MATERNAL SEPSIS

PAUL J. WENDEL, MD

PROFESSOR AND DIRECTOR

MATERNAL/FETAL MEDICINE

UNIVERSITY OF TENNESSEE HEALTH SCIENCE CENTER

MEMPHIS, TN

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OBJECTIVE OF THIS LECTURE

Review the risk factors predisposing pregnant patients to sepsis.

1. Discuss underlining physiologic derangements leading to morbidity/mortality from sepsis.
2. Review diagnostic workup for septic patient.
3. Describe management and treatment plan for septic pregnant patient.

REMEMBER… TO ERR IS HUMAN!!

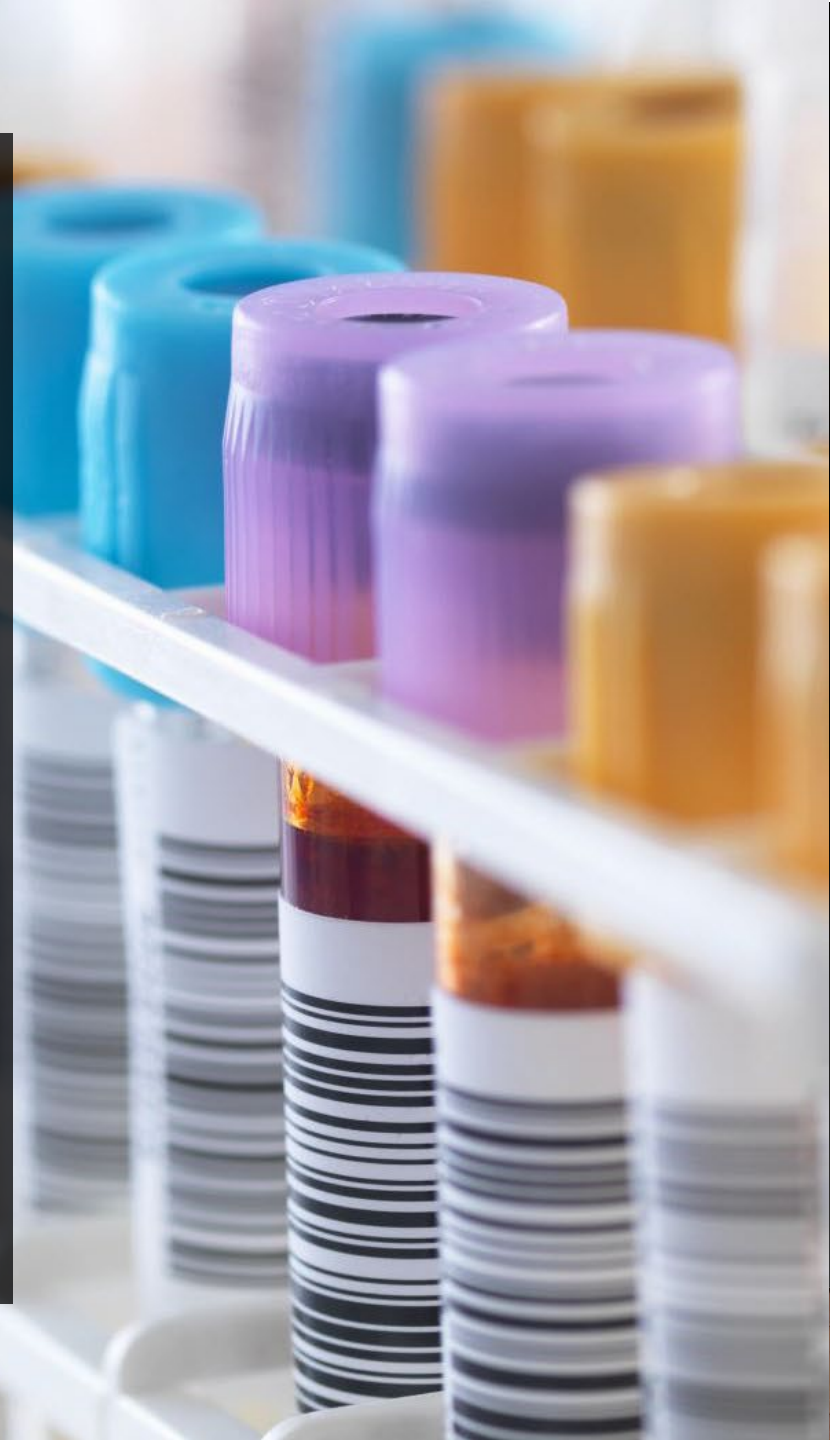
- Medical world to look at itself to see what role it played in poor medical outcomes.
- Mistakes/missed opportunities
- Set the stage for the initiatives in our various medical organizations for
  - Quality
  - Safety
  - Prevention
- Lead to development of safety bundles to address the areas of greatest impact in our field
  - Hypertension
  - Bloods loss/ hemorrhage
  - VTE/stroke
  - Infection/sepsis

BACKGROUND

- Sepsis/ Septic shock
  - Medical emergencies
  - Preventable causes of maternal death
- In the US, Sepsis is the 2nd leading cause of maternal death
  - 14 % of pregnancy related deaths despite complication of 4/10,000 births
  - 63 % of sepsis deaths by independent review found Substandard care (mostly delay in treatment) on the obstetrical unit

SEPSIS BACKGROUND

- Rates of maternal sepsis increasing
  - Texas hospitalizations for sepsis in pregnancy doubled from 2001 to 2010 (6/10000 to 12/10000)
  - When abortions/fetal demises included pregnancy associated sepsis increased from 11/10,000 (2001) to 26/10,000 in 2010.
- Nation wide inpatient sample from 1998-2008
  - 10 % increase per year in maternal sepsis/ sepsis related deaths in the U.S



SEPSIS – RISK FACTORS FOR PREGNANCY ASSOCIATED SEPSIS

- Social determinants
  - Nulliparity
  - Black race
  - Public or no insurance
- Obstetrical risk factors
  - Cesarean delivery
  - Assisted reproductive technologies
  - Multiple gestations
- 50% of maternal deaths from sepsis had more than 1 chronic co-morbidities
  - Chronic renal disease
  - Chronic liver disease
  - CHF (congestive heart failure)

SEPSIS – BACKGROUND

- 2002 – Surviving Sepsis Campaign (SSC) was launched with the goal of reducing sepsis and sepsis shock
  - Developed evidence-based guidelines
  - Promoted resuscitation and management bundles
- 2016 – update to guidelines – 3rd international consensus
  - Streamlines definitions/clinical criteria
  - Eliminated terms
  - Severe sepsis
  - Systematic inflammatory response syndrome (SIRS)
- 2021 Surviving Sepsis Campaign (SSC) issued new guideline
  - Up to date/evidence based clinical guidelines for treating adult patients with sepsis/sepsis shock
- This MFM consult series summaries the guidelines and adapts them to pregnancy/postpartum.

SEPSIS – DEFINITION

- Life threatening organ dysfunction caused by dysregulated host response to infection
- *Organ dysfunction defined as*
  - An increase by > 2 points on the **S**equential **O**rgan **F**ailure **A**ssessment **S**core (SOFA)

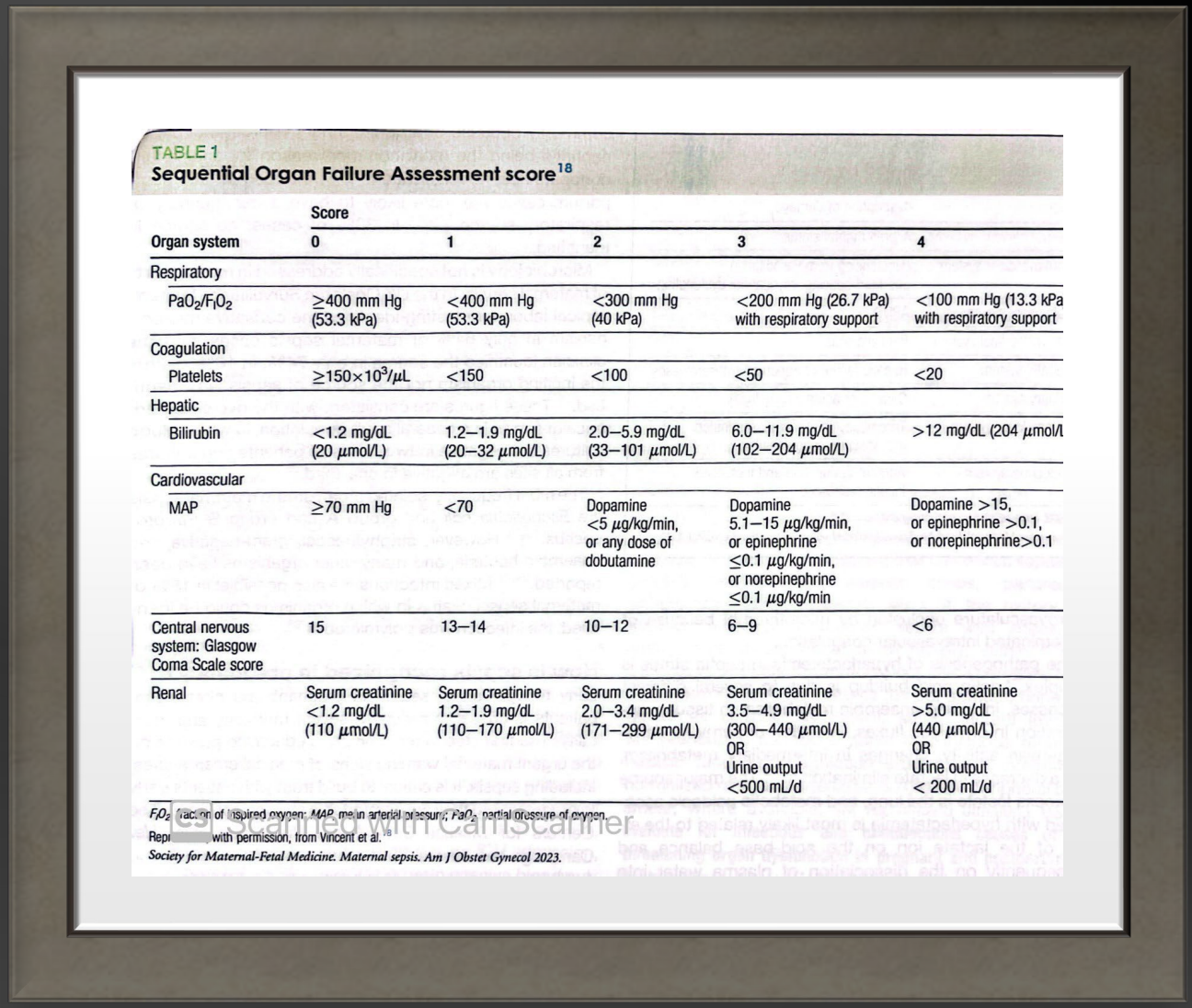


TABLE 1
Sequential Organ Failure Assessment score[18]

Organ system	Score 0	1	2	3	4
Respiratory					
PaO_2/F_IO_2	≥400 mm Hg (53.3 kPa)	<400 mm Hg (53.3 kPa)	<300 mm Hg (40 kPa)	<200 mm Hg (26.7 kPa) with respiratory support	<100 mm Hg (13.3 kPa with respiratory support
Coagulation					
Platelets	≥150×10³/μL	<150	<100	<50	<20
Hepatic					
Bilirubin	<1.2 mg/dL (20 μmol/L)	1.2–1.9 mg/dL (20–32 μmol/L)	2.0–5.9 mg/dL (33–101 μmol/L)	6.0–11.9 mg/dL (102–204 μmol/L)	>12 mg/dL (204 μmol/l
Cardiovascular					
MAP	≥70 mm Hg	<70	Dopamine <5 μg/kg/min, or any dose of dobutamine	Dopamine 5.1–15 μg/kg/min, or epinephrine ≤0.1 μg/kg/min, or norepinephrine ≤0.1 μg/kg/min	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	Serum creatinine <1.2 mg/dL (110 μmol/L)	Serum creatinine 1.2–1.9 mg/dL (110–170 μmol/L)	Serum creatinine 2.0–3.4 mg/dL (171–299 μmol/L)	Serum creatinine 3.5–4.9 mg/dL (300–440 μmol/L) OR Urine output <500 mL/d	Serum creatinine >5.0 mg/dL (440 μmol/L) OR Urine output < 200 mL/d

F_IO_2 fraction of inspired oxygen; *MAP* mean arterial pressure; PaO_2 partial pressure of oxygen.
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Society for Maternal-Fetal Medicine. Maternal sepsis. Am J Obstet Gynecol 2023.

SEPSIS - DEFINITION

- Pregnancy is a state of
  - Expounded plasma volume
  - Increased cardiac output
  - Peripheral Vasodilation
- None of the existing definitions or scoring systems account for physical changes of pregnancy
- Analysis showed that sepsis cutoffs for clinical parameters overlapped with the normal range for pregnancy/labor/postpartum
  - Respiratory rate
  - Heart rate
  - pCO2
  - WBC

  Serum creatine normal @ 1.2 mg/dl

SEPSIS – DEFINITIONS

- The Presence of a "fever"
  - Neither necessary nor sufficient to determine if sepsis is present

- "clinician should consider the diagnosis of sepsis in pregnancy and postpartum with the otherwise unexplained end organ damage in the presence of suspected infections process. **Regardless of the Presence of fever**."

SEPSIS – PATHOLOGY

SEPSIS RESULTS IN A DYSREGULATED HOST RESPONSE TO INFECTION, AND ANY ORGAN CAN BE AFFECTED.

TABLE 2

Organ damage caused by sepsis

System	Description of damage
Central nervous system	Altered mental status
Cardiovascular system	Hypotension from vasodilation and third-spacing; myocardial dysfunction
Pulmonary system	ARDS
Gastrointestinal system	Paralytic ileus
Hepatic system	Hepatic failure or abnormal transaminases
Urinary system	Oliguria or acute kidney injury
Hematologic system	Thrombocytopenia or disseminated intravascular coagulopathy
Endocrine system	Adrenal dysfunction and increased insulin resistance

ARDS, acute respiratory distress syndrome.

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SEPSIS – PATHOPHYSIOLOGY

- Sepsis > excessive inflammatory response > increased vascular permeability> extravasation of albumin and fluid > intravascular hypovolemia
- Sepsis > cytokine release > to decrease Systematic Vascular Resistance (SVR) > leads to resultant increase cardiac output to compensate (60 % of patients with sepsis have ejection fraction of < 45%)

SEPSIS PATHOPHYSIOLOGY

- Septic cardiomyopathy> decrease diastolic dysfunction
- Decrease cardiac compliance > decrease filling time and decrease stroke volume
  - increased risk of pulmonary edema from fluid resuscitation
- Decreased stoke volume/cardiac output > hypotension > tissue ischemia> organ dysfunction > disseminated intravascular coagulopathy> microvascular occlusion from microthrombi

SEPSIS – BIOLOGIC MARKER

- Lactic acid build up due to
  - Anerobic metabolism in tissue
  - Accelerated glycolytic fluxes
  - inhibition of pyruvate dehydrogenase (Krebs cycle)
  - Decrease In lactate elimination

SEPSIS – CAUSES IN PREGNANCY

- Most frequently identified organism in maternal sepsis
  - Escherichia coli
  - Group A strep
  - Group B strep

  15 % of maternal deaths, infections was polymicrobial

TABLE 3
Common sources of infection in sepsis

Sources	Antepartum	Postpartum
Obstetrical	Septic abortion	Endometritis
	Chorioamnionitis	Wound infection
Nonobstetrical	Urinary tract infection	Urinary tract infection
	Pneumonia	Pneumonia
	Appendicitis	Gastrointestinal

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SEPSIS – INITIAL MANAGEMENT

- Heightened suspicion of sepsis/organ dysfunction
- History + Physical with emphasis on infectious causes
- Employ screening tools/ scoring systems
- Laboratory evaluation
  - CBC and diff
  - Cultures (blood, specimen, urine)
  - Serum lactate
  - CMP (with renal and hepatic components)
  - COAGS
  - Peripheral smear/ Arterial Blood gas
- Serum lactate > 2 milli-moles/liter/ l – possible/likely sepsis
  - (Intrapartum lactate typically > 2 and late stages of labor > 4)
- procalcitonin's - biomarkers of response of infection
  - Have not correlated with decrease in mortality, ICU stay, or hospital length of stay in OB population
  - **“No role for procalcitonin in pregnant woman”**

SEPSIS – RECOGNITION AND DIAGNOSIS

- "Recommend hospitals use of performance improvement plan for sepsis in pregnancy with screening tools/metrics
- Multiple screenings tools exist
  - SSOFA (quick sofa)
  - MEOWS (modified early OB warning system)
  - SOS (sepsis in OB score)
  - CMQCC(California maternal quality care collaboration)
  - MEWT (maternal early warning triggers)
- All have strengths and weaknesses in sensitivity/PPV/NPV
- The implementation of an early warning system decreases maternal risk/ morbidly

TABLE 4

Proposed broad-spectrum empiric antibiotic coverage in sepsis complicating pregnancy

Source infection	Recommended antibiotics
Community-acquired pneumonia	Cefotaxime, ceftriaxone, ertapenem, or ampicillin plus azithromycin, clarithromycin, or erythromycin.[55]
Hospital-acquired pneumonia	Low-risk patients may be treated with ceftriaxone, ampicillin-sulbactam, ertapenem, meropenem, imipenem, or cefepime. Patients at high risk of mortality may need double coverage for *Pseudomonas* (beta lactam plus an aminoglycoside or a quinolone) and MRSA coverage with vancomycin or linezolid.[56,57]
Chorioamnionitis	Ampicillin plus gentamicin.[58] Add anaerobic coverage with clindamycin or metronidazole if cesarean delivery required.
Endomyometritis	Ampicillin, gentamicin, and metronidazole (or clindamycin). Alternatively, may use cefotaxime or ceftriaxone plus metronidazole.[59]
Urinary tract infections	Gentamicin with ampicillin Alternatively, may use monotherapy with a carbapenem or piperacillin-tazobactam.[60]
Abdominal infections	Ceftriaxone, cefotaxime, ceftazidime, or cefepime plus metronidazole.[61] Complicated cases may require monotherapy with a carbapenem or piperacillin-tazobactam.
Skin and soft tissues (necrotizing)	Vancomycin plus piperacillin-tazobactam.[62] If group A *Streptococcus* or *Clostridium perfringens* are present, use penicillin G plus clindamycin.

MRSA, methicillin-resistant Staphylococcus aureus.

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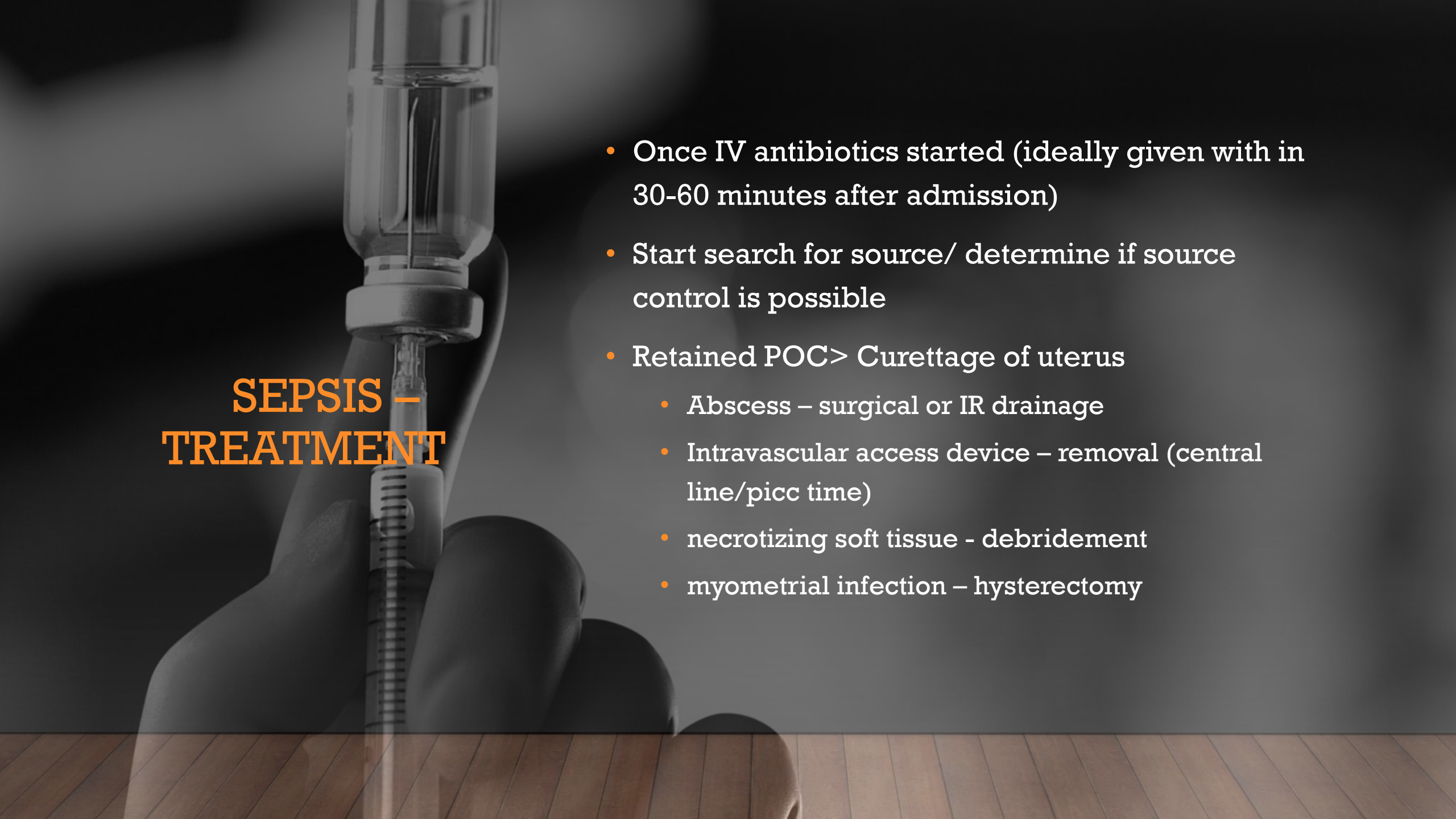
SEPSIS – TREATMENT

- Early administration of appropriate IV antibiotic is critical
- In 82 patients' cases of maternal sepsis admitted for delivery
  - If IV antibiotics started < 1 hour– mortality was 8.3 %
  - If IV antibiotics were given > 1hour – mortality was 20 %
- The presumed source of infection should be direct IV antibiotics choices
- since sepsis is frequently polymicrobial
  - Coverage should include both anaerobic and aerobic gram pos and gram neg bacteria



SEPSIS – TREATMENT

- Once IV antibiotics started (ideally given with in 30-60 minutes after admission)
- Start search for source/ determine if source control is possible
- Retained POC> Curettage of uterus
  - Abscess – surgical or IR drainage
  - Intravascular access device – removal (central line/picc time)
  - necrotizing soft tissue - debridement
  - myometrial infection – hysterectomy

SEPSIS – FLUID MANAGEMENT

- Fluid resusation is integral for favorable initial response especially if following preterm
  - Hypotension (maternal)
  - Hypoperfusion of tissues
- Fever, venous > dilation and capillary leak > decrease preload > decrease CO > increase tissue dysfunction
- RX – Aggressive fluid resuscitation
  - 30 ml/kg of fluids/ 0ver 3 hours
  - (non-pregnant literature) (3 liters over 3 hours)
  - fluid replacement should be altered to 1-2 liters of balanced crystalloid over 3 hours (lactated ringers' solution)
  - Thus, In pregnancy with the already decreased colloid osmotic pressure, the risk of pulmonary edema is higher

SEPSIS – BLOOD PRESSURE SUPPORT

- In hypotensive septic patients
  - Non fluid responders
  - Not candidates for further fluid resuscitation (pulmonary edema)
- Vasopressor and inotropes are used to increase blood pressure and increase cardiac contractility
  - Constricts pathologically dilated systemic circulation
  - Maintains adequate tissue perfusion

SEPSIS – VASOPRESSORS

- Guidelines recommend
  - norepinephrine at first time vasopressor
  - Maintain initial Mean Arterial Pressure (MAP) of 65
  - Lower MAP targets "may be" acceptable in pregnancy but must screen for organ hypoperfusion
    - Altered mental status
    - Oliguria
    - Increase serum lactate
    - Cold extremities
    - Fetal compromise (oligohydramnios or fetal heart rate abnormalities)

SEPSIS – ROLE FOR CORTICOSTEROIDS

- In nonpregnant patients in whom hemodynamic stability can not be maintained with use of vasopressors
- Systematic corticosteroid **“may”** accelerate resolution of shock in patients with ongoing need for blood pressure support
- Hydrocortisone IV 200 mg /day
  - 50 mg every 6 hours for 7 days

SEPSIS – OTHER CONSIDERATIONS

- In the non pregnant population
  - Lessons extrapolated from septic patients should be considered

1. Stress ulcer prophylaxis (GI bleed)
2. VTE Prophylaxis with low molecular weight heparin (LMWH)
   - 37 % of patients with septic developed VTE
3. Insulin to prevent glucose levels > 180 mg/dl

- Blood glucose of > 180 mg/dl is associated with increase mortality in critically ill patients

SEPSIS – IS DELIVERY INDICATED ?

- Sepsis alone "**not**" an indication of delivery (except in cases of intra-amniotic infections)
- Primary objective of treatment/ resuscitation
  - cardiopulmonary support
  - Antimicrobial treatment of suspected infection
- Only after stabilization of the fetus should fetal monitoring begin.

SEPSIS – MATERNAL OUTCOMES

- Overall mortality in adult patients admitted to ICU is increased
  - between 2000-2012 for patients < 44-year-olds
- 8 % in patients in absence comorbidities
- 12 % all septic pregnant patients hospitalized
- In the US, sepsis is one of the leading causes of severe maternal **morbidities**
- Estimated 50 patients experience life threatening morbidity from sepsis for each maternal death
  - Chronic organ dysfunction
  - Amputations
  - Depression/anxiety/ panic attacks
  - Disabling muscle/ joint pain
  - Decreased cognitive function
- Infertility and hysterectomy may result/ which are unique morbidities to some survivors of maternal sepsis

SEPSIS – FETAL OUTCOME

- Preterm delivery is common after maternal diagnosis of sepsis
  - Ireland – 2015 – if bacteremia present PTB was 16.8 % (3x higher than controls from same institution)
  - Overall, 69 % of all maternal admissions either miscarried or delivered preterm
- French study of women admitted with sepsis with bacteremia
  - 29 % risk of PTD / 10% fetal mortality
  - In 2nd trimester, fetal death was 40 %

SEPSIS – CAN OUTCOMES BE IMPROVED?

- In studies of sepsis related maternal mortality
  - Most had delay in care
  - Many had delay in escalation of care
  - Most deaths presented initially afebrile
  - Even after diagnosis of sepsis, 73% were started on IV antibiotics that provided inadequate coverage.

SEPSIS – FUTURE CONSIDERATIONS

- Multidisciplinary renews for systems improvements should be conducted to assess
  - Screening programs
  - Quality of care
  - Identity of bias if care existed
- Multidisciplinary case renewed should
  - 1. identify all maternal sepsis cases
  - 2. determine adherence to sepsis protocol
  - 3. Determine if instances of bias occurred
    - Race
    - Ethnicity
    - Socioeconomic status
    - Insurance status
    - History of substance abuse
- 4. identify/implement ways to make system improvements

Summary of recommendations

Number	Recommendation	GRADE
1	We recommend that clinicians consider the diagnosis of sepsis in pregnant or postpartum patients with otherwise unexplained end-organ damage in the presence of a suspected or confirmed infectious process, regardless of the presence of fever.	1C
2	We recommend that sepsis and septic shock in pregnancy be considered medical emergencies and that treatment and resuscitation begin immediately.	Best Practice
3	We recommend that hospitals and health systems use a performance improvement program for sepsis in pregnancy with sepsis screening tools and metrics.	1B
4	We recommend that institutions develop their own procedures and protocols for the detection of maternal sepsis, avoiding the use of a single screening tool alone.	1B
5	We recommend obtaining tests to evaluate for infectious and noninfectious causes of life-threatening organ dysfunction in pregnant and postpartum patients with possible sepsis.	Best Practice
6	We recommend that an evaluation for infectious causes in pregnant or postpartum patients in whom sepsis is suspected or identified include appropriate microbiologic cultures, including blood, before starting antimicrobial therapy, as long as there are no substantial delays in starting antibiotics.	Best Practice
7	We recommend obtaining a serum lactate level in pregnant or postpartum patients in whom sepsis is suspected or identified.	1B
8	In pregnant or postpartum patients with septic shock or a high likelihood of sepsis, we recommend administration of empiric broad-spectrum antimicrobial therapy, ideally within 1 h of recognition.	1C
9	After a diagnosis of sepsis in pregnancy is made, we recommend rapid identification or exclusion of an anatomic source of infection and emergency source control when indicated.	Best Practice
10	We recommend early intravenous administration (within the first 3 h) of 1 to 2 L of balanced crystalloid solutions in sepsis complicated by hypotension or suspected organ hypoperfusion.	1C
11	We recommend the use of a balanced crystalloid solution as a first-line fluid for resuscitation in pregnant and postpartum patients with sepsis or septic shock.	1B
12	We recommend against the use of starches or gelatin for resuscitation in pregnant and postpartum patients with sepsis or septic shock.	1A
13	We recommend ongoing, detailed evaluation of the patient's response to fluid resuscitation guided by dynamic measures of preload.	1B
14	We recommend the use of norepinephrine as the first-line vasopressor during pregnancy and the postpartum period with septic shock.	1C
15	We suggest using intravenous corticosteroids in pregnant or postpartum patients with septic shock who continue to require vasopressor therapy.	2B
16	Because of an increased risk of VTE in sepsis and septic shock, we recommend the use of pharmacologic VTE prophylaxis in pregnant and postpartum patients in septic shock.	1B
17	We suggest initiating insulin therapy at a glucose level >180 mg/dL in critically ill pregnant patients with sepsis.	2C
18	If a uterine source for sepsis is suspected or confirmed, we recommend prompt delivery or evacuation of uterine contents to achieve source control, regardless of gestational age.	1C
19	Because of an increased risk of physical, cognitive, and emotional problems in survivors of sepsis and septic shock, we recommend ongoing comprehensive support for pregnant and postpartum sepsis survivors and their families.	Best Practice

VTE, venous thromboembolism.

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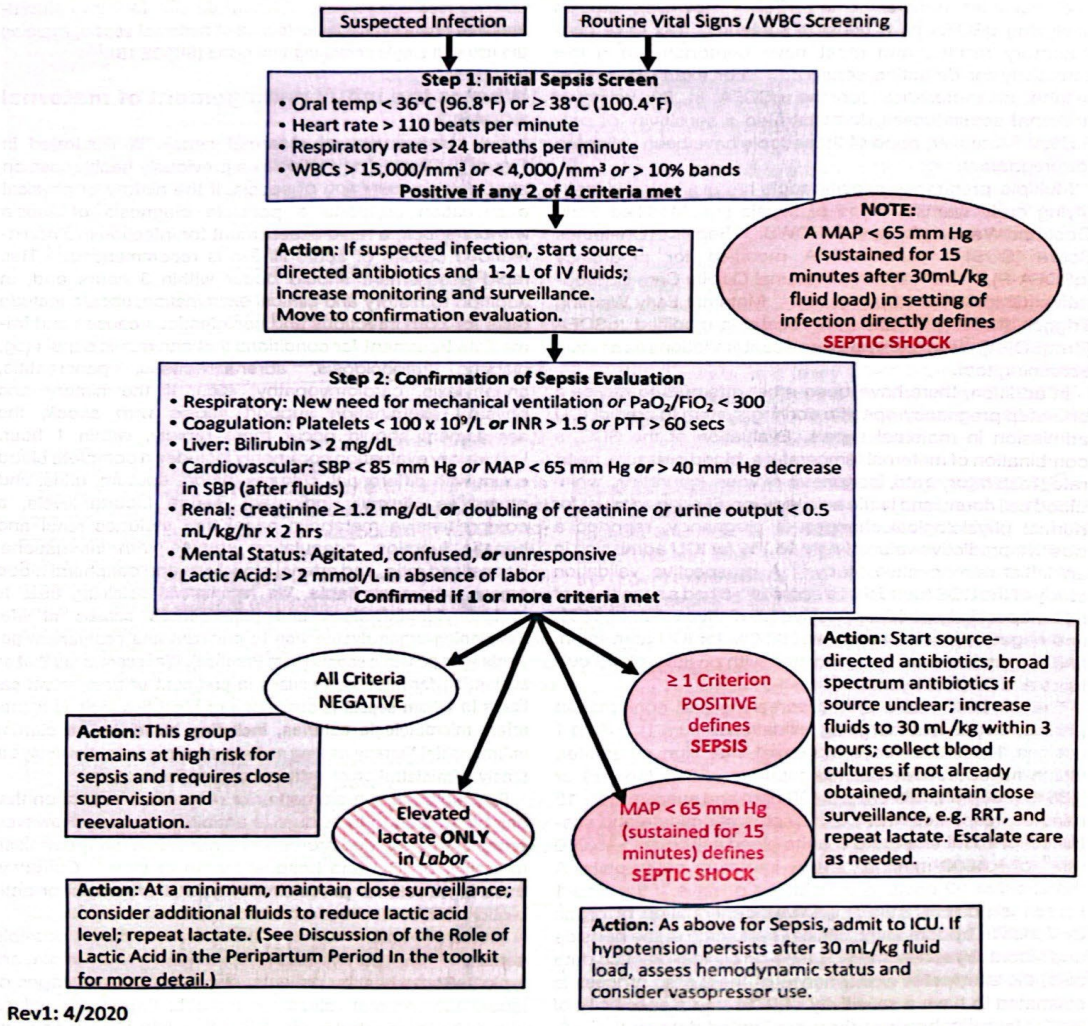
FIGURE 1
California Maternal Quality Care Collaborative 2-step system for diagnosis of maternal sepsis[38]



Rev1: 4/2020

FiO_2, fraction of inspired oxygen; *ICU*, intensive care unit; *INR*, international normalized ratio; *IV*, intravenous; *MAP*, mean arterial pressure; *PaO_2*, partial pressure of oxygen; *PTT*, partial thromboplastin time; *RRT*, rapid response team; *SBP*, systolic blood pressure; *WBC*, white blood cell.

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