Sepsis in Pregnancy

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Bacterial Sepsis in Pregnancy

- Sepsis in pregnancy remains an important cause of maternal death.
- Sepsis may be defined as infection plus systemic manifestations of infection.
- Severe sepsis may be defined as sepsis plus sepsis-induced organ dysfunction or tissue hypoperfusion.
- Septic shock is defined as the persistence of hypoperfusion despite adequate fluid replacement therapy

Which women are at risk of sepsis in pregnancy?

- **Multiple risk factors for severe sepsis have been identified by the Confidential Enquiries into Maternal Deaths (CEMD):**
- Obesity
- Impaired glucose tolerance / diabetes
- Impaired immunity/ immunosuppressant medication
- Anemia
- Vaginal discharge
- History of pelvic infection
- History of group B streptococcal infection
- Amniocentesis and other invasive procedures
- Cervical cerclage
- Prolonged spontaneous rupture of membranes
- GAS infection in close contacts / family members Of black or other minority ethnic group origin

What should prompt recognition of sepsis in the pregnant woman?

- All healthcare professionals should be aware of the symptoms and signs of maternal sepsis and critical illness and of the rapid, potentially lethal course of severe sepsis and septic shock. Suspicion of significant sepsis should trigger an urgent referral to secondary care.
- Clinical signs suggestive of sepsis include one or more of the following: pyrexia, hypothermia, tachycardia, tachypnea, hypoxia, hypotension, oliguria, impaired consciousness and failure to respond to treatment.
- These signs, including pyrexia, may not always be present and are not necessarily related to the severity of sepsis.
- Regular observations of all vital signs (including temperature, pulse rate, blood pressure and respiratory rate) should be recorded on a Modified Early Obstetric Warning Score (MEOWS) chart.
- All staff taking observations should have annual training in the use of the MEOWS chart.

Clinical features suggestive of sepsis

- Fever
- Diarrhea or vomiting - may indicate exotoxin production (early toxic shock)
- Rash (generalized streptococcal maculopapular rash or purpura fulminans)
- Abdominal /pelvic pain and tenderness
- Offensive vaginal discharge (smelly suggests anaerobes; serosanguinous suggests streptococcal infection)
- Productive cough
- Urinary symptoms

What are the appropriate investigations when sepsis is suspected?

- **Blood cultures** are the key investigation and should be obtained prior to antibiotic administration;
- however, **antibiotic treatment** should be started without waiting for microbiology results.
- **Serum lactate** should be measured within **six hours** of the suspicion of severe sepsis in order to guide management.
- Serum lactate ≥4 mmol/l is indicative of tissue hypoperfusion.
- Any **relevant imaging studies** should be performed promptly in an attempt to confirm the source of infection.

Tasks to be performed within the first six hours of the identification of severe sepsis

- Obtain blood cultures prior to antibiotic administration
- Administer broad-spectrum antibiotic within one hour of recognition of severe sepsis
- Measure serum lactate
- In the event of hypotension and/or a serum lactate >4mmol/l deliver an initial minimum 20ml/kg of crystalloid or an equivalent.
- Apply vasopressors for hypotension that is not responding to initial fluid resuscitation to maintain mean arterial pressure (MAP) >65mmHg
- In the event of persistent hypotension despite fluid resuscitation (septic shock) and/or lactate >4mmol/l
- a. Achieve a central venous pressure (CVP) of >8mmHg
- b. Achieve a central venous oxygen saturation (ScvO2) >70% or mixed venous oxygen saturation (ScvO2) > 65%

Who should be involved in the collaborative care of women with sepsis?

- If sepsis is suspected, regular frequent observations should be made.
- The use of a MEOWS chart is recommended. There should be an urgent referral to the critical care team in severe or rapidly deteriorating cases, and the involvement of a consultant obstetrician.
- The expert advice of a consultant microbiologist or infectious disease physician should be sought urgently when serious sepsis is suspected.

Modified Early Warning Score (MEWS)

Score	3	2	1	0	1	2	3
Resp. frekv.		<9		9-14	15-20	21-29	30
Puls/min		≤ 40	41-50	51-100	101-110	111-129	≥ 130
Sys t. BT	≤ 70	71-80	81-100	101-199		≥ 200	
Temp °C		≤35	35,1-36	36,1-38	38,1-38,5	>38,5	
CNS			Nytilkommen forvirring	Klar og orientert	Reagerer på tiltale	Reagerer på smerte	Reagerer ikke
Urin	0 ml/t	< 20 ml/t	<35 ml/t		Stor urinprod.		

Om personalet har en alvorlig uro over hvordan pasientens tilstand utvikler seg, eller om SaO_2 akutt endres til < 90 % med O_2 (gitt etter avdelingens rutiner for oksygenbehandling) → Kontakt intensiv ved MEWS > 4 calling nr: 26915

What empirical and specific antimicrobial therapy should be used to treat the woman?

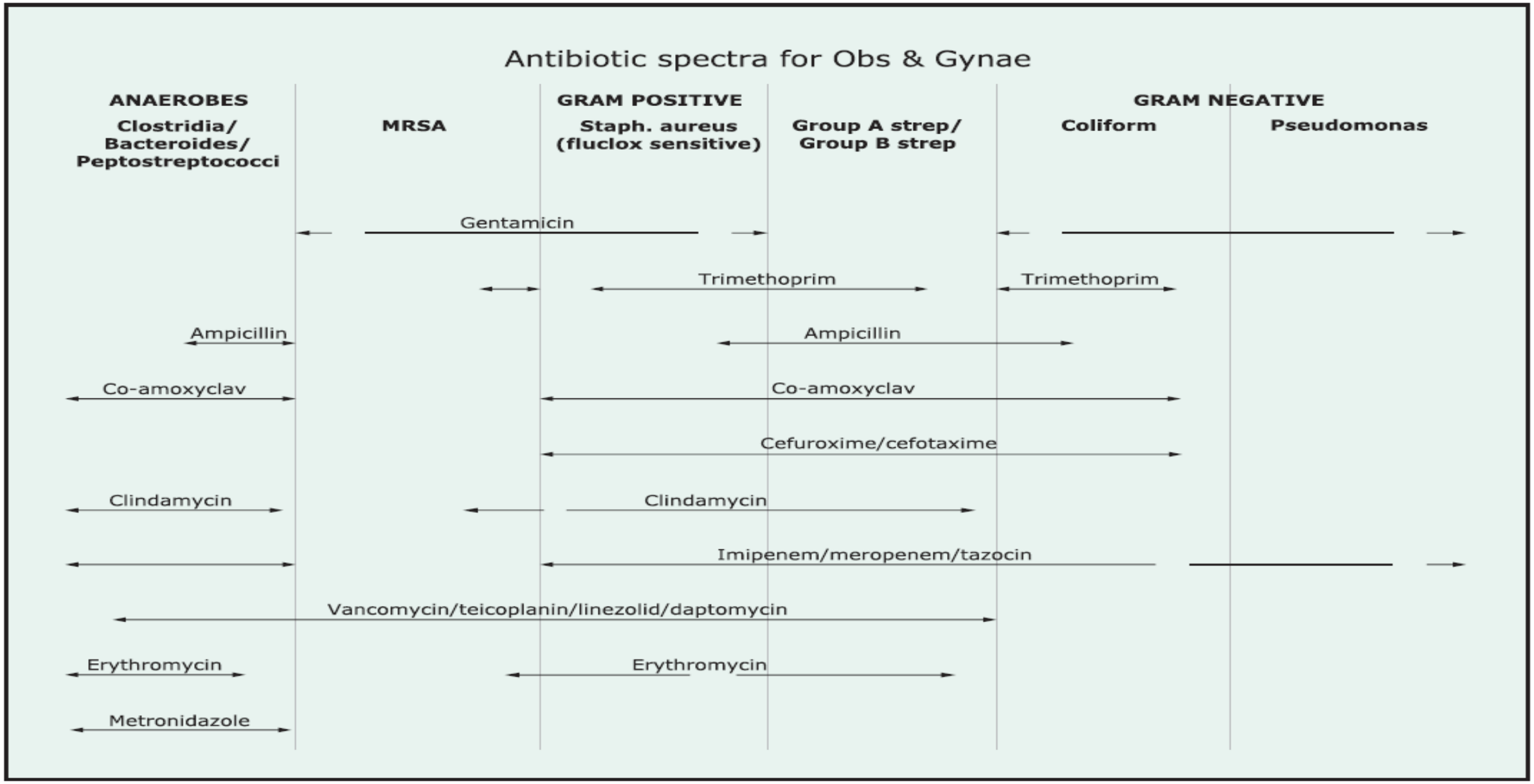
- Administration of intravenous **broad spectrum antibiotics** is recommended within one hour of suspicion of severe sepsis, with or without septic shock.

- If genital tract sepsis is suspected, prompt early treatment with a combination of high-dose broad spectrum intravenous antibiotics may be lifesaving.

Antimicrobial choices and limitations of antimicrobial

- Co-amoxiclav: Does not cover MRSA or *Pseudomonas*, and there is concern about an increase in the risk of necrotizing enterocolitis in neonates exposed to co-amoxiclav in utero.
- Metronidazole: Only covers anaerobes.
- Clindamycin: Covers most streptococci and staphylococci, including many MRSA, and switches off exotoxin production with significantly decreased mortality. Not renally excreted or nephrotoxic.
- Piperacillin–tazobactam (Tazocin) and carbapenems :Covers all except MRSA and are renal sparing (in contrast to aminoglycosides).
- Gentamicin: (as a single dose Poses no problem in normal renal function but if doses are to be given regularly serum levels must be of 3–5mg/kg) monitored.

Antibiotic spectra for obstetrics and gynaecology.



What is the role of intravenous immunoglobulin (IVIG)?

- **IVIG is recommended for severe invasive streptococcal or staphylococcal infection if other therapies have failed.**

How should the fetus be monitored and when and how should the baby be delivered?

- In a critically ill pregnant woman, birth of the baby may be considered if it would be beneficial to the mother or the baby or to both.
- A decision on the timing and mode of birth should be made by a senior obstetrician following discussion with the woman if her condition allows.
- If preterm delivery is anticipated, cautious consideration should be given to the use of antenatal corticosteroids for fetal lung maturity in the woman with sepsis.
- During the intrapartum period, continuous electronic fetal monitoring is recommended.
- Changes in cardiotocography (CTG), such as changes in baseline variability or new onset decelerations, must prompt reassessment of maternal mean arterial pressure, hypoxia and acidemia.
- Epidural/spinal anesthesia should be avoided in women with sepsis and a general anesthetic will usually be required for caesarean section.

How should the fetus be monitored and when and how should the baby be delivered?

- During the intrapartum period, continuous electronic fetal monitoring is recommended in the presence of maternal pyrexia (defined as a temperature >38.0 °C once, or 37.5 °C on two occasions 2 hours apart) and this should also apply to sepsis without pyrexia.

What prophylaxis should be considered for the neonate, other family members and healthcare workers?

- Local and national guidelines should be followed in consultation with the local health protection unit or lead for communicable disease control.
- When a mother has been found to have invasive group A streptococcal infection in the peripartum period, the neonatologist should be informed and prophylactic antibiotics administered to the baby.
- Close household contacts of women with group A streptococcal infection should be warned to seek medical attention should symptoms develop, and the situation may warrant antibiotic prophylaxis.
- Healthcare workers who have been exposed to respiratory secretions of women with group A streptococcal infection should be considered for antibiotic prophylaxis.

What infection control issues should be considered?

- Group A Β-hemolytic *Streptococcus* and MRSA are easily transmitted via **the hands** of healthcare workers and via close contact in households.
- Local infection control guidelines should be followed for hospital–specific isolation and contact precautions.
- Invasive group A streptococcal infections are notifiable and the infection control team and the consultant for communicable diseases should be informed.

- Women suspected of or diagnosed with group A *Streptococcus* sepsis should be isolated in a single room within suite facilities to minimize the risk of spread to other women.

Infection, documented or suspected, and some of the following:

- **General variables:**
- Fever (>38ºC)
- Hypothermia (core temperature <36ºC)
- Tachycardia (>100 beats per minute)
- Tachypnoea (>20 breaths per minute)
- Impaired mental state
- Significant edema or positive fluid balance (>20ml/kg over 24 hours)
- Hyperglycemia in the absence of diabetes (plasma glucose >7.7 mmol/l)

Infection, documented or suspected, and some of the following:

- **Inflammatory variables:**
- White blood cell (WBC) count >12 x 109/l (note that a transient leucocytosis is common in labor)
- Leucopenia (WBC count <4 x 109/l)
- Normal WBC count with >10% immature forms
- Plasma C-reactive protein >7mg/l
- **Hemodynamic variables:**
- Arterial hypotension (systolic blood pressure <90mmHg; mean arterial pressure <70mmHg or systolic blood pressure decrease >40mmHg)
- **Tissue perfusion variables:**
- Raised serum lactate > 4 mmol/l
- Decreased capillary refill or mottling

Infection, documented or suspected, and some of the following:

- **Organ dysfunction variables:**
- Arterial hypoxemia (PaO2 (arterial oxygen partial pressure) /FIO2 (fraction of inspired oxygen) <40kPa).
- Sepsis is severe if <33.3kPa in the absence of pneumonia or <26.7kPa in the presence of pneumonia.
- Oliguria (urine output <0.5ml/kg/hr for at least two hours, despite adequate fluid resuscitation)
- Creatinine rise of >44.2µmol/l. Sepsis is severe if creatinine level >176µmol/l
- Coagulation abnormalities (International Normalized Ratio [INR] >1.5 or activated partial thromboplastin time [APTT] >60s)
- Thrombocytopenia (platelet count <100 x 109/l)
- Hyperbilirubinemia (plasma total bilirubin> 70µmol/l)
- Ileus (absent bowel sounds)

Staphylococcal toxic shock

- 1. Fever > = 39.9°C
- 2. Rash – diffuse macular erythroderma
- 3. Desquamation – 10 to 14 days after onset of illness, especially palms and soles.
- 4. Hypotension – systolic BP < 90 mm Hg adults
- 5. Multisystem involvement

Staphylococcal toxic shock

- Three or more of the following systems affected:
- Gastrointestinal – vomiting or diarrhea at onset illness
- Muscular – severe myalgia or elevated creatinine phosphokinase
- Mucous membranes – vaginal, oro-pharyngeal or conjunctival hyperemia
- Renal – creatinine twice the upper limit of normal
- Hepatic – total bilirubin twice the upper limit of normal
- Hematological – platelets < = 100 x 109/l
- Central nervous system – disorientation or alterations in consciousness without focal neurological signs

Streptococcal toxic shock syndrome

- A. Isolation of beta-hemolytic group A *Streptococcus* from:
- 1. normally sterile site – blood, CSF, peritoneal fluid, tissue biopsy
- 2. non-sterile site – throat, vagina, sputum

Streptococcal toxic shock syndrome

- B. Clinical case definition
- 1. Hypotension plus
- 2. Two or more of the following:
- Renal impairment – creatinine >176μmol/l
- Coagulopathy – platelets < 100 x 109/l or disseminated intravascular
- Hepatic – total bilirubin twice the upper limit of normal coagulation
- Liver involvement – alanine transaminase or aspartame
- Acute respiratory distress syndrome
- Generalized erythematous macular rash (present in 10%) – may
- Desquamate Soft tissue necrosis including necrotizing fasciitis, myositis or gangrene

Case classification:

- Probable – four of the five clinical findings positive Probable – meets clinical case definition (above) plus isolation from non-sterile site
- Confirmed – case with all five clinical findings
- Definite – meets clinical case definition (above) plus isolation of group A *Streptococcus* from a normally sterile site

Approach to Resuscitation in Pregnancy

- Optimal stabilization of the fetus depends on adequate resuscitation of the mother.
- Initial resuscitation should include IV fluid administration and optimized positioning.
- The left lateral decubitus position maximizes patient hemodynamics in the third trimester, improving preload by decreasing inferior vena cava compression.
- Fluid resuscitation should begin within the first three hours of presentation with an initial recommended volume of 30 milliters per kilogram of crystalloid if either hypotension or lactic acid >4 millimoles per liter (mmol/L) is present.
- Due to increased blood volume in pregnancy, a lactic acid threshold of 4 mmol/L may lack sensitivity in this population.

Approach to Resuscitation in Pregnancy

- No specific guidelines exist for vasopressors preference in pregnant patients.
- Although there is no explicit recommendation for mean arterial pressure optimization for sepsis in pregnancy, 65 mm Hg is a reasonable resuscitation goal.
- Fetal monitoring can provide further titration feedback.
- The 2016 Society of Critical Care Medicine guidelines do not offer recommendations tailored for the pregnant patient, although their current data support the use of norepinephrine as the first-line vasopressor in pregnant septic patients.
- Due to the paucity of data, there is scant evidence to suggest that administration of norepinephrine causes negative fetal outcomes, or to suggest how norepinephrine administration impacts fetal outcome.

Approach to Resuscitation in Pregnancy

- The choice for second-line vasopressor has been extrapolated from controlled studies with spinal anesthetics and is therefore controversial for application in sepsis.
- Phenylephrine and ephedrine are often used as second-line agents, although with known tachyphylaxis.
- Unlike ephedrine, phenylephrine does not alter the fetal acid-base status, although its alpha stimulation generates reflex maternal bradycardia and diminished cardiac output.
- In comparison, ephedrine does not generate bradycardia, although its indirect action to release pre-existing maternal catecholamines may prove less efficacious in a septic patient who has already exhausted her endogenous stores and expended her cardiac reserve.

Approach to Resuscitation in Pregnancy

- The data on vasopressor use in pregnancy are typically derived from C-section deliveries, many of which are elective.
- In the Task Force on Obstetric Anesthesia, the American Society of Anesthesiologists recommended phenylephrine over ephedrine because of the preferred fetal acid-base status, as ephedrine causes fetal acidemia.

Approach to Resuscitation in Pregnancy

- Other treatment considerations in maternal sepsis include glucose control, steroids, and venous thromboembolism (VTE) prophylaxis.
- Maternal hyperglycemia can directly cause fetal hyperglycemia and ultimately acidosis, decreasing uterine blood flow and lowering fetal oxygenation.
- Maternal blood glucose should be maintained less than 180 grams per deciliter.
- Steroids are recommended by the American College of Obstetrics and Gynecology in women between 24 weeks and 33 weeks and six days who are at risk of a preterm delivery within seven days, which is inclusive of those with rupture of membranes.

Approach to Resuscitation in Pregnancy

- Hydrocortisone should be considered in those patients who do not improve with IV fluids and vasopressors.
- Pregnancy alone confers a five-fold increased risk of deep vein thrombosis as compared to the non-pregnant population.
- As septic pregnant patients are at high risk of VTE, patients without contraindications should receive both intermittent compression devices and either daily LMWH or 2-3 times daily administration of unfractionated heparin.
- Direct oral anticoagulants are not currently recommended.

Table 4. Chronologic presentation of sepsis etiologies and recommended antibiotics.

Infection	Time Frame	Evaluation	Management
Pelvic inflammatory disease	1st trimester	Pelvic examination, transvaginal ultrasound to evaluate for tubo-ovarian abscess if suspected[93–95]	Azithromycin and cefoxitin[92]
Appendicitis	2nd trimester more commonly than 1st and 3rd trimester	Ultrasound, if equivocal then magnetic resonance imaging	Definitive treatment is surgery, cefoxitin + clindamycin, cefoxitin + metronidazole[89]
Pyelonephritis	2nd and 3rd trimester more commonly than 1st trimester	Urinalysis, urine culture; obtain imaging to evaluate for renal abscess if patient is clinically toxic or hemodynamically unstable[70,71,73]	Immunocompetent: ceftriaxone, cefepime, ampicillin + gentamicin Immunocompromised: piperacillin/tazobactam, carbapenem[73,75,76,106]
Pneumonia	1st, 2nd, and 3rd trimester	Chest radiograph, consider ultrasound[46,58–60]	Pneumococcal beta-lactam + macrolide MRSA coverage if suspected: vancomycin, linezolid[12,62]
Endometritis	Post-partum	Computed tomography[105]	IV gentamicin + clindamycin, doxycycline + cefoxitin, ampicillin/sulbactam[100,101]

MRSA, methicillin-resistant *Staphylococcus aureus*; *IV,* intravenous.


Thank You!