

Maternal Sepsis

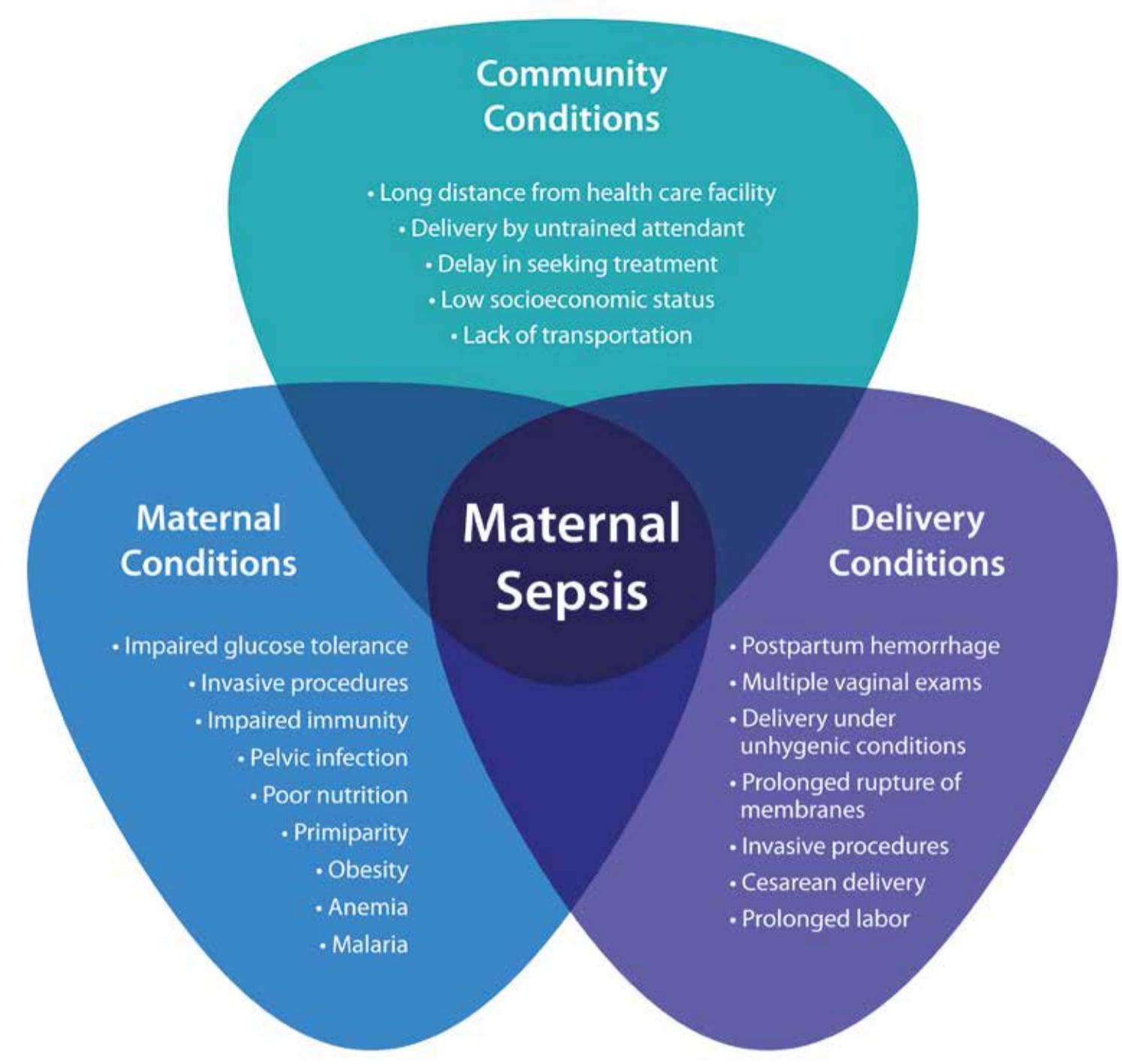
Prevention Recognition Treatment



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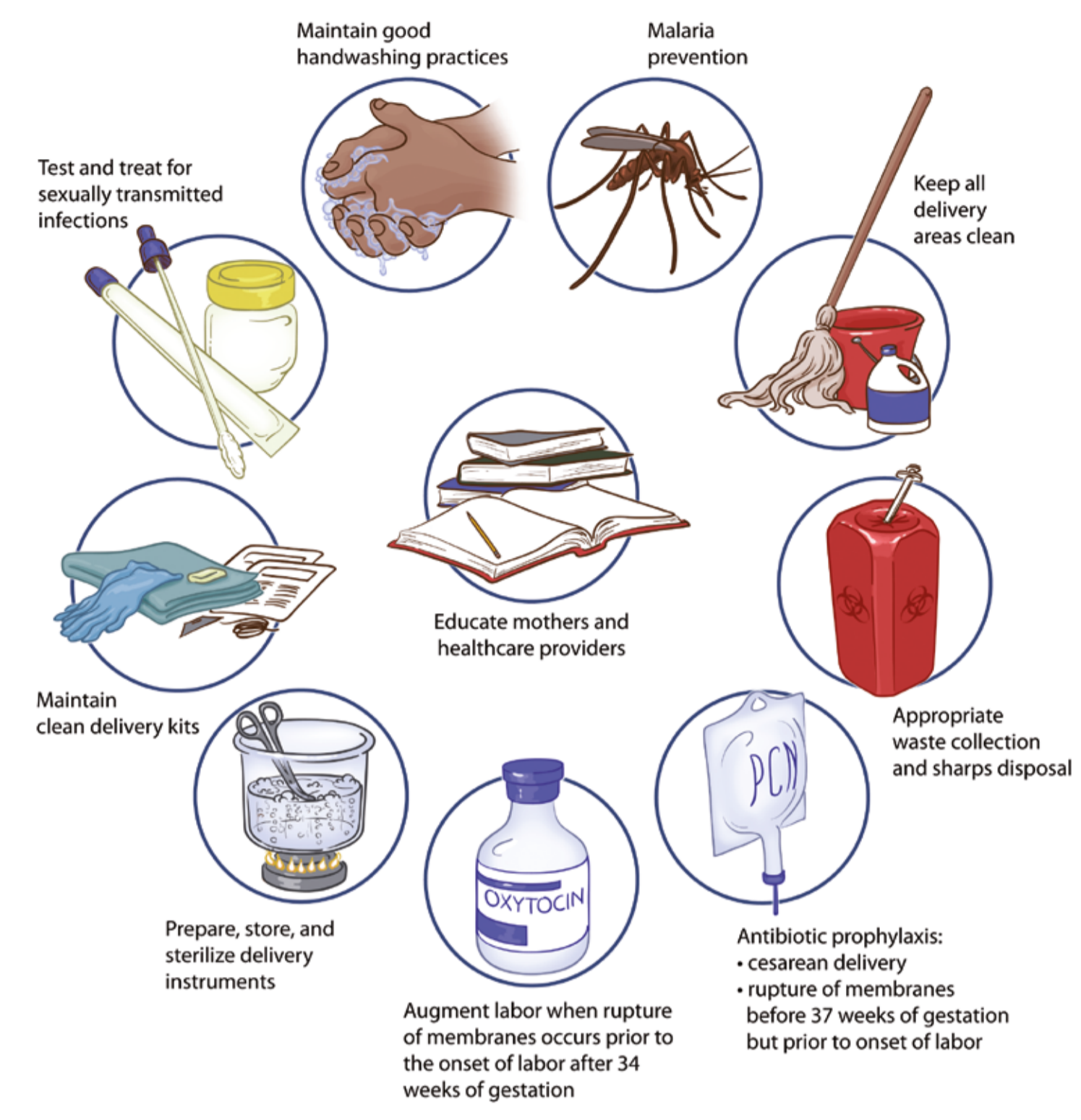
1 Risk Factors

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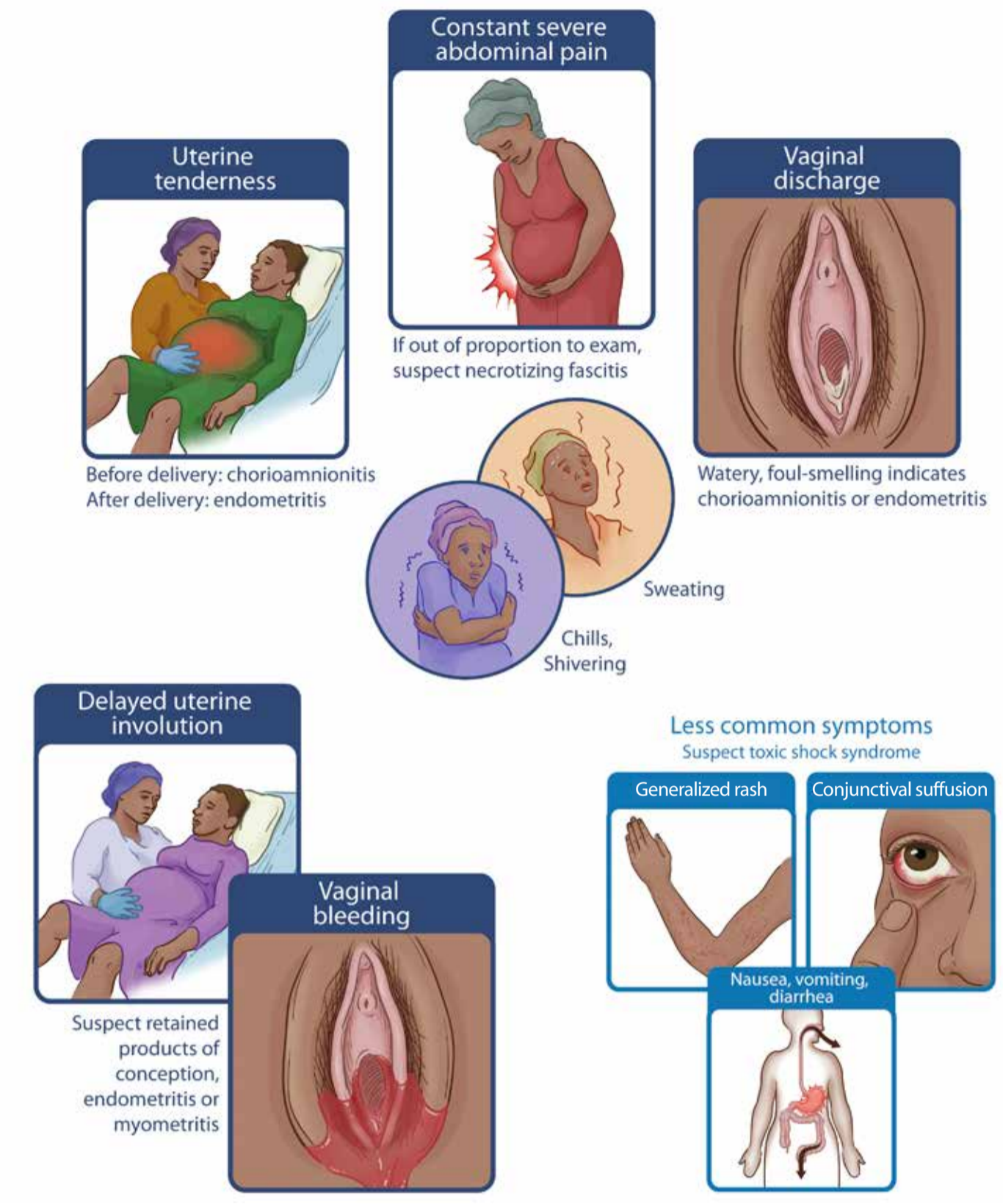
2 Prevent

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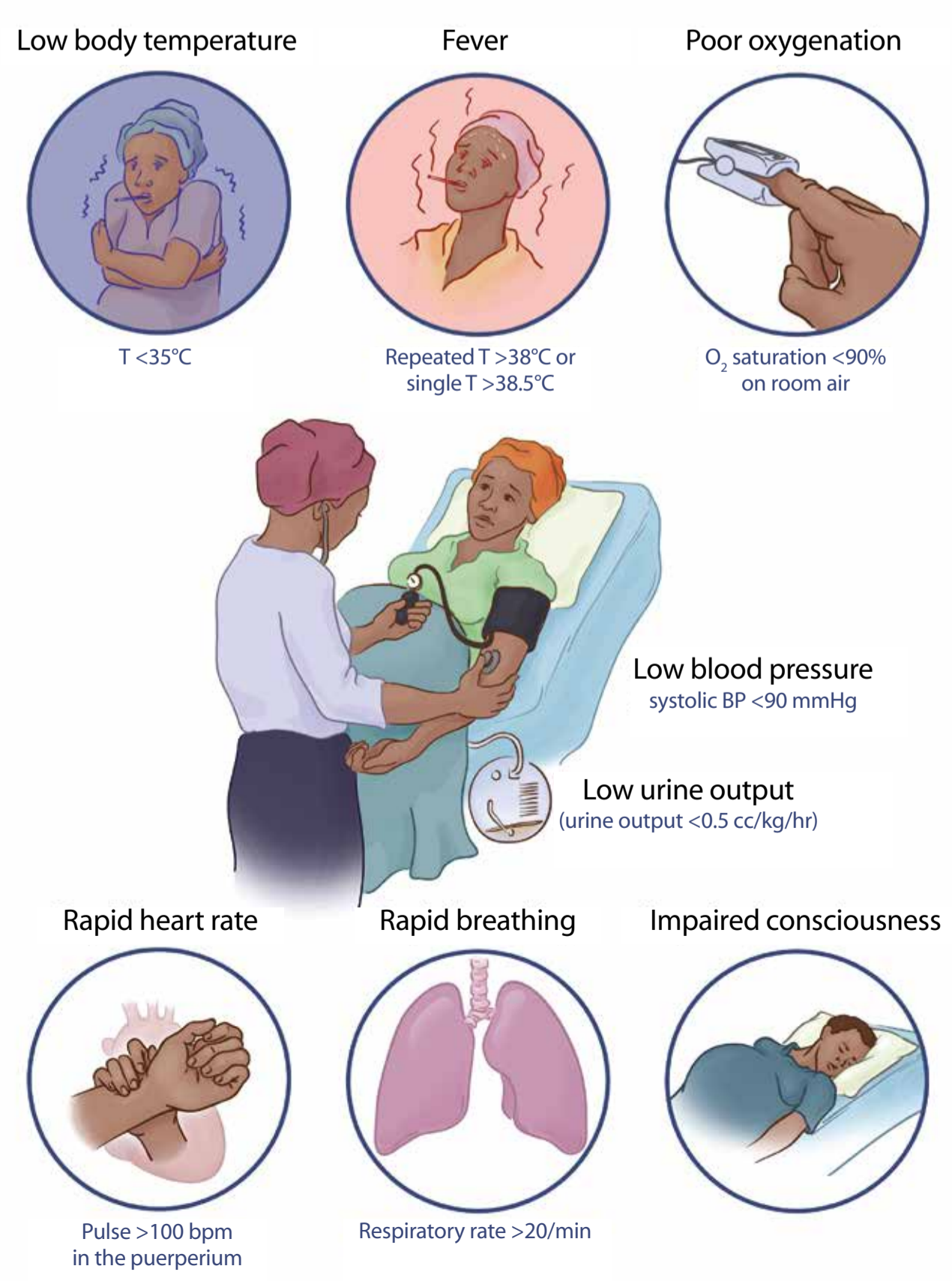
3 Recognize: Symptoms

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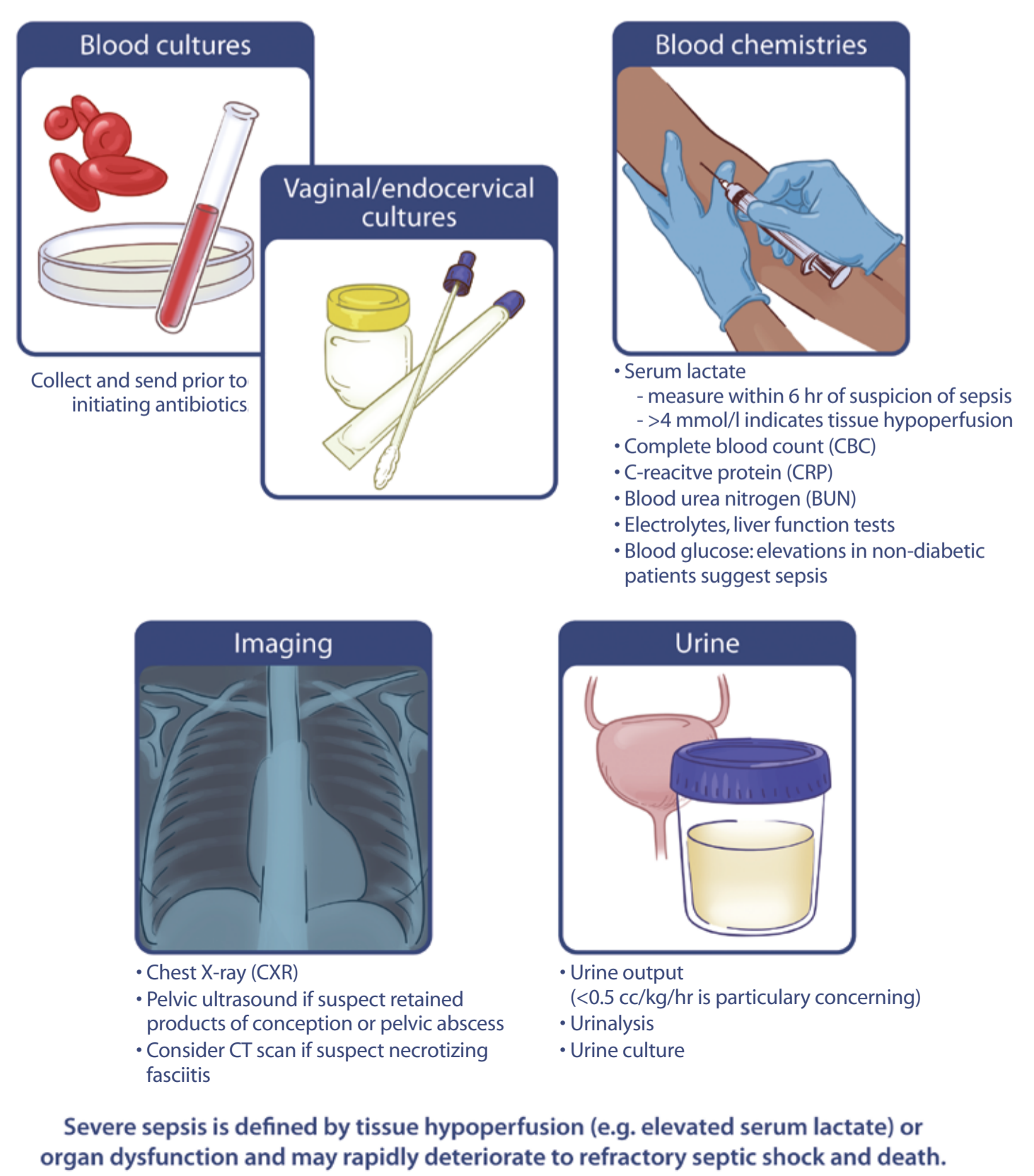
4 Recognize: Clinical features

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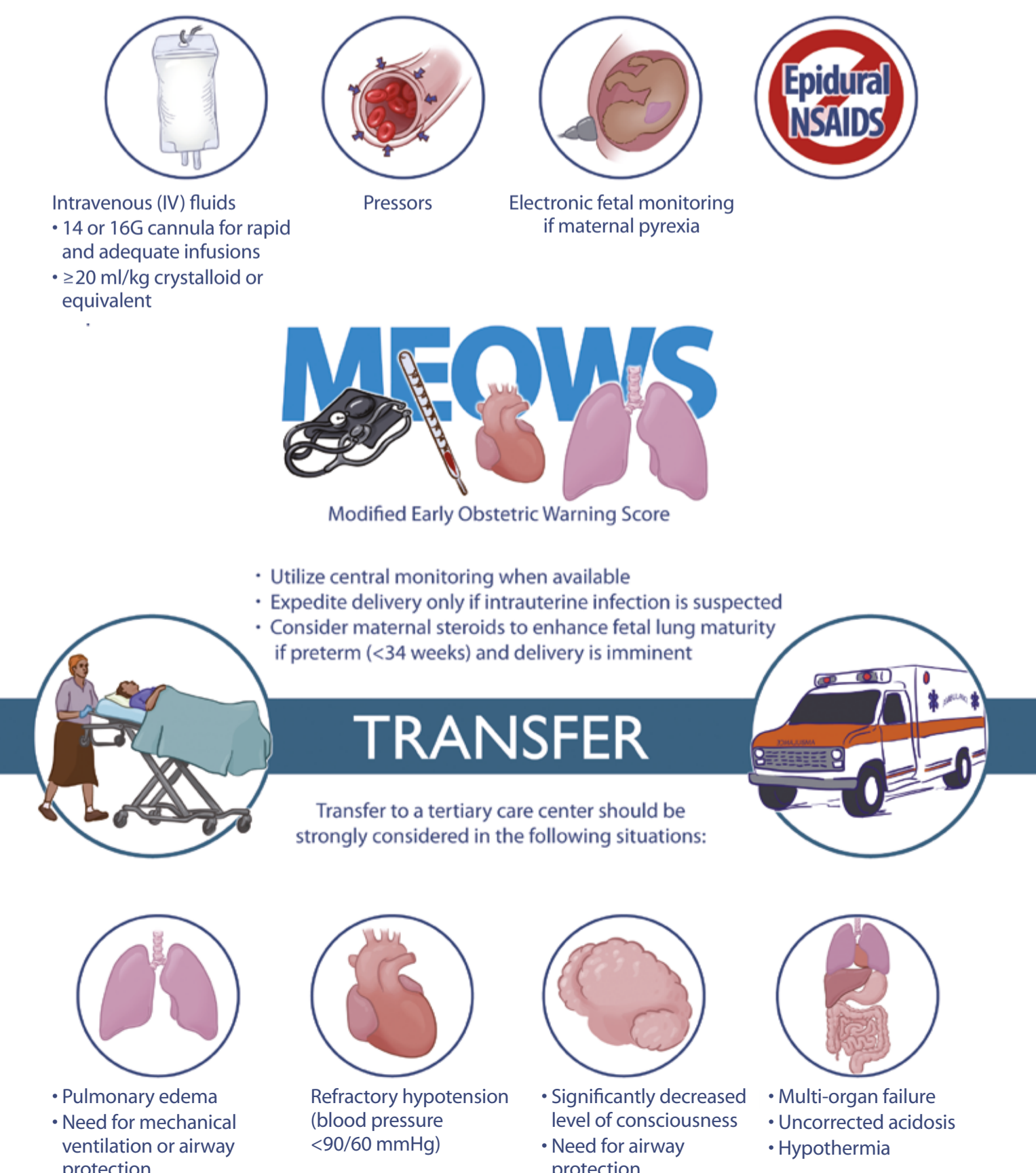
5 Investigate: Laboratory

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6 Resuscitate

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7 Antibiotics & Bacteria

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Implications & Definition

Globally, 210 million women become pregnant each year and 130 million births occur. An estimated 358,000 women die every year from the complications of childbirth. The vast majority (99%) of childbirth-related deaths occur in poorly resourced areas of the world. Up to 15% of these deaths are due to puerperal sepsis.

Maternal (puerperal) sepsis is a highly lethal condition. In the absence of treatment, maternal sepsis may lead to death or serious long-term morbidity such as chronic pelvic pain, pelvic inflammatory disease and secondary infertility. As many as 5.2 million new cases of maternal sepsis are thought to occur annually and an estimated 62,000 maternal deaths result from this condition. Of course, a very large proportion of maternal deaths worldwide go unrecorded, particularly if delivery occurs outside of a hospital.

Reduction of maternal mortality by 75% between 1990 and 2015 is the first target of the fifth United Nations Millennium Development Goal (MDG). In Africa and Asia, puerperal sepsis is the second commonest cause of maternal mortality after hemorrhage, causing 9.7% and 11.6% of deaths, respectively. In Latin America and the Caribbean, puerperal sepsis causes 7.7% of deaths. In industrialized countries puerperal sepsis is rare, causing only 2.1% of maternal deaths. For maternal sepsis, there is a stark disjunction between the technical means to reduce mortality and severe morbidity and the increased attention to improved emergency obstetric care that will be needed if the MDG is to be achieved. The main barrier to success appears to be an insufficient application of available interventions. Our goal in providing this document is to aid in that application.

Puerperal sepsis is only a subset of puerperal infection. The World Health Organization (WHO) defines puerperal sepsis as infection of the genital tract occurring at any time between the onset of the rupture of membranes or labor and the 42nd day postpartum.

World Health Organization Definition of PUERPPERAL SEPSIS*		
Time of Onset	Fever	Associated Symptoms
Between the onset of rupture of membranes or labor and the 42nd day postpartum	At least 38.0°C on 2 occasions (at least four hours apart) or one temperature of at least 38.5°C	<ul style="list-style-type: none">• Pelvic pain• Abnormal color, consistency or amount of vaginal discharge• Malodorous vaginal discharge• Delay in the postpartum rate of reduction in uterine size (<2 cm/day over the first 8 days after delivery)

*This definition includes chorioamnionitis and endometritis.

Severe sepsis is defined as sepsis combined with sepsis-induced organ dysfunction or tissue hypoperfusion. Its mortality rate is 20–40%, but rises to as high as 60% if septic shock develops

Puerperal infections include not only infections that lead to sepsis, but also all genital tract, extra-genital and incidental infections. These include infections of the genitourinary system related to labor and delivery and the puerperium (infections related to the uterus like endometritis and infections related to the urinary tract), infections related to the birth process but not of the genitourinary system and incidental infections (such as malaria and respiratory tract infections). The newer Global Burden of Disease (GBD) definition excludes mastitis and surgical site infections because both are short in duration, have no long-term consequences and have essentially no mortality.



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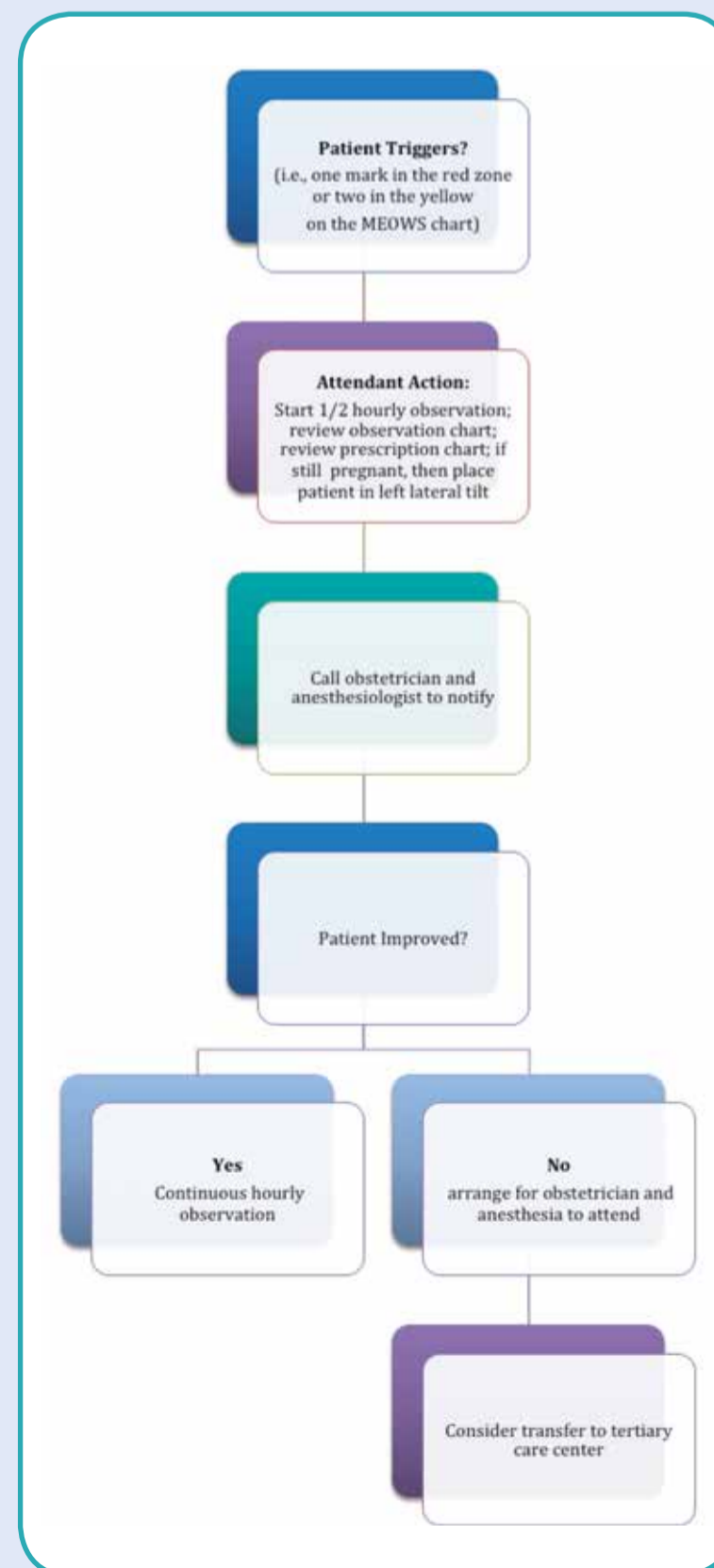
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4 Maternal Sepsis Evaluation

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Regular observation of all vital signs (including temperature, pulse rate, blood pressure and respiratory rate) should be recorded on a Modified Early Obstetric Warning Score (MEOWS) (next page) or similar chart. In addition to clinical status, there are several laboratory studies that should be obtained in the evaluation of maternal sepsis. Blood and genital tract cultures are key to the investigation and should be obtained prior to antibiotic administration; however, **antibiotic treatment should be started without waiting for microbiology results**. Urine output should be closely monitored and is best accomplished by use of a catheterized urinary collecting system. A complete blood count and serum C reactive protein (CRP), blood urea and electrolyte levels should be obtained. The presence of a metabolic acidosis on electrolyte testing is concerning. A serum lactate level should be measured within six hours of the suspicion of severe sepsis in order to guide management. A serum lactate >4 mmol/l is indicative of tissue hypoperfusion. Blood sugar elevations in the absence of diabetes also suggest sepsis. Relevant imaging studies should be performed promptly in an attempt to confirm the source of infection. During the intrapartum period, continuous electronic fetal monitoring (EFM) is recommended in the presence of maternal pyrexia (defined as a temperature >38.5°C once or >38.0°C on two occasions 4 hours apart) or signs of sepsis in the absence of pyrexia.

The birth attendant should frequently assess the need for assistance (i.e., obstetrician/gynecologist and anesthesiologist) and the need for transfer to a tertiary care center. A system should also be in place to implement these actions when deemed necessary. The flow chart outlines actions that will optimize maternal care.



1 Maternal Sepsis Risk Factors

Risk factors for puerperal sepsis surround three central components: 1) community-related factors, 2) delivery conditions, and 3) maternal comorbid conditions.

Community-related Factors: Low socioeconomic status contributes to poor nutrition, lack of knowledge of symptoms and signs of the problem (sepsis), lack of available clinical resources and sub-optimal design or construction of buildings, water and sanitation systems. Access to facilities may be lacking due to limited means of transportation and long distance from the patient's house to the healthcare facility. Healthcare providers in poorly resourced areas often lack surveillance data and have an impaired ability to order appropriate laboratory tests and to prescribe effective antibiotics. Cultural factors may also delay care seeking behavior.

Delivery Conditions: Births under unhygienic conditions and delivery by an untrained birth attendant significantly increase patient risk. The World Health Organization has estimated that the incidence of maternal sepsis would decrease by 50% if the majority of deliveries took place in a birthing facility. Other risky delivery conditions include: prolonged rupture of membranes, prolonged labor, multiple vaginal exams, cesarean delivery, and postpartum hemorrhage. A study at Ife State Hospital in Nigeria showed that 31.5% of maternal sepsis cases were associated with premature rupture of membranes (PROM), 65.7% of maternal sepsis cases were associated with labor lasting over 12 hours and 50.7% of maternal sepsis cases were associated with multiple vaginal examinations. **Cesarean delivery is the single most important risk factor**, with a sepsis rate of 5.0% when prophylactic antibiotics are used and 10.1% if prophylactic antibiotics are not used. Other procedures that increase the risk of puerperal infection include instrument-assisted delivery, episiotomy, amniocentesis, cerclage, postpartum hemorrhage and retained products of conception.

Maternal Comorbid Conditions: Several aspects of maternal health are significant risk factors for the development of maternal sepsis.

These include:

- 1) poor nutrition
- 2) primiparity
- 3) anemia (due to poor nutrition, sickle cell disease, thalassemia or malaria)
- 4) obesity
- 5) impaired glucose metabolism and diabetes mellitus
- 6) infections
 - a) HIV/AIDS,
 - b) pelvic infections
 - c) group B streptococcal infections
 - d) group A streptococcal infection in close contacts
 - e) malaria (accounts for up to 15% of cases of maternal anemia)
 - i) in endemic areas, malaria may be responsible for up to 60% of fetal losses and 10% of maternal deaths



This wall chart was written and developed by Elizabeth K. VonderHaar MD, Kayla L. Asay MD, Stacy Cheavens Turpin MS, CMI and Danny J. Schust MD, University of Missouri School of Medicine, Columbia, Missouri, USA

5 Maternal Sepsis Evaluation

Every institution should have a standard method for recording and reporting maternal status during the peripartum period. If your institution does not currently have one in place, consider utilizing the MEOWS chart (below).

2 Maternal Sepsis Prevention

Prevention begins with preparation. There is an urgent need for multimodal prevention approaches to gain widespread adoption.

These approaches include:

- 1) guideline use
- 2) education and training
- 3) organizational changes
- 4) surveillance
- 5) quality improvement

Maternal and provider education in maternal nutrition helps to maintain healthy pregnancies.

Training of traditional birth attendants (TBAs) in appropriate puerperal care can reduce the risk of maternal sepsis by 83%.

Healthcare hand washing should be a universal practice. In locations where clean running water is unavailable, alcohol based antiseptic products should be used.

Maternal infections can occur throughout pregnancy. Some predispose to preterm delivery. Others do not, but may be encountered in the puerperal period. Co-existing maternal genital tract infections increase the rate of maternal sepsis. Providers should screen for sexually transmissible infections (including Gonorrhoea, Chlamydia and Trichomoniasis) and treat them when diagnosed.

Preparation of "clean delivery kits" with bags containing sterile draping and packaged sterile instruments can reduce risks.

In the setting of rupture of membranes before 37 weeks of gestation and before onset of labor, preventive antibiotics reduce sepsis by 52–90%. Using medications to induce labor when rupture of membranes occurs prior to the onset of labor after 34 weeks of gestation reduces sepsis by 35–70%.

Active labor management (i.e., use of oxytocin to maintain adequate uterine contractions) may potentially reduce cesarean rates by 12–23%. When cesarean delivery is required, use of pre-operative prophylactic antibiotics reduces endometritis (66–75%), sepsis (46–61%) and mortality (50–72%).

Facilities should maintain appropriate sharps disposal and appropriate waste collection and disposal. All patient care areas should be maintained with the highest possible level of hygiene. Delivery instruments should be appropriately prepared, stored and sterilized prior to use.

Pregnant women are more commonly infected with malaria than their non-pregnant counterparts. In endemic areas, malarial infections can be a significant contributor to maternal morbidity and mortality. The WHO recommends malaria prevention and control during pregnancy. This includes use of insecticide-treated bed nets and antibiotic chemoprophylaxis.

6 Maternal Sepsis Resuscitate

Suspicion of significant sepsis should trigger urgent referral to a specialized care, possibly in an intensive care unit.

If transfer will be delayed or is unavailable, the following measures should be taken. 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 (prior page). This should be made available to the transporting team when they arrive.

In preterm pregnancies, do not attempt delivery unless intrauterine infection is suspected. Intrauterine infection increases the risk of neonatal encephalopathy and cerebral palsy and is an indication for delivery. Attempting delivery in a mother who is medically unstable increases maternal and fetal mortality rates.

When available, continuous electronic fetal monitoring should be utilized in the presence of maternal pyrexia. Maternal steroid administration may be considered to promote fetal lung maturity when preterm delivery is imminent (less than 34 weeks of gestational age).

If sepsis is suspected in a laboring woman, epidural/spinal anesthesia should be avoided. A general anesthetic is a safer option for the patient if cesarean delivery is required. Non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided for pain relief in cases of sepsis as they impede the ability of polymorphonuclear cells (PMNs) to fight group A streptococcal (GAS) infection. Acetaminophen or equivalent can be administered for fever >38.0°C.

In the event of significant maternal hypotension and/or a serum lactate >4 mmol/l, obtain immediate IV access and infuse a minimum 20 ml/kg of crystalloid or an equivalent. Administer vasopressors for maternal hypotension that is not responding to fluid resuscitation to maintain a mean arterial pressure >65 mmHg. In the event of persistent hypotension and/or persistent lactate >4 mmol/l despite fluid resuscitation (septic shock): 1) establish central vascular access and administer crystalloid and vasopressors to achieve a central venous pressure (CVP) of at least 8 mmHg and 2) target a central venous oxygen saturation (ScvO₂) of at least 70% or a mixed venous oxygen saturation (SvO₂) of at least 65%.

Transfer

There are several maternal characteristics that warrant immediate transfer to a more acute care setting or rapid enlistment of practitioners with substantial experience in caring for sepsis in pregnant women.

These include:

- 1) maternal hypotension or elevations in the maternal serum lactate level that persist despite fluid resuscitation. These findings suggest an imminent need for inotrope support
- 2) uncorrected acidosis
- 3) hypothermia
- 4) significantly decreased level of consciousness and necessity for airway protection or mechanical ventilation
- 5) pulmonary edema
- 6) multi-organ failure, including the need for renal dialysis

It is essential that the decision to call for help or to activate patient transfer be made early since processes may be fairly prolonged in less-resourced settings.

3 Maternal Sepsis Recognition

All healthcare professionals should be aware of the signs and symptoms of maternal sepsis and septic shock and of their rapid and potentially lethal course.

Suspicion of significant sepsis should trigger an urgent referral/transfer to secondary or tertiary care.

Sepsis is infection plus systemic manifestations of infection. Severe sepsis also manifests associated organ dysfunction or tissue hypoperfusion and a mortality rate of 20–40%. Septic shock is characterized by the persistence of hypoperfusion despite adequate fluid replacement therapy, and has a mortality rate of 60%. Mortality increases by about 6–8% every hour if not treated by appropriate antibiotics in adequate doses once sepsis is recognized. Tissue hypoperfusion or organ dysfunction should be rapidly recognized by measuring venous lactate levels, O₂ saturation by pulse oximetry and renal and liver function tests, and treatment should be initiated immediately upon diagnosis.

Significant signs that should encourage one to evaluate and treat a patient for sepsis include but are not limited to:

abdominal pain	pyrexia (>38.5°C once, or >38.0°C on two occasions 4 hours apart)
hypothermia (<35.0°C)	tachypnea (respiratory rate >20 breaths per minute)
oliguria (urine output <0.5 cc/kg/hr)	hypoxia (O ₂ saturation <90% on room air)
hypotension (systolic BP <90 mmHg)	tachycardia (heart rate >100 bpm; >90 bpm in puerperium)
leukocytosis (white blood cell [WBC] count >12.0 x 10 ⁹ /L or >12 000/mm ³)	
leukopenia (WBC count <4 x 10 ⁹ /L or <4000/mm ³)	
impaired consciousness	failure to respond to treatment
increased vaginal bleeding	postpartum decrease in uterine size (involution) <2 cm/day

If uterine tenderness is present before delivery, concern should arise for chorioamnionitis. If uterine tenderness is present after delivery, concern should arise for endometritis. If available, electronic fetal monitoring should be implemented as persistent fetal tachycardia (fetal heart rate greater than 160 bpm) in the setting of other signs of maternal infection suggests chorioamnionitis. Endometritis is more likely to occur after instrumented delivery or cesarean delivery. Delayed uterine involution and increased vaginal bleeding postpartum may indicate retained products of conception or uterine infection.

Constant severe abdominal pain and tenderness unrelieved by analgesia suggests genital tract sepsis.

Toxic shock syndrome (TSS) caused by staphylococcal or streptococcal exotoxins can produce confusing symptoms including nausea, vomiting and diarrhea, watery vaginal discharge, generalized rash and conjunctival suffusion. Severe pain out of proportion to clinical signs is concerning for necrotizing fasciitis

Laboratory studies that should be obtained upon suspicion of maternal sepsis include:

Complete blood counts (leukocytosis >12.0 x 10⁹/L or low white blood cell counts <4 x 10⁹/L are concerning) **Serum lactate** should be drawn within 6 hours of suspicion of sepsis; levels greater than 4 mmol/l indicate tissue hypoxia

Serum C reactive protein (normal levels vary based on age and gender, levels for concern are anything greater than 2 standard deviations above the mean)

Blood urea nitrogen and electrolyte evaluations and liver function tests should aid in diagnosis and management

Blood glucose: elevations (>7 mmol/l or 126 mg/dl) in non-diabetics suggests sepsis

Relevant imaging studies: Chest X-ray for evaluation of pulmonary edema, possible pneumonia
Pelvic ultrasound to identify fluid collections or retained products of conception
CT scan if concern for necrotizing fasciitis

7 Maternal Sepsis Antibiotics

Organisms most frequently identified in women with maternal sepsis:

<i>Neisseria gonorrhoeae</i>	<i>Chlamydia trachomatis</i>	Group A streptococci
Group B streptococci	<i>Ureaplasma urealyticum</i>	<i>Mycoplasma hominis</i>
<i>Staphylococcus aureus</i>	<i>Escherichia coli</i>	Proteus species
<i>Klebsiella species</i>	Bacteroides species	<i>Gardnerella vaginalis</i>

The major pathogens causing sepsis in the puerperium are:

Group A strep (GAS; <i>Streptococcus pyogenes</i>)	<i>Escherichia coli</i> (E. coli)
<i>Streptococcus pneumoniae</i>	Methicillin-resistant <i>Staphylococcus aureus</i> (MRSA)
<i>Clostridium septicum</i>	<i>Morganella morganii</i>

Our knowledge of the etiology of maternal sepsis in resource-poor countries is frustratingly limited. The most common organisms identified in pregnant women dying from sepsis are Lancefield group A beta-hemolytic streptococci and *E. coli*. Mixed infections with both Gram-positive and Gram-negative organisms are common, especially in chorioamnionitis; these include *Staphylococcus aureus* (*S. aureus*), methicillin-resistant *S. aureus* (MRSA), and *Streptococcus pneumoniae*. Coliform infection is particularly associated with urinary sepsis, preterm premature rupture of membranes and cerclage. Anaerobes such as Peptostreptococcus, Bacteroides species and Clostridium species are also seen. When compared with multiple other antibiotic regimens, administration of clindamycin plus an aminoglycoside for endometritis has been shown to reduce treatment failures by 30% (very strong evidence) and wound infection or other complications by 22–48% (moderate evidence). A combination of amoxicillin, gentamicin and metronidazole is commonly used due to its broad spectrum of coverage and frequent availability. Similar studies on antibiotic choice in the treatment of chorioamnionitis have shown no significant differences among several recommended antibiotic regimens.

Blood and urine cultures should be obtained the moment sepsis is considered. The source of sepsis should be sought aggressively and addressed expeditiously. Administration of intravenous broad spectrum antibiotics is recommended within one hour of the suspicion of sepsis, with or without concomitant septic shock.

Absolute indications for IV antibiotics include: abdominal pain, fever (greater than 38.0°C) and tachycardia (greater than 100 beats per minute—except for in the puerperium, when the cut-off is 90 bpm). Several antibiotic regimens are acceptable and choice may be based largely on medication availability. The 2003–2005 Confidential Enquiry into Maternal and Child Health report proposes the use of cefuroxime and metronidazole for genital tract sepsis. However, cefuroxime is no longer part of many hospital formularies because its association with *Clostridium difficile* infections. Further, neither agent provides coverage for MRSA, Pseudomonas or extended spectrum beta-lactamase species. A combination of either piperacillin/tazobactam or a carbapenem plus clindamycin provides particularly broad bacterial coverage in the treatment of severe sepsis.

Specific antimicrobial choices and their limitations:

Co-Amoxiclav: Does not cover MRSA or Pseudomonas; possible increase in the risk of necrotizing enterocolitis in neonates exposed *in utero*

Metronidazole: Only covers anaerobes

Cefuroxime: No longer a part of many hospital formularies because of the association with *C. difficile* infections; does not cover MRSA, Pseudomonas or extended spectrum beta lactamase species

Clindamycin: Covers most streptococci and staphylococci including many MRSA species; inhibits production of superantigens and other exotoxins which significantly decreases maternal mortality; drug is not renally-excreted or nephrotoxic

Piperacillin/Tazobactam and Carbapenems: Covers all implicated pathogens except MRSA; renal sparing (in contrast to aminoglycosides)

Gentamicin: Poses no problem if renal function is unimpaired; if doses are to be repeated, serum levels must be monitored