POSTPARTUM ENDOMETRITIS

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INTRODUCTION

- Postpartum endometritis refers to infection of the decidua (ie, pregnancy endometrium).
- It is a common cause of postpartum fever and uterine tenderness and is 10- to 30-fold more common after cesarean than vaginal delivery.
- Most infections are mild and resolve with antibiotic therapy; however, in a minority of patients, the infection extends into the peritoneal cavity resulting in peritonitis, intraabdominal abscess, or sepsis.
- Rare patients develop necrotizing myometritis, necrotizing fasciitis of the abdominal wall, septic pelvic thrombophlebitis, or toxic shock syndrome.

MICROBIOLOGY

- Postpartum endometritis is typically a polymicrobial infection involving a mixture of two to three aerobes and anaerobes from the genital tract.

- Aerobes include groups A and B streptococci, Staphylococcus, Klebsiella, Proteus, Enterobacter, Enterococcus, and Escherichia coli.

- Anaerobes include Peptostreptococcus, Peptococcus, Bacteroides, Fusobacterium, Prevotella, and Clostridium.

- In HIV-infected women, the microbiology can be broader and include other less likely pathogens, such as herpes simplex virus and Cytomegalovirus.

- Rare, but potentially lethal, causes of endometritis include Clostridium sordellii , Clostridium perfringens, and streptococcal or staphylococcal toxic shock syndrome .

RISK FACTORS

- Cesarean delivery is the dominant risk factor for development of postpartum endometritis, especially when performed after the onset of labor .
- Among women who receive antibiotic prophylaxis, which has become standard practice, the frequency of postpartum endometritis is approximately 7.0 percent for cesareans performed after the onset of labor and 1.5 percent for those that are scheduled (without antibiotic prophylaxis, the frequencies are approximately 18 and 4 percent, respectively).
- Antibiotic prophylaxis is not standard practice for laboring women expecting to deliver vaginally; the frequency of postpartum endometritis in these women ranges from 0.2 to 2.0 percent.
- Patients with bacterial vaginosis (BV) who undergo cesarean delivery appear to be at particularly high risk for postpartum endometritis. Nearly sixfold increase in risk

Other risk factors for postpartum endometritis include:

- Chorioamnionitis
- Prolonged labor
- Prolonged rupture of membranes
- Multiple cervical examinations
- Internal fetal or uterine monitoring
- Large amount of meconium in amniotic fluid
- Manual removal of the placenta
- Low socioeconomic status
- Maternal diabetes mellitus or severe anemia
- Preterm or postterm birth
- Operative vaginal delivery
- Obesity
- HIV infection
- Colonization with group B Streptococcus
- Nasal carriage of Staphylococcus aureus
- Heavy vaginal colonization by E. coli

CLINICAL FINDINGS

- The key clinical findings present in most women with postpartum endometritis are:

- Fever
- Uterine tenderness
- Tachycardia that parallels the rise in temperature
- Midline lower abdominal pain

- The uterus may be slightly soft and subinvoluted, which can lead to excessive uterine bleeding.

- Additional findings observed in some women include malodorous purulent lochia, headache, chills, malaise, and/or anorexia.

- The time of onset of signs and symptoms depends on several factors, including whether intrauterine infection developed antepartum, intrapartum, or postpartum and the bacterium or bacteria causing the infection.

- For example, group A Streptococcus infection should be suspected in patients with an early-onset infection and high fever.

ALARM FINDINGS

The following findings are one academic teaching hospital's criteria for suspecting severe infection/sepsis in febrile postpartum patients, based on expert opinion:

- Fever ≥103°F (39.4°C) or
- Fever ≥102°F (38.9°C) plus one or more of the following:

• Heart rate ≥110 beats/minute, sustained for at least 30 minutes Respiratory rate ≥20 respirations/minute, sustained for at least 30 Minutes.

• Manual white blood cell (WBC) differential showing ≥10 percent Bands.

• Blood pressure ≤90/60 mmHg, sustained for at least 30 minutes.

- An elevated lactic acid concentration (>2 mmol/L) is also a marker for serious infection.
- In severely ill postpartum patients (eg, those with tachycardia, tachypnea, hypotension out of proportion to the clinical scenario), sepsis should still be considered even if they are afebrile.
- In a study of maternal deaths in Michigan, 3 of the 11 mothers who died of sepsis had no fever during the hospitalization.

LABORATORY

- The WBC count is elevated (15,000 to 30,000 cells/microL), but this can be a normal finding in postpartum women secondary to the physiologic leukocytosis of pregnancy and the effects of labor .

- Mean WBC counts in laboring patients range from 10,000 to 16,000 cells/microL, with an upper level as high as 29,000 cells/microL.

- A left shift (bandemia) and a rising, rather than falling, neutrophil count postpartum are suggestive of an infectious process.

- Bacteremia occurs in 5 to 20 percent of patients.

IMAGING

- There are no characteristic sonographic findings associated with postpartum endometritis .
- Imaging findings are nonspecific and overlap with expected postpartum changes (nonspecific uterine enlargement, endometrial fluid, and/or gas).
- Computed tomography shows similar findings as ultrasound .

DIAGNOSTIC EVALUATION

The diagnostic evaluation of postpartum patients with fever and/or pain includes:

- **History/physical** examination to determine the possible source of the signs and symptoms.

- **Complete blood count** with differential.

- **Urine culture**.

ROLE OF BLOOD AND ENDOMETRIAL CULTURES

- In uncomplicated infections, it is not important to establish the microbiologic cause since empiric treatment with broad spectrum antibiotics is usually effective.

- **Blood cultures** – There is no consensus on whether blood cultures should be obtained routinely during the initial evaluation.

- Although bacteremia occurs in 5 to 20 percent of patients, blood cultures are costly, the initial choice of antibiotic therapy has to be made before the results are available, and the results usually do not lead to a change in the initial empiric antibiotic regimen.

- For these reasons, we do not obtain blood cultures routinely in women with endometritis.

- However, blood cultures can be useful in guiding the choice of antimicrobial treatment in patients who have alarm findings , are immunocompromised, are septic, or fail to respond to empiric antibiotic therapy within 24 to 48 hours.

- Interestingly, only a single organism may be identified in culture despite polymicrobial endometrial infection.

ENDOMETRIAL CULTURES

- Endometrial cultures are not performed because of the difficulty in obtaining an uncontaminated specimen through the cervix.
- Furthermore, they yield results too late for clinical use while rarely changing treatment.

DIAGNOSIS

Diagnostic criteria for postpartum endometritis

- Postpartum endometritis is primarily a clinical diagnosis based on characteristic signs and symptoms and presence of risk factors.

- In the United States, the diagnosis is made in a patient with at least two of the following signs or symptoms.

- Fever (≥100.4°F [38°C])
- Pain or tenderness (uterine or abdominal) with no other recognized cause
- Purulent drainage from the uterus

- The presence of tachycardia and/or leukocytosis supports the diagnosis, but these findings are nonspecific.
- Fever is a key sign because variable degrees of midline abdominal pain, uterine tenderness, and leukocytosis are common after cesarean delivery, and to a lesser extent after vaginal delivery, in the absence of infection.
- Some degree of malodorous yellow-red lochia is also normal after any delivery.
- Imaging is not helpful for making the diagnosis, but it can be helpful to exclude other diagnoses (eg, retained products of conception, infected hematoma, uterine abscess).

ENDOMETRITIS WITH TOXIC SHOCK SYNDROME

- **Group A Streptococcus** infection should be suspected in patients with early-onset infection (within the first 48 hours postpartum) and high fever (>101.3°F [38.5°C]).

- High fever with hypotension and tachycardia plus involvement of at least two other organ systems (eg, renal, liver, or pulmonary insufficiency; coagulopathy; soft tissue necrosis; erythematous macular rash with desquamation) suggests toxic shock syndrome.

ENDOMETRITIS WITH TOXIC SHOCK SYNDROME

- An influenza-like syndrome characterized by fever, chills, myalgia, nausea, vomiting, and diarrhea occurs in approximately 20 percent of patients.

- Although pain is often severe with GAS, the uterus may be boggy and nontender in patients with necrotizing myometritis due to diminished innervation .

- For patients that meet the above clinical criteria, isolation of GAS from a normally sterile site (eg, blood, cerebrospinal fluid, joint fluid, pleural fluid, pericardial fluid, peritoneal fluid, tissue biopsy, or surgical wound) confirms the diagnosis.

ENDOMETRITIS WITH TOXIC SHOCK SYNDROME

- **Staphylococcal toxic shock syndrome** is characterized by high fever >102°F (38.9°C), hypotension, diffuse erythroderma, desquamation (unless the patient dies before desquamation can occur), and involvement of at least three organ systems.

- Onset may be early (within 24 hours of delivery) and difficult to distinguish from GAS toxic shock in the absence of laboratory confirmation .

ENDOMETRITIS WITH TOXIC SHOCK SYNDROME

- **C. sordellii** has been associated with a distinctive, lethal toxic shock-like syndrome.

- **C. perfringens** should be considered in patients who rapidly become gravely ill with evidence of intravascular hemolysis, which may be severe.

DIFFERENTIAL DIAGNOSIS

- In women with postpartum fever but no or minimal uterine tenderness or purulent vaginal discharge, other sources of postpartum fever should be considered.

- Any disorder associated with fever, such as appendicitis or viral syndrome, can present with fever in the postpartum period.

- Many of these disorders can be diagnosed or excluded by history and physical examination alone; in the remainder, laboratory and/or imaging studies will clarify the diagnosis.

Some common causes of fever in postpartum patients include:

- Surgical site infection (eg, cesarean delivery incision, episiotomy incision, perineal lacerations) is typically evident on physical examination of the surgical site (eg, local erythema, edema, and/or tenderness).

- Mastitis or breast abscess is usually evident on physical examination of the breast (eg, local erythema, edema, and/or tenderness) and typically occurs later in the postpartum course (the first three months of breastfeeding).

- Breast engorgement (fullness and firmness accompanied by pain and tenderness) may also lead to a low-grade fever in women 24 to 72 hours postpartum.

- Pyelonephritis is characterized by fever (>100.4°F [38°C]), chills, flank pain, costovertebral angle tenderness, and possibly lower urinary tract symptoms. Pyuria and/or a positive urine culture supports the diagnosis.

- Aspiration pneumonia presents with fever, dyspnea, and possibly hypoxemia. Lung auscultation may reveal diffuse crackles, and a chest radiograph will show infiltrates.

- 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 Clostridioides (formerly 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.

TREATMENT

- Broad spectrum parenteral antibiotics that include coverage for betalactamase-producing anaerobes are typically recommended, given the microbiology of these infections.

- Oral antibiotics are an option for mild endometritis diagnosed after the patients have been discharged, especially those post vaginal birth.

PREFERRED INITIAL REGIMEN (NO GBS COLONIZATION)

The following intravenous (IV) regimen is for patients with normal renal function and results in resolution of infection in 90 to 97 percent of cases:

- Clindamycin 900 mg every 8 hours plus

- Gentamicin 5 mg/kg every 24 hours (preferred) or 1.5 mg/kg every 8 hours (without a loading dose)

- Extended interval dosing of gentamicin (5 mg/kg every 24 hours) is more convenient and cost-effective and as efficacious and safe as thrice daily dosing (1.5 mg/kg IV every 8 hours) for patients with normal renal function and, thus, is preferred (risk of treatment failure with once versus thrice daily dosing.

- Gentamicin levels do not need to be monitored in patients receiving a gentamicin dose every 24 hours who have normal renal function and an expected short duration of therapy (≤72 hours or three doses), which is common in this population.

- One concern with this regimen is increasing resistance to clindamycin among anaerobic bacteria, with widely varying rates of resistance among different geographic regions and institutions.

- In geographic regions or institutions where B. fragilis has significant clindamycin resistance, ampicillin-sulbactam (3 g IV every six hours) is a reasonable alternative.

- Another concern regarding this regimen is increasing resistance of group B Streptococcus (GBS) isolates to clindamycin.

PREFERRED INITIAL REGIMEN (GBS COLONIZATION)

Resistance to clindamycin in GBS isolates ranges from 13 to 43 percent. For those patients who are known to be colonized with GBS as a result of universal screening, we suggest:

- Clindamycin 900 mg every 8 hours plus
- Gentamicin 5 mg/kg every 24 hours (preferred) or 1.5 mg/kg every 8 hours (without a loading dose) plus
- Ampicillin 2 g IV every 6 hours

or

- Ampicillin-sulbactam 3 g IV every 6 hours

OTHER INTRAVENOUS DRUG OPTIONS

- The combination of gentamicin, ampicillin, and metronidazole is another option that provides good activity against most anaerobes; however, metronidazole is avoided in breastfeeding women when similarly effective drugs with better safety profiles are available.

DURATION OF THERAPY

- A response to the initial antibiotic regimen should be evident within 24 to 48 hours.
- IV treatment is typically continued until the patient is clinically improved (no fundal tenderness) and afebrile for 24 to 48 hours.
- Oral antibiotic therapy after successful parenteral treatment is unnecessary as it did not improve outcome in randomized trials .

OPTIONS WHEN INTRAVENOUS THERAPY IS NOT POSSIBLE

- Clindamycin 600 mg orally every 6 hours plus gentamicin 4.5 mg/kg intramuscularly every 24 hours

or

- Amoxicillin-clavulanic acid 875 mg orally every 12 hours

or

- Cefotetan 2 g intramuscularly every 8 hours

or

- Meropenem or imipenem with cilastatin 500 mg intramuscularly every 8 hours

or

- Amoxicillin 500 mg plus metronidazole 500 mg orally every 8 hours

- If an oral antibiotic regimen is administered, we suggest a 14 day course.

- If an intramuscular antibiotic regimen is used, we suggest 48 to 72 hours of intramuscular therapy and then switching to an oral antibiotic to complete a seven-day course.

PERSISTENT POSTPARTUM FEVER

- As discussed above, most patients respond favorably to the initial antibiotic regimen within 24 to 48 hours.
- If the patient has not improved by this time or has deteriorated, then the antibiotic regimen is modified and an evaluation for other sources of infection is indicated.

- Approximately 20 percent of treatment failures are due to organisms, such as enterococci, that are resistant to cephalosporins or clindamycin plus gentamicin.

- In the absence of information from blood cultures, the addition of ampicillin 2 g IV every six hours to the clindamycin plus gentamycin regimen, as well as a repeat physical examination to exclude another source of fever, can be an effective approach if the patient was not already on ampicillin .

- Alternatively, the initial antibiotics can be discontinued, and ampicillin-sulbactam can be initiated if the patient was not already on ampicillin.

- Vancomycin can be used instead of ampicillin in patients with immunoglobulin E (IgE)-mediated, immediate allergic reactions, including anaphylaxis.

- If adding ampicillin or changing to ampicillin-sulbactam does not result in clinical improvement within 24 hours of the change in antibiotic regimen, then physical examination, complete blood count with differential, blood and urine cultures, and pelvic imaging (eg, ultrasound, CT) to evaluate for other etiologies of signs and symptoms are performed.

- Sources of persistent fever include an infected hematoma, pelvic cellulitis or abscess, surgical site infection, septic pelvic thrombophlebitis, ovarian vein thrombosis, and myometrial necrosis.

- The possibility of a nonpelvic source of fever, such as pneumonia or pyelonephritis, should also be reconsidered

- Retained products of conception after delivery (almost always vaginal delivery) can cause acute or chronic endometritis related to microbial infection of the necrotic products of conception.

- Ultrasound may demonstrate the retained tissue.

- Curettage to remove the necrotic material may be necessary to resolve the infection.

- It is important to not curette the endometrium too vigorously as this can lead to uterine perforation, adhesion formation, and subsequent infertility (ie, Asherman syndrome). For this reason, suction curettage is preferable to sharp curettage.

- The possibility of drug fever should be considered in the absence of any positive findings on physical examination or imaging studies and a pulse rate that does not vary significantly and does not parallel the patient's temperature.

- Drug fever can be defined as "a disorder characterized by fever coinciding with the administration of the drug and disappearing after the discontinuation of the drug, when no other cause for the fever is evident after a careful physical examination and laboratory investigation."

RELAPSE OF ENDOMETRITIS

- For patients who present with recurrent signs/symptoms of endometritis after having been treated for endometritis on initial hospitalization, the details of the therapy and relevant laboratory/imaging results from initial hospitalization should be reviewed, if available.

- If prior cultures were performed, then we target antibiotic therapy to cover the organisms that were identified.
- ● If no organism was identified, then we restart the same regimen that was administered during the initial hospitalization.
- ● If the regimen used during the initial hospitalization is not known, then we start clindamycin, gentamicin, and ampicillin at the doses described above.
- Other sources of infection and causes of fever should be considered, with appropriate intervention.

LATE-ONSET POSTPARTUM ENDOMETRITIS

- Most cases of endometritis develop within the first week after delivery, but 15 percent present between one and six weeks postpartum.
- Delayed presentation is more common after vaginal than cesarean delivery, and it may present as late postpartum hemorrhage.
- Most women with late postpartum endometritis have mild clinical signs and symptoms.
- Parenteral, inpatient treatment is probably unnecessary, although the optimum route of drug delivery has not been evaluated in comparative trials.

For broad spectrum oral therapy, we use:

- Amoxicillin-clavulanate 875 mg orally twice a day for seven days.
- In penicillin-allergic patients, we use clindamycin 600 mg orally every six hours for seven days.
- We do not consider these drugs contraindicated in breastfeeding mothers.

PREVENTION

At cesarean delivery

- **Role of antibiotic prophylaxis** – Antibiotic prophylaxis within 60 minutes prior to making the skin incision is routinely recommended as it significantly reduces the incidence of postcesarean delivery endometritis, for both planned and intrapartum procedures.

- Vaginal preparation with an antiseptic solution (eg, povidone-iodine, chlorhexidine) immediately before cesarean delivery also reduces the incidence of postcesarean endometritis.

- Intrauterine antibiotic irrigation just before closure of hysterotomy incision may be as effective as preoperative intravenous (IV) infusion, probably because the drug is absorbed into the systemic circulation.

- Nevertheless, irrigation has fallen out of favor because it does not appear to offer any advantage over IV therapy and may have disadvantages, such as variable absorption.

- Role of placental delivery method – For women undergoing cesarean delivery, four randomized trials with a total of over 2000 subjects reported that spontaneous delivery of the placenta resulted in a significant reduction in postpartum endometritis compared with manual removal.

AT VAGINAL DELIVERY

- **Role of antibiotic prophylaxis** – Women undergoing vaginal delivery are not routinely given antibiotic prophylaxis given their low rate of postpartum endometritis (0.2 to 2.0 percent).

- There are few data from randomized trials regarding the efficacy of antibiotic prophylaxis to prevent endometritis in women at high risk.

- **Role of placental delivery method** – Spontaneous rather than manual delivery of the placenta is routine at vaginal delivery, but manual extraction is sometimes necessary.

- No randomized trials have evaluated use of prophylactic antibiotics in women who undergo manual removal of placenta .

WOMEN WITH BACTERIAL VAGINOSIS

- The risk of postpartum endometritis may be reduced by treating women with symptomatic bacterial vaginosis (BV) late in pregnancy.

- We do not routinely screen asymptomatic women for BV to reduce the risk of postpartum endometritis as there are no data that this is a cost-effective approach.

- Thanks