New Concept and Management for Sepsis in Pregnancy and the Puerperium

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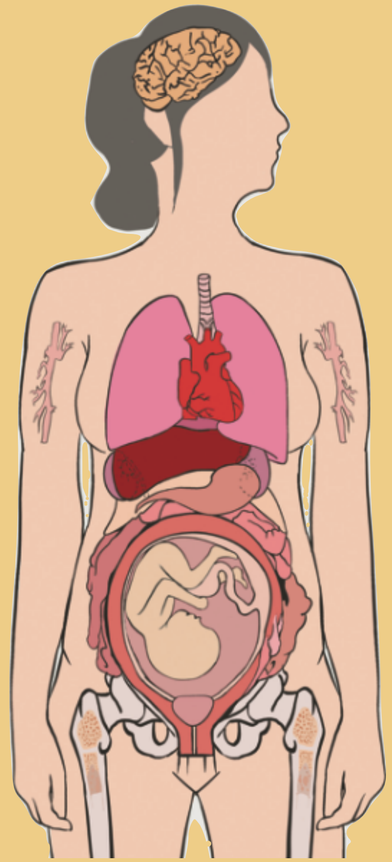

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Maternal-Fetal Medicine

Review

OPEN

New Concept and Management for Sepsis in Pregnancy and the Puerperium

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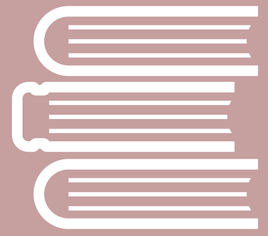
2. Pathophysiology
3. Causes, risk factors, and microorganisms
4. Screening and diagnosis
5. Management
6. Gaps and future directions

Introduction



Maternal Sepsis

Definition & Epidemiology

- Sepsis: A **life-threatening condition** with **organ dysfunction** resulting from **infection**
- Maternal sepsis: Sepsis occur during **pregnancy, childbirth, post-abortion**, **postpartum** period
- **Prevalance** : 4.4% among live births (WHO)
- **Incidence**: 9–49 per 100,000 deliveries in high- income countries (Depend on definition of population study)
- **Labor and puerperium** may have 2-3 fold increased risk of sepsis compared to the antenatal period.

Main Cause of Maternal Death!

A major contributor to severe maternal morbidity

- 11 % of maternal death worldwide,
  3rd most common direct cause of maternal death.

- USA: 3rd or 4th leading cause of maternal mortality
- Low- and middle-income countries: rate of fatality after puerperal infection can be as high as 50%.

- Mortality of sepsis in general population: 25-30%
- Mortality of septic shock: 40-70%

Failure to Recongize Sepsis Early

Significant cause of preventable morbidity

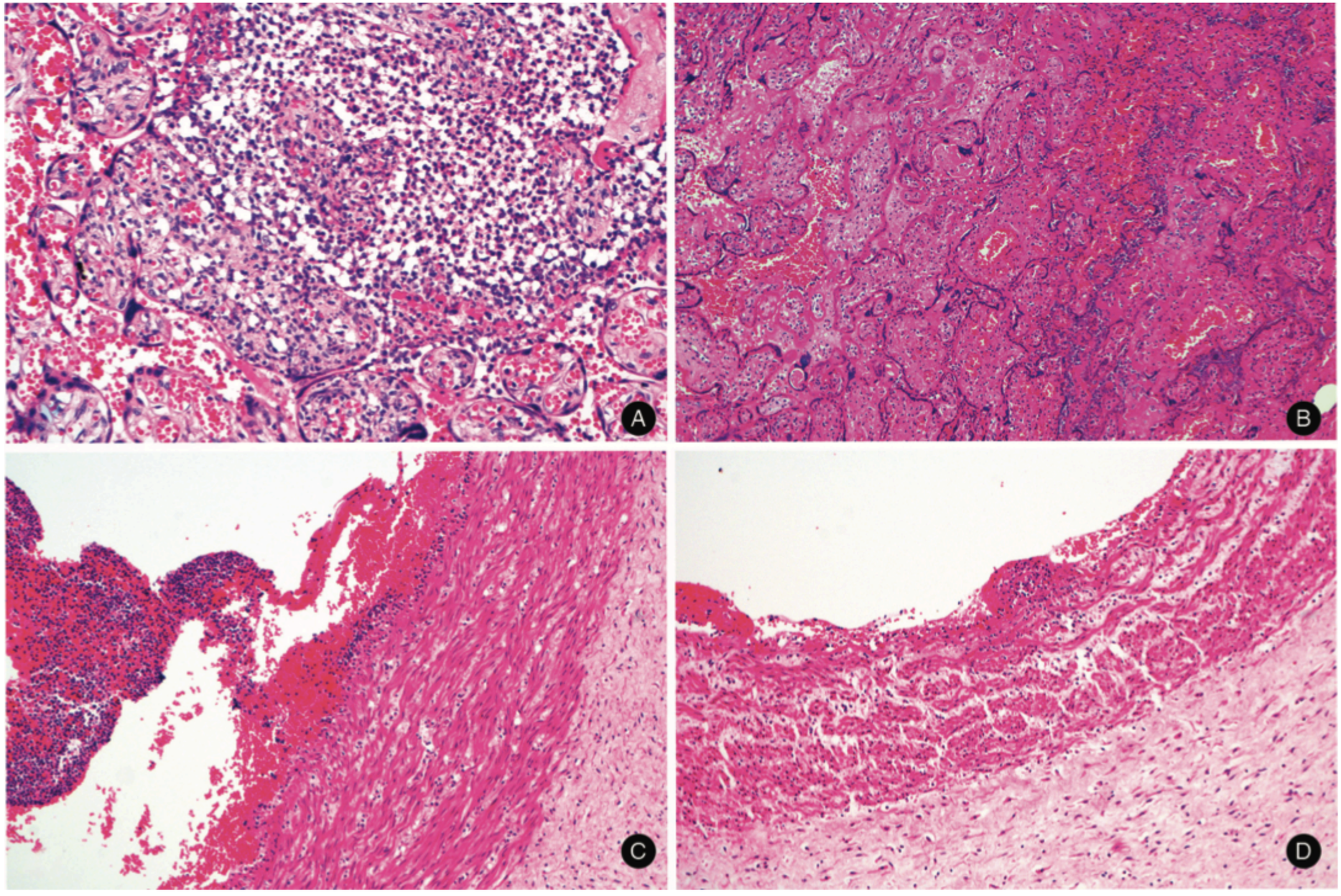
- **Only a few evidence-based and pregnancy-specific guideline** regarding on how to best treat, prevent, recognized early warning signs of peri-partum sepsis.
- This review aim to discussed new definition, recommended diagnosis and management strategies of sepsis adapted to pregnant and post-partum woman.

Pathophysiology

Pathophysiology

- **Multifaceted host response** to an **infecting pathogen** that may be significantly amplified by endogenous factors.
- “Sepsis 1”, “Sepsis 2” focused solely on **inflammatory process** (Older definition)

Inflammation	• **Early activation** of both **pro- and anti-inflammatory** responses
Modifications in non-immunological pathway	• **Major modifications in non-immunologic pathway:** Cardiovascular, Neuronal, Autonomic, Hormonal, Bioenergetics, Metabolic, and Coagulation
Clinical presentations	• **Many systems involved**: respiratory, cardiovascular, hepatic and gastrointestinal, renal, hematological, endocrinological, and central nervous system


A
B
C
D

Maternal sepsis may cause intraaminiotic infection

What we worry about!

- Premature rupture of membranes (PROM) or preterm labor or birth
- Cerebral white matter damage, cerebral palsy or neurodevelopmental delay
- Stillbirth
- Early- or late-onset sepsis
- Perinatal death

Causes, Risk factors, and Microorganisms

Causes

Obstetric

- **Changes in maternal immune responses** protect fetus from rejection.
  → May predispose pregnant patients to infections
- **Uterine infection** (chorioamnionitis and endomyometritis), septic abortion, and wound infection
- **Infection follow Invasive procedures**:
  Amniocentesis, chorionic villus sampling, cervical cerclage, or percutaneous umbilical blood sampling.
- Most common source of bacteremia is **chorioamnionitis**
  (47%, Surgers L et al.)

Causes

Non-Obstetric cause, Maternal critical illness-related sepsis

- **Non-obstetrics**: pyelonephritis and pneumonia
- **Maternal critical illness-related**:
  - Severe hemorrhage, obstetric (amniotic fluid/pulmonary) embolism,
  - Acute fatty liver of pregnancy (AFLP)
  - Congestive heart failure, cardio- pulmonary arrest,
  - Major trauma
  - 2019 coronavirus disease infection related.

Risk Factors

Antepartum

- Group A streptococcal infection in close contacts; History of GBS infection
- Invasive procedures: amniocentesis and cervical cerclage
- A lack of prenatal care
- Preeclampsia
- The use of antibiotics within 2 weeks of birth,
  (including prophylaxis for cesarean sections)

Risk Factors

Intrapartum & postpartum

- Induction of labor
- Prolonged ROM
- Instrumented or cesarean delivery
- Mastitis
- PPH
- Retained products of conception
- Wound hematoma

Risk Factors

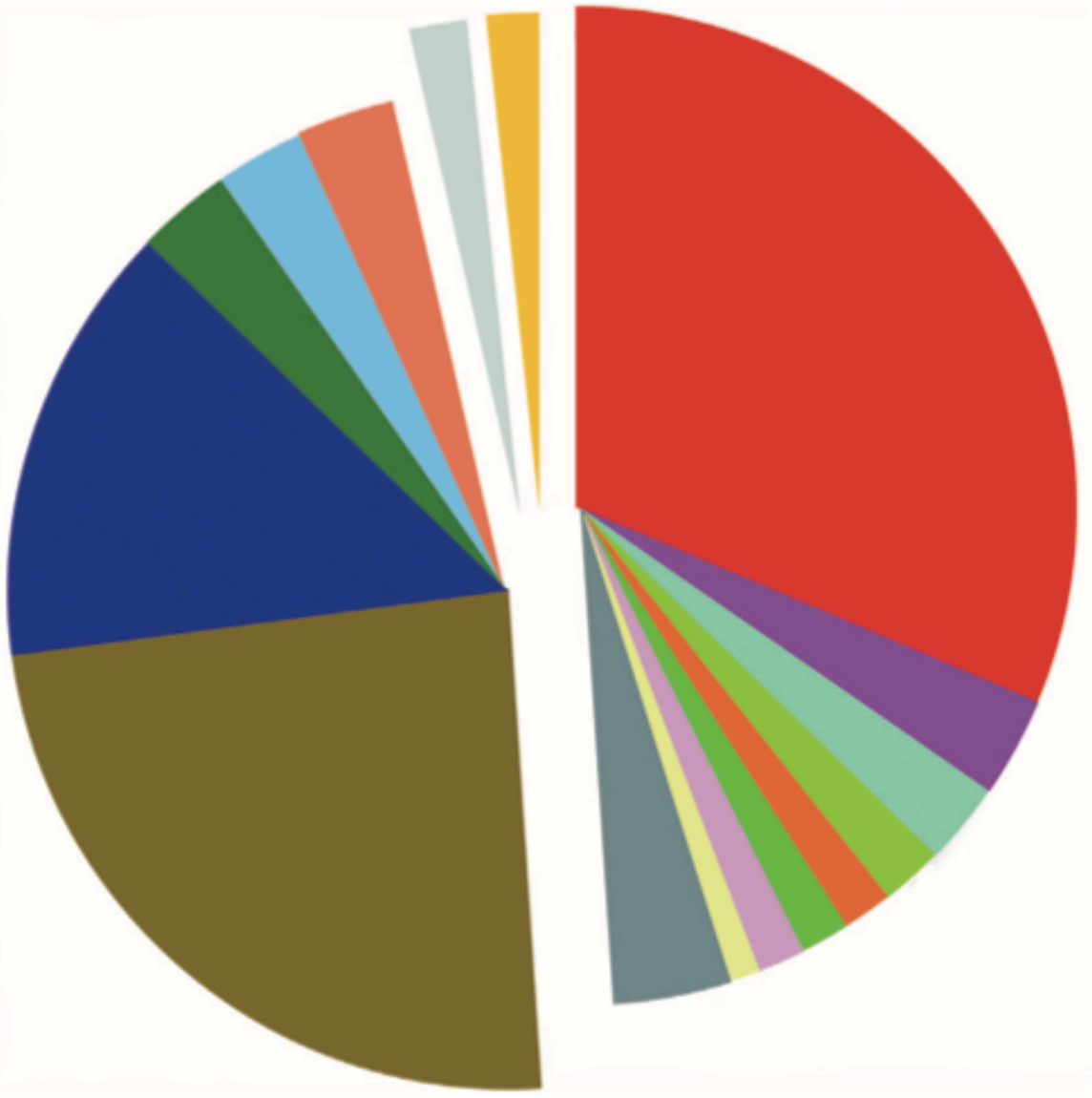
Patient related

- Anemia, chronic HTN, DM;
- decreased function of the spleen; immunosuppression;
- group A streptococcal infection in patients with close contact with individuals with a history of pelvic infection;
- Obesity, poverty, poor nutrition.

Microorganisms

Most common

- **Escherichia coli, Streptococcus, Staphylococcus** and other GNB
- Group A Streptococcus: cause sepsis following abortion, or labor, causing shock with mortality of 30-60%.
- **Candida Sepsis**: chorioamnionitis, stillborn birth, abortion, preterm birth, and congenital Candida infection in newborn
- Rare microorganisms: Clostridium innoocuum, Clostridium novyi, Plasmodium vivax, and Chlamydia psittacosis



- Escherichia coli 386 strains,31.4%
- Clostridium 40 strains,3.3%[a]
- Klebsiella 33 strains,2.7%[b]
- Acinetobacter 25 strains,2.0%[c]
- Enterobacter 20 strains,1.6%[d]
- Bacteroides 20 strains,1.6%[e]
- Proteus mirabilis 19 strains,1.5%
- Pseudomonas 12 strains,1.0%[f]
- Other G⁻ bacteria 47 strains,3.8%[g]

G⁻ bacteria 602 strains, 48.9%

- Streptococcus 295 strains,24.0%[h]
- Staphylococcus 176 strains,14.3%[i]
- Enterococcus 38 strains,3.1%[j]
- Listeria monocytogenes 36 strains,2.9%
- Other G⁺ bacteria 39 strains,3.2%[k]

G⁺ bacteria 584 strains, 47.5%

- Other anaerobe 23 strains,1.9%
- Non-bacteria 21 strains,1.8%[l]

G⁻ bacteria :gram-negative bacteria;G⁺ bacteria:gram-positive bacteria

Screening and Diagnosis

Screening tools for maternal sepsis

Early warning scores

- **SIRS:** Systemic inflammatory response syndrome
- **qSOFA:** quick sequential organ failure assessment
- **omqSOFA:** obstetrically modifed quick sequential organ failure assessment

Table 1

Definitions of SIRS, qSOFA, and omqSOFA criteria.

Tool	Definition
SIRS	≥2 of the following: (1) Temperature >38°C or <36°C; (2) HR >90 bpm (3) RR >20 breaths/min or $PaCO_2$ <32 mm Hg; (4) WBC $<4 \times 10^9$/L or $>12 \times 10^9$/L
qSOFA	≥2 of the following: (1) RR ≥22 breaths/min; (2) SBP: ≤100 mm Hg; (3) Altered mentation
omqSOFA	≥2 of the following: (1) RR ≥25 breaths/min; (2) SBP≤ 90 mm Hg; (3) Altered mentation

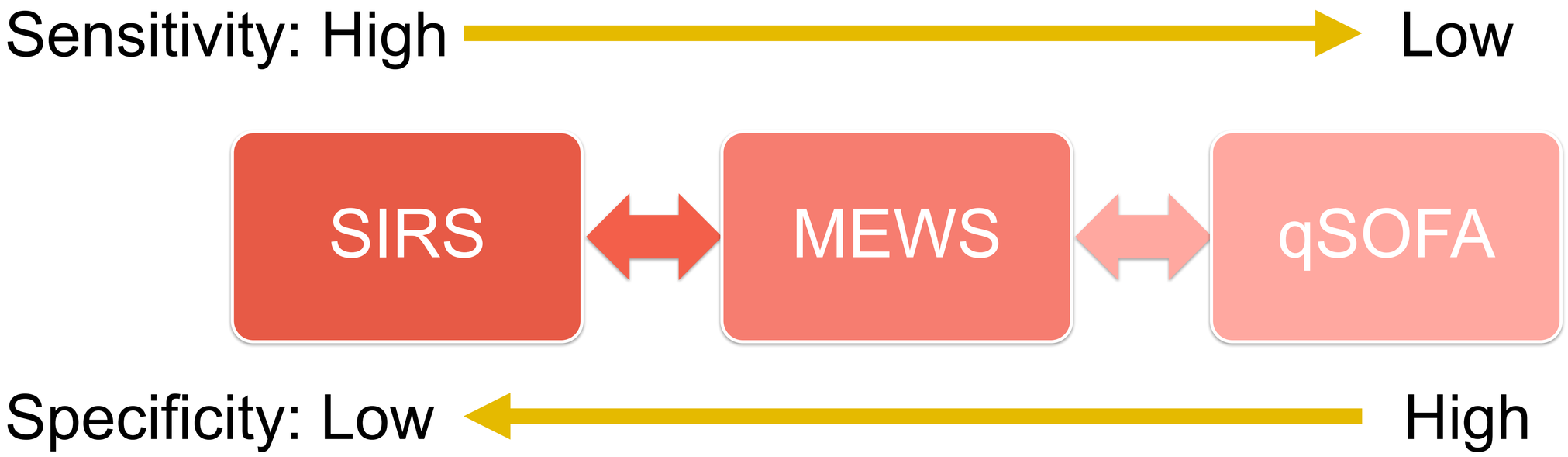
Maternal Early Warning Signs (MEWS)

One or more of the following

- SBP<90, or >160 mmHg
- DBP >100 mmHg
- HR <50, or >120 bpm
- RR <10 or >30 /min
- SpO2 < 95% on room air, at sea level
- Oliguria, <35ml/hr for ≥2 hr
- Maternal agitation, confusion, or unresponsiveness; Patient with preeclampsia reporting a non-remitting headache or shortness of breath

Screening tools for maternal sepsis

Sensitivity vs Specificity



Diagnosis

SOFA score

Table 2

Sequential (sepsis-related) organ failure assessment score.*

	Score				
Organ system variables	**0**	**1**	**2**	**3**	**4**
Respiration					
PaO_2/FiO_2, mm Hg (kPa)	≥400 (≥53.3)	300–<400 (40–<53.3)	200–<300 (26.7–<40)	100–<200 (13.3–<26.7) with respiratory support	<100 (<13.3) with respiratory support
Coagulation					
Platelets × $10^3/\mu L$	≥150	100–<150	50–<100	20–<50	<20
Liver					
Bilirubin, mg/dL (μmol/L)	<1.2 (<20)	1.2–1.9 (20–32)	2.0–5.9 (33–101)	6.0–11.9 (102–204)	> 12.0 (>204)
Cardiovascular					
	MAP ≥70 mm Hg	MAP <70 mm Hg	Dopamine <5 or any dose of dobutamine†	Dopamine 5.1–15 or epinephrine ≤0.1 or norepinephrine ≤0.1†	Dopamine >15 or Epinephrine >0.1 or Norepinephrine >0.1†
Central nervous system					
Glasgow coma scale score‡	15	13–14	10-12	6–9	<6
Renal					
Creatinine, mg/dL (μmol/L)	<1.2 (<110)	1.2–1.9 (110–170)	2.0–3.4 (171–299)	3.5–4.9 (300–440)	>5.0 (>440)
Urine output, mL/dL	–	–	–	200–<500	<200

Sequential organ failure assessment (SOFA) score of ≥2 with a suspicion of infection. In individuals with no baseline disease, the initial SOFA score should be zero. The higher SOFA score, the probability of mortality is more increased.

FiO_2: Fraction of inspired oxygen; MAP: Mean arterial pressure; PaO_2: Partial pressure of oxygen; –: Not applicable.

* Adapted from Vincent *et al.*[77]

† Catecholamine doses are given as μg/kg/min for at least 1 hour.

‡ Glasgow Coma scale scores range from 3 to 15; higher score indicates better neurological function.

SEPSIS CLINICAL CRITERIA

INFECTION

+

CHANGE IN:

SEPSIS-RELATED
ORGAN
FAILURE
ASSESSMENT

≥2

PaO_2 / FiO_2

HYPOTENSION OR VASOPRESSORS

PLATELETS

GLASGOW COMA SCALE

BILIRUBIN

CREATININE, OLIGURIA

Diagnosis

Diagnostic procedure / Differential diagnosis

- **Identify infection source**: Blood culture, culture from possible infection source, lab, and image study for evaluation
- **Differential diagnosis**: Hypovolemic shock, hemorrhagic shock, pulmonary embolism, myocardial infection, acute pancreatitis, DKA, primary adrenal insufficiency, transfusion reaction.

Management

Management

Hour-1 bundle

Cultures prior to antibiotics;
Lactate measurement;
Broad-spectrum antibiotics
Crystalloid fluid
Vasopressors

Investigations

Imaging studies as indicated;
PCT used to help diagnosis and guide antimicrobial use

Source control

Priority and may involve abscess drainage or delivery of fetus

Fetal considerations

Electronic FHR monitoring at 24 weeks of pregnancy;
Steroids for fetal lung maturity after 23 to 24 gestational weeks

Complications prevention

Early enteral feeding
Initiate DVT prophylaxis
Avoid hyperglycemia above 180 mg/dL

Hour 1 bundle

- **Blood cultures** before antibiotics, **lactate** measurement,
- The administration of **broad- spectrum antibiotics**,
- The administration of a 30 mL/kg **crystalloid fluid** bolus in cases of hypotension or high serum lactate levels of at least 4 mmol/L, and the administration of **vasopressors** to maintain a MAP ≥ 65mm Hg

Antibiotics

The early and appropriate use of antibiotics is crucial

- Covering the most common bacteria: E. coli, Staphylococcus, Streptococcus, and other gram-negative bacteria.
- a **broad-spectrum carbapenem** (eg, meropenem, or doripenem) or **extended- range penicillin/b-lactamase inhibitor combination** (eg, tazocin) is used.
- Several third- or higher-generation cephalosporins can also be used, especially as part of a multidrug regimen.

The surviving sepsis campaign

- Strongly recommends **antibiotic stewardship** in the **de-escalation of antibiotics tailored to specific microorganisms** to prevent drug resistance.
- Duration: **suggest 7-10 days**.
- **PCT level** can be used as a biomarker for the initiation, de-escalation, and discontinuation of antimicrobial therapy.
- Inability to decrease PCT is a predictor of mortality

Source control

Source control is a priority

- **Abscess drainage**, **delivery of the fetus** if the uterus is the source
- direct mortality ↑ with each 6-hour delay in achieving source control.
- A prospective case-control study (UK, 2011 to 2012) found the **median gestational age to be 35 weeks** and the **median diagnosis-to-delivery interval was 0 day**
- **Hysterectomy** were performed on 5.4% of severe sepsis case.

Extracorporeal membrane oxygenation (ECMO)

Treatment for respiratory failure in ICU

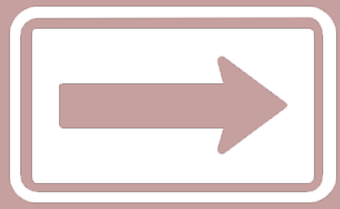
- Based on published reports, overall maternal and fetal survival rate on ECMO were 80% or 70%, respectively. ECMO may be the choice for the treatment of refractory sepsis.

Fetal consideration

Stabilize the mother first, and the fetal status will also improve.

- Decision of delivery/ expectant management:
  Patient’s condition, GA, chorioamnionitis, stage of labor.
- Antenatal sepsis: frequent assessment of fetal status after viability.
- Infection outside of uterus: **prolonging pregnancies**
- Infection of the uterus: **delivery of the fetus** is required.
- Betamethasone should be administered if GA < 34 weeks.
- A previable fetus (<23 to 24 weeks) may not need fetal monitoring

Gaps an Future Directions



GAPS

- Women's **lack of recognition of symptoms signs** or of the risk for sepsis during the initial birth hospitalization or postpartum period.
- Health-care facilities and providers need to **reduce barriers for women who seek care, recognize early symptoms, and respond with appropriate treatment.**

Future direction

- It is important from both a clinical and research viewpoint to **remain up to date and understand the change in terminology of sepsis.**
- **Further research into risk factor**s for maternal sepsis is required to **reduce the incidence and to facilitate early identification** and treat

Conclusion

- **Maternal sepsis remains a major cause** for ICU admission and is a leading cause of **morbidity and mortality** for pregnant woman.
- Include obstetric, non-obstetric, and obstetrical critical illness causes
- The most commonly pathogens include **E. coli, Streptococcus, Staphylococcus**, and other gram-negative bacteria.
- Management of sepsis during pregnancy **should follow the same basic principles** as in general population.

Thank you for listening! ☺