ Ceph Anaphylaxis	
Vancomycin	1 gm IV q 12 hrs < 80 kg*
and	
Gentamicin	5 mg/ kg IV per pharmacy
and	
Metronidazole	500 mg PO q 8rs
	***** Consult pharmacy 1.5-2.0 g

Duration
Continue intravenous treatment until the patient is clinically improved (no fundal tenderness) and afebrile for at least 24 to 48 hours. Oral antibiotic therapy after successful parenteral treatment is not required, as randomized trials have shown that it does not improve outcome .

If bacteremia was present with a positive blood culture, oral antibiotic therapy is indicated after parenteral antibiotics to complete a seven-day total course of antibiotic therapy.
If the bacteremia is related to group A streptococcal or staphylococcal infection, then consultation with an infectious disease specialist is advised as a longer course of therapy may be indicated.

Intravenous access not available
If intravenous access is not available:
-Amoxicillin-clavulanic acid 875 mg orally every 12 hours OR
-Cefotetan 2 g intramuscularly every 8 hours OR
-Meropenem or imipenem-cilastatin 500 mg intramuscularly every 8 hours OR
-Amoxicillin 500 mg plus metronidazole 500 mg orally every 8 hours

If a prolonged oral antibiotic regimen must be administered for logistics, then use a 14 day course. If an intramuscular antibiotic regimen is used, use 48 to 72 hours of intramuscular therapy and then switch to an oral antibiotic to complete a seven day course.

Sepsis
Endomyometritis can progress rapidly to sepsis. Please consult the ANMC Adult Sepsis / Systemic Inflammatory Response (SIRS) guideline.

C. Prevention: Surgical Preparation

Chlorhexidine Vaginal Preps Background:

From Prevention of infection after gynecologic procedures. ACOG Practice Bulletin No. 195

Recommendation:
1.) Perform preoperative surgical site skin preparation with an alcohol-based agent unless contraindicated.

Chlorhexidine–alcohol is an appropriate choice. Chlorhexidine gluconate and iodophors have a broad spectrum of antimicrobial activity. Alcohol-based and aqueous-based types of each are commercially available, but chlorhexidine is most frequently alcohol based and iodophors aqueous based.

Chlorhexidine appears to achieve greater reductions in skin microflora and has greater residual activity after application than povidone–iodine. In addition, unlike povidone–iodine, chlorhexidine is not inactivated by blood or serum proteins. In the CDC systematic review (Berrios-Torres 2017), meta-analysis of five randomized controlled trials (RCTs) that included 1,976 patients noted that chlorhexidine–alcohol was associated with a reduced risk of surgical site infection compared with aqueous iodophor. The CDC review authors found no difference between chlorhexidine–alcohol and iodophor alcohol in a meta-analysis of six RCTs of 1,323 patients. In a prospective randomized clinical trial of 849 patients, preoperative cleansing of the patient's skin with chlorhexidine–alcohol (2% chlorhexidine gluconate plus 70% isopropyl alcohol) was found to be superior (41% reduction in infections) to cleansing with 10% povidone–iodine for preventing superficial and deep incisional infection within 30 days after clean-contaminated surgeries including hysterectomy. There were no serious adverse events associated with the use of either type of antiseptic. In a retrospective cohort study of patients who underwent abdominal hysterectomy in the Michigan Surgical Quality Collaborative, patients who received preoperative chlorhexidine–alcohol-based skin antisepsis had a 44% lower odds of developing a surgical site infection compared with povidone–iodine (adjusted OR, 0.56; 95% CI, 0.37–0.85).

For povidone–iodine scrubs for abdominal preparation, recommended scrub time can be as long as 5 minutes. The solution should then be removed with a towel and the surgical site painted with a topical povidone–iodine solution, which should be allowed to dry for 2 minutes before draping. Scrub time (gentle, repeated back-and-forth strokes) for chlorhexidine–alcohol preparations should last for 2 minutes for moist sites (inguinal fold and vulva) and 30 seconds for dry sites (abdomen), and allowed to dry for 3 minutes.

Vaginal cleansing with either 4% chlorhexidine gluconate or povidone–iodine should be performed before hysterectomy or vaginal surgery. Currently, only povidone–iodine preparations are approved by the U.S. Food and Drug Administration (FDA) for vaginal surgical site antisepsis. The CDC has recommended alcohol-based preparations, which typically include chlorhexidine, for external perioperative skin preparation, based on studies that suggest superiority over aqueous povidone–iodine preparations, raising the question of chlorhexidine use for vaginal surgical site antisepsis.

In the United States, 4% chlorhexidine gluconate soap (containing 4% isopropyl alcohol) is often used off-label to prepare the vagina in women with iodine allergy, and some U.S. institutions prefer it for routine cases. To avoid irritation, chlorhexidine gluconate with high concentrations of alcohol (eg, 70% isopropyl alcohol, commonly used for skin preparation) is contraindicated for surgical preparation of the vagina. However, solutions that contain lower concentrations, such as the commonly used 4% chlorhexidine gluconate soap containing 4% alcohol, are usually well

tolerated and may be used for vaginal surgical preparation as an alternative to iodine-based preparations in cases of allergy or when preferred by the surgeon.

References: Peripartum Uterine Infection

Intrapartum management of intraamniotic infection. Committee Opinion No. 712. American College of Obstetricians and Gynecologists. Obstet Gynecol 2017;130:e95–101.

Use of prophylactic antibiotics in labor and delivery. ACOG Practice Bulletin No. 199. American College of Obstetricians and Gynecologists. Obstet Gynecol 2018;132:e103-19.

Royal College of Obstetricians and Gynaecologists. Sepsis in Pregnancy, Bacterial (Green-top Guideline No. 64a) https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg64a/ (Accessed 10/15/19)

Tita, T, et al for the C/SOAP Trial Consortium. Adjunctive Azithromycin Prophylaxis for Cesarean Delivery. N Engl J Med 2016; 375:1231-1241 September 29, 2016

Skeith AE, Niu B, Valent AM, Tuuli MG, Caughey AB.. Adding Azithromycin to Cephalosporin for Cesarean Delivery Infection Prophylaxis: A Cost-Effectiveness Analysis. Obstetrics & Gynecology 2017;130:1279-84

Ward E, Duff P. A comparison of 3 antibiotic regimens for prevention of postcesarean endometritis: An historical cohort study. Am J Obstet Gynecol. 2016 Jun;214(6):751.e1-4.

References: Prevention - Surgical Preparation

(CHG resources, chronologically)

Prevention of infection after gynecologic procedures. ACOG Practice Bulletin No. 195. American College of Obstetricians and Gynecologists. Obstet Gynecol 2018;131:e172–89.

Hadiati DR, Hakimi M, Nurdiati DS, da Silva Lopes K, Ota E. Skin preparation for preventing infection following caesarean section. Cochrane Database Syst Rev. 2018 Oct 22;10:CD007462.

Haas DM, Morgan S, Contreras K, Enders S. Vaginal preparation with antiseptic solution before cesarean section for preventing postoperative infections. Cochrane Database Syst Rev. 2018 Jul 17;7:CD007892. (Accessed 10/15/19)

Berrios-Torres SI, Umscheid CA, Bratzler DW, Leas B, Stone EC, Kelz RR, et al. Centers for Disease Control and Prevention guideline for the prevention of surgical site infection, 2017. Healthcare Infection Control Practices Advisory Committee. JAMA Surg 2017;152:784–91.

Springel EH, Wang XY, Sarfoh VM, Stetzer BP, Weight SA, Mercer BM. A randomized open-label controlled trial of chlorhexidine-alcohol vs povidone-iodine for cesarean antisepsis: the CAPICA trial. Am J Obstet Gynecol. 2017 Oct;217(4):463.

Guidelines on core components of infection prevention and control programmes at the national and acute health care facility level. WHO Guidelines Approved by the Guidelines Review Committee. Geneva: World Health Organization; 2016. (Accessed 10/15/19)

Tuuli MG, Liu J, Stout MJ, Martin S, Cahill AG, Odibo AO, Colditz GA, Macones GA. A Randomized Trial Comparing Skin Antiseptic Agents at Cesarean Delivery. N Engl J Med. 2016 Feb 18;374(7):647-55. doi: 10.1056/NEJMoa1511048. Epub 2016 Feb 4.

Ngai IM, Van Arsdale A, Govindappagari S, Judge NE, Neto NK, Bernstein J, Bernstein PS, Garry DJ. Skin Preparation for Prevention of Surgical Site Infection After Cesarean Delivery: A Randomized Controlled Trial. Obstet Gynecol. 2015 Dec;126(6):1251-7.

Quandary: What to do for vaginal prep, OR Manager. 27(8), August,2011, p 1-5. (Accessed 10/15/19) https://www.ormanager.com/wp-content/uploads/2012/06/ORMVol27No08Vaginalprep.pdf

Levin I, Amer-Alshiek J, Avni A, Lessing JB, Satel A, Almog B. Chlorhexidine and alcohol versus povidone-iodine for antisepsis in gynecological surgery. J Womens Health (Larchmt). 2011 Mar;20(3):321-4. doi: 10.1089/jwh.2010.2391. Epub 2011 Feb 16.

Allegranzi B, Bagheri Nejad S, Combescure C, Graafmans W, Attar H, Donaldson L, Pittet D. Burden of endemic health-care-associated infection in developing countries: systematic review and meta-analysis. Lancet. 2011 Jan 15;377(9761):228-41.

Darouiche RO, Wall MJ Jr, Itani KM, Otterson MF, Webb AL, Carrick MM, Miller HJ, Awad SS, Crosby CT, Mosier MC, Alsharif A, Berger DH. Chlorhexidine-Alcohol versus Povidone-Iodine for Surgical-Site Antisepsis. N Engl J Med. 2010 Jan 7;362(1):18-26. doi: 10.1056/NEJMoa0810988.

Culligan PJ, Kubik K, Murphy M, Blackwell L, Snyder J. A randomized trial that compared povidone iodine and chlorhexidine as antiseptics for vaginal hysterectomy. Am J Obstet Gynecol. 2005 Feb;192(2):422-5.

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