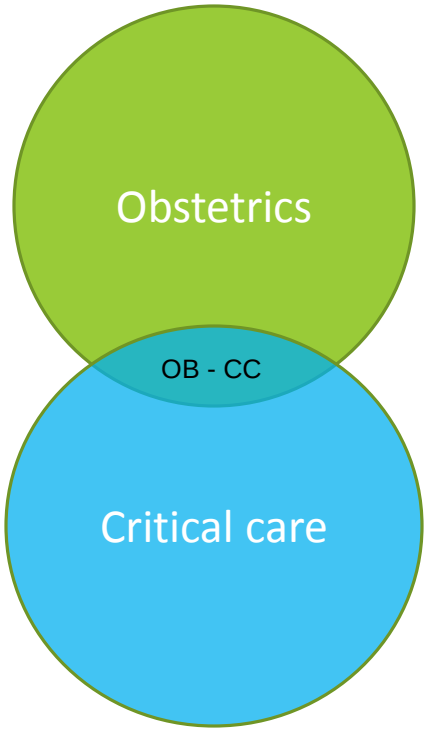
Sepsis in Pregnancy

MICHEL BOIVIN

CRITICAL CARE OBSTETRICS

Maternal Sepsis



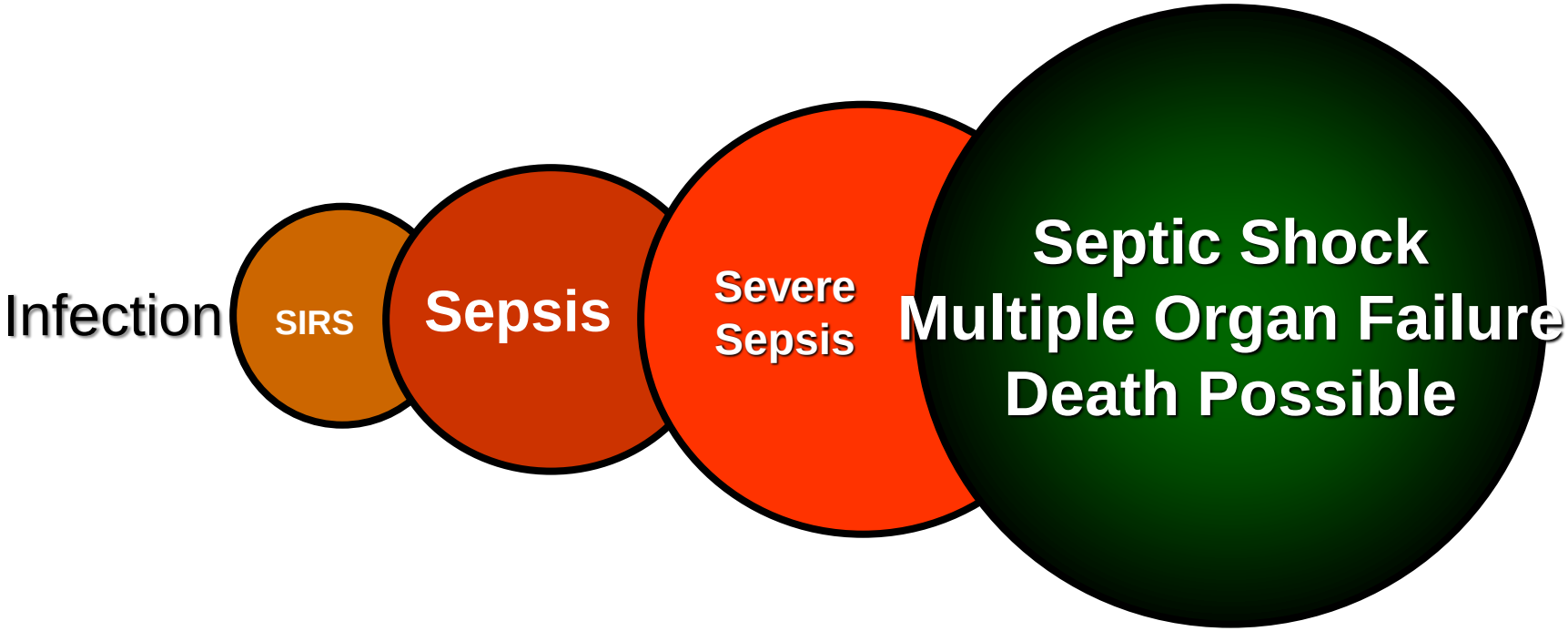
Objectives

Review epidemiology, definitions, physiology and etiology of Maternal sepsis

Review early goal-directed therapy with considerations of the pregnant patient

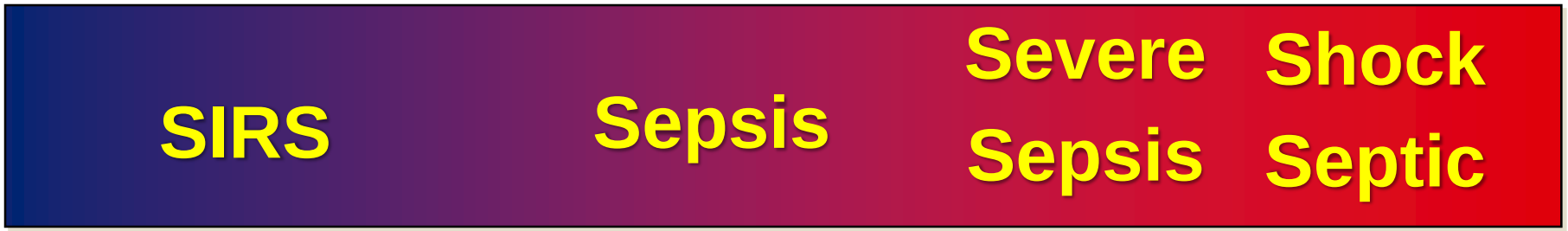
Review of sepsis-related conditions and complications particular to the pregnant patient.

Sepsis: A Deadly Continuum of Disease



Mortality:	~10%	~15%	~25-50%

Sepsis: A Deadly Continuum



A clinical response arising from a nonspecific insult, with ≥2 of the following:

- T >38°C or <36°C
- HR >90 beats/min
- RR >20/min
- WBC >12,000/mm^3 or <4,000/mm^3 or >10% bands

SIRS with a presumed or confirmed infectious process

Sepsis with evidence of organ dysfunction

Refractory Hypotension Related to Sepsis

Chest 1992;101:1644.

In the Pregnant patient…

- These values weren’t validated

- They don’t take into account maternal physiology

- Correlation to outcome has not been done

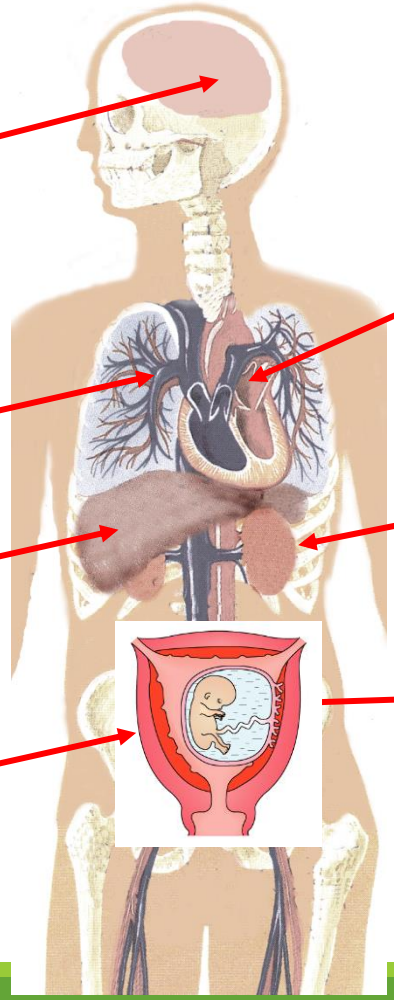
New thinking about Sepsis

Box 2. Key Concepts of Sepsis

- Sepsis is the primary cause of death from infection, especially if not recognized and treated promptly. Its recognition mandates urgent attention.
- Sepsis is a syndrome shaped by pathogen factors and host factors (eg, sex, race and other genetic determinants, age, comorbidities, environment) with characteristics that evolve over time. What differentiates sepsis from infection is an aberrant or dysregulated host response and the presence of organ dysfunction.
- Sepsis-induced organ dysfunction may be occult; therefore, its presence should be considered in any patient presenting with infection. Conversely, unrecognized infection may be the cause of new-onset organ dysfunction. Any unexplained organ dysfunction should thus raise the possibility of underlying infection.
- The clinical and biological phenotype of sepsis can be modified by preexisting acute illness, long-standing comorbidities, medication, and interventions.

Singer et. al., JAMA 2016

Acute Organ Dysfunction as the Hallmark of Severe Sepsis



Altered
Consciousness
Confusion
Psychosis

Tachypnea
PaO2 <70 mm Hg
SaO2 <90%
PaO2/FiO2 ≤300

Jaundice
↑ Enzymes
↓ Albumin
↑ PT

Fetal distress

Tachycardia
Hypotension
↓ CVP
PAOP

Oliguria
Anuria
↑ Creatinine

↓ Platelets
↑ PT/APTT
↓ Protein C
↑ D-dimer

Lactic acidosis

Used with permission, S.Simpson, MD, KU, 2008

SOFA scores

Table 1. Sequential [Sepsis-Related] Organ Failure Assessment Score[a]

	Score				
System	0	1	2	3	4
Respiration					
Pao_2/Fio_2, mm Hg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation					
Platelets, $\times 10^3/\mu L$	≥150	<150	<100	<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 dobutamine (any dose)[b]	Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1[b]	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1[b]
Central nervous system					
Glasgow Coma Scale score[c]	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/d				<500	<200

Abbreviations: Fio_2, fraction of inspired oxygen; MAP, mean arterial pressure; Pao_2, partial pressure of oxygen.

[a] Adapted from Vincent et al.[27]

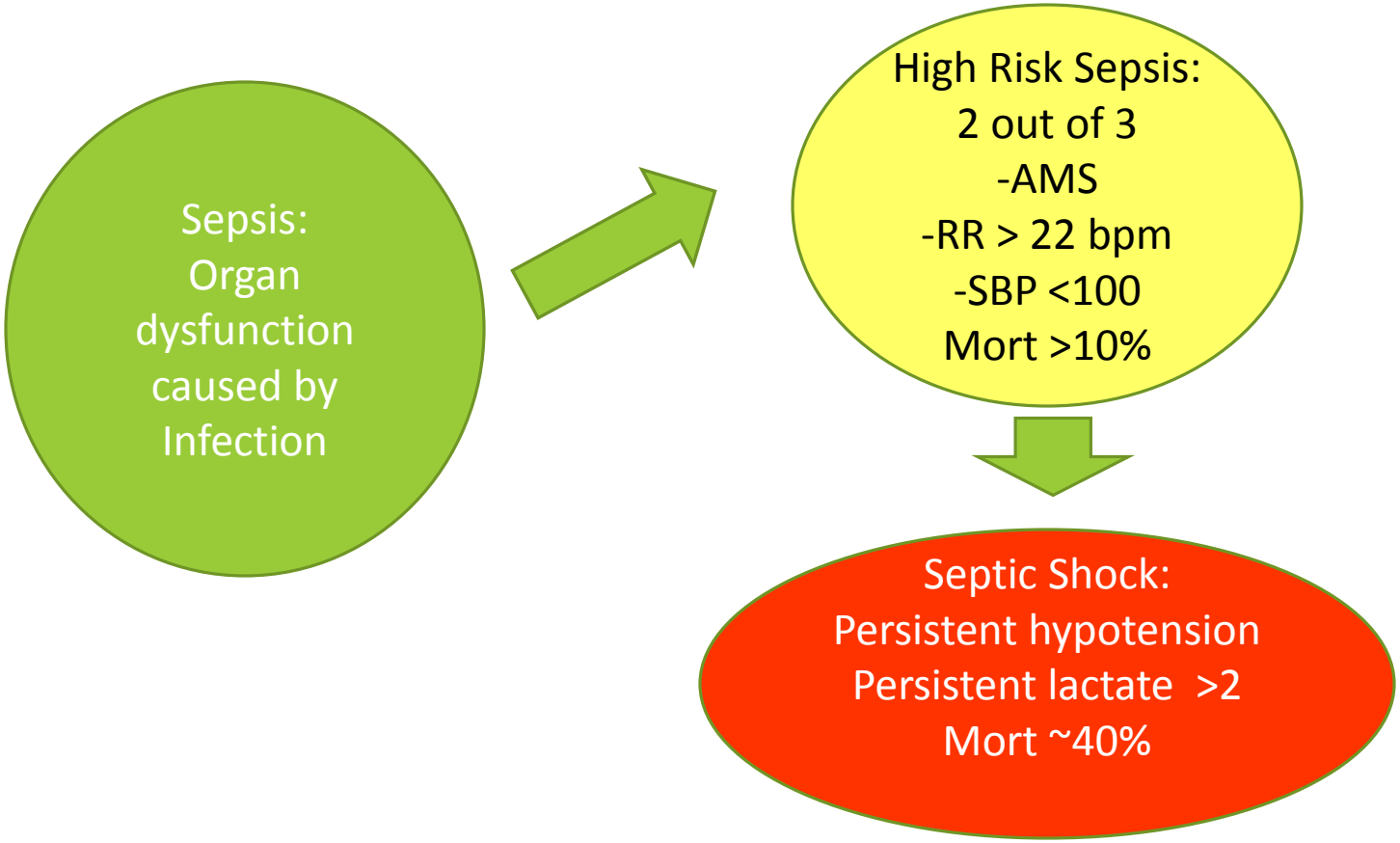
[b] Catecholamine doses are given as μg/kg/min for at least 1 hour.

[c] Glasgow Coma Scale scores range from 3-15; higher score indicates better neurological function.

Change in Score ≥2 predicts mortality from infection ~ 10%.

Singer et. al., JAMA 2016

Proposed Changes



Singer et. al., JAMA 2016

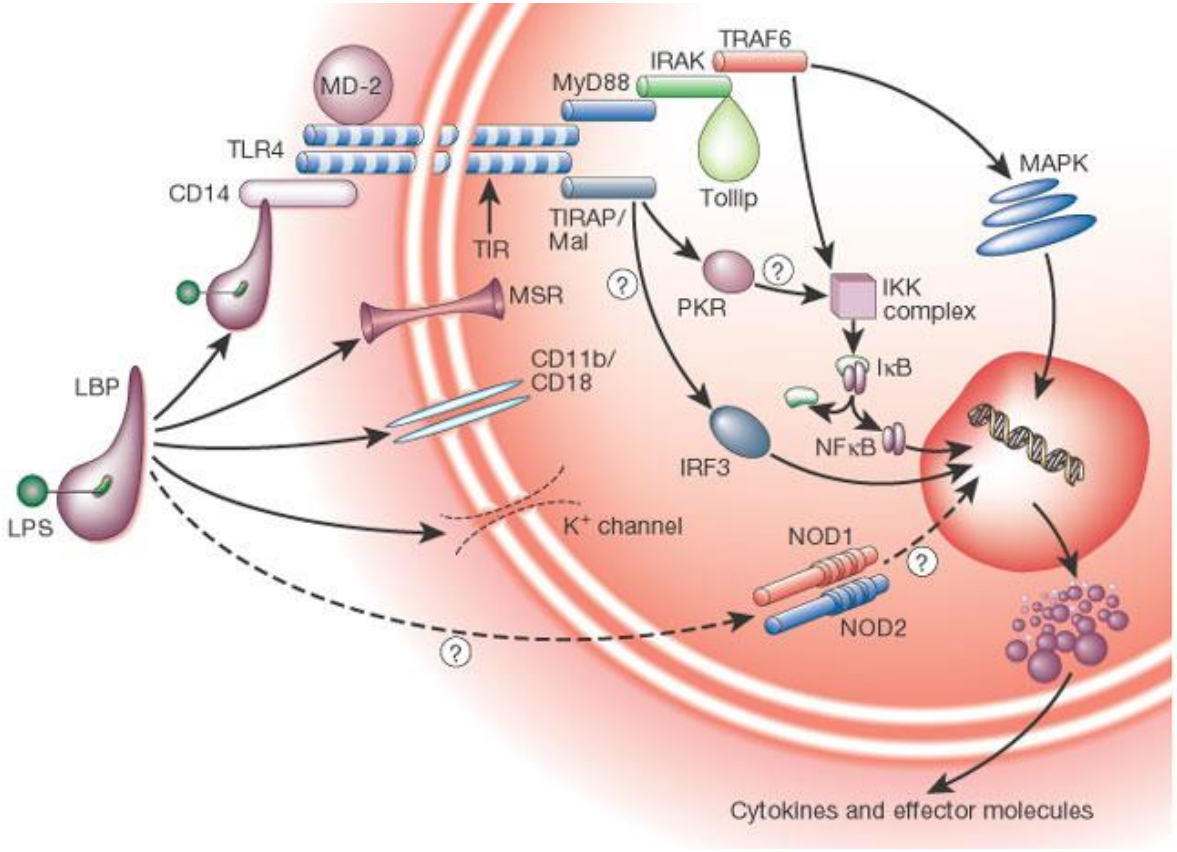
Maternal early warning criteria

Systolic BP (mm Hg)	<90 or >160
Diastolic BP (mm Hg)	>100
Heart rate (beats per min)	<50 or >120
Respiratory rate (breaths per min)	<10 or >30
Oxygen saturation on room air, at sea level, %	<95
Oliguria, mL/hr for ≥2 hours	<35
Maternal agitation, confusion, or unresponsiveness; patient with preeclampsia reporting a non-remitting headache or shortness of breath	

These triggers cannot address every possible clinical scenario that could be faced by an obstetric clinician and must not replace clinical judgment. As a core safety principle, bedside at any point.

BP: blood pressure.

Sepsis Mechanism

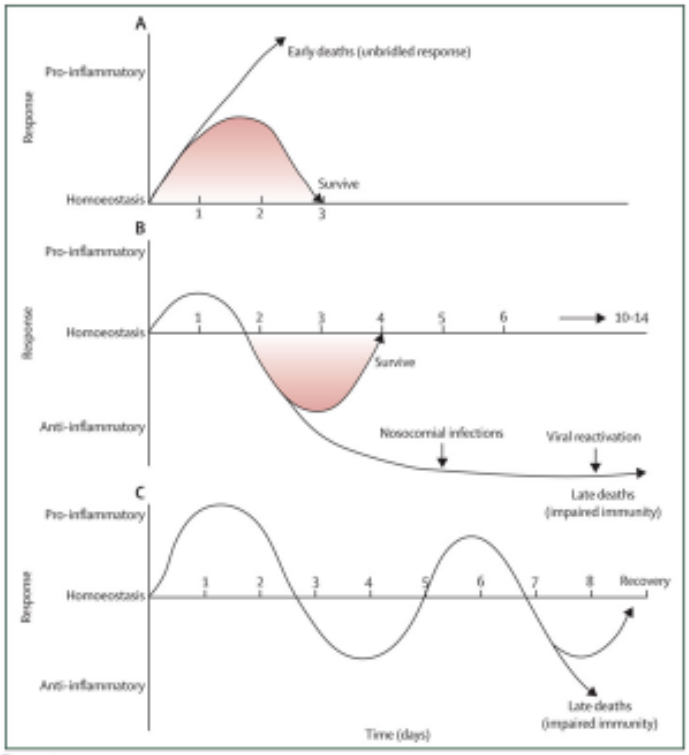


Evolution of thinking in sepsis

- Sepsis used to be thought of as killing patients due to profound immune activation and pro-inflammatory response

- We now know many patients develop profound immunosuppression after the initial insult.

- Some patients may alternate due to secondary infections



Hotchkiss et al., Lancet Inf Dis 2013

Epidemiology of Maternal Sepsis

- Bacteremia is ~ 0.75 % of OB admissions
- Only 10% develop severe sepsis
- Most important direct cause of Maternal Death in the U.K.
- Mortality rates low and actually better than non-Obstetric patients.

Guinn et al. Ob Gyn Clin N.A., 2007

Risk Factors

Table 1. Risk factors for maternal sepsis in pregnancy as identified by the Confidential Enquiries into Maternal Deaths[1,2]

Obesity
Impaired glucose tolerance / diabetes
Impaired immunity/ immunosuppressant medication
Anaemia
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

Bacterial Sepsis in Pregnancy , RCO&G, 2012

Treatment of Sepsis

Treat infection: Antibiotics *and* Source Control

Intravascular volume resuscitation

Cardiovascular support

Support of dysfunctional organ systems

EGDT Goals

ID and treat infection / inflammatory focus

Treat global tissue hypoxia

- Reverse functional hypovolemia
- Maintain MAP > 60-65

Support organ dysfunction

Interventions are time-dependent

Early Goal Directed Therapy

Current UNM Practice

- Blood Cultures

-Lactate Measured

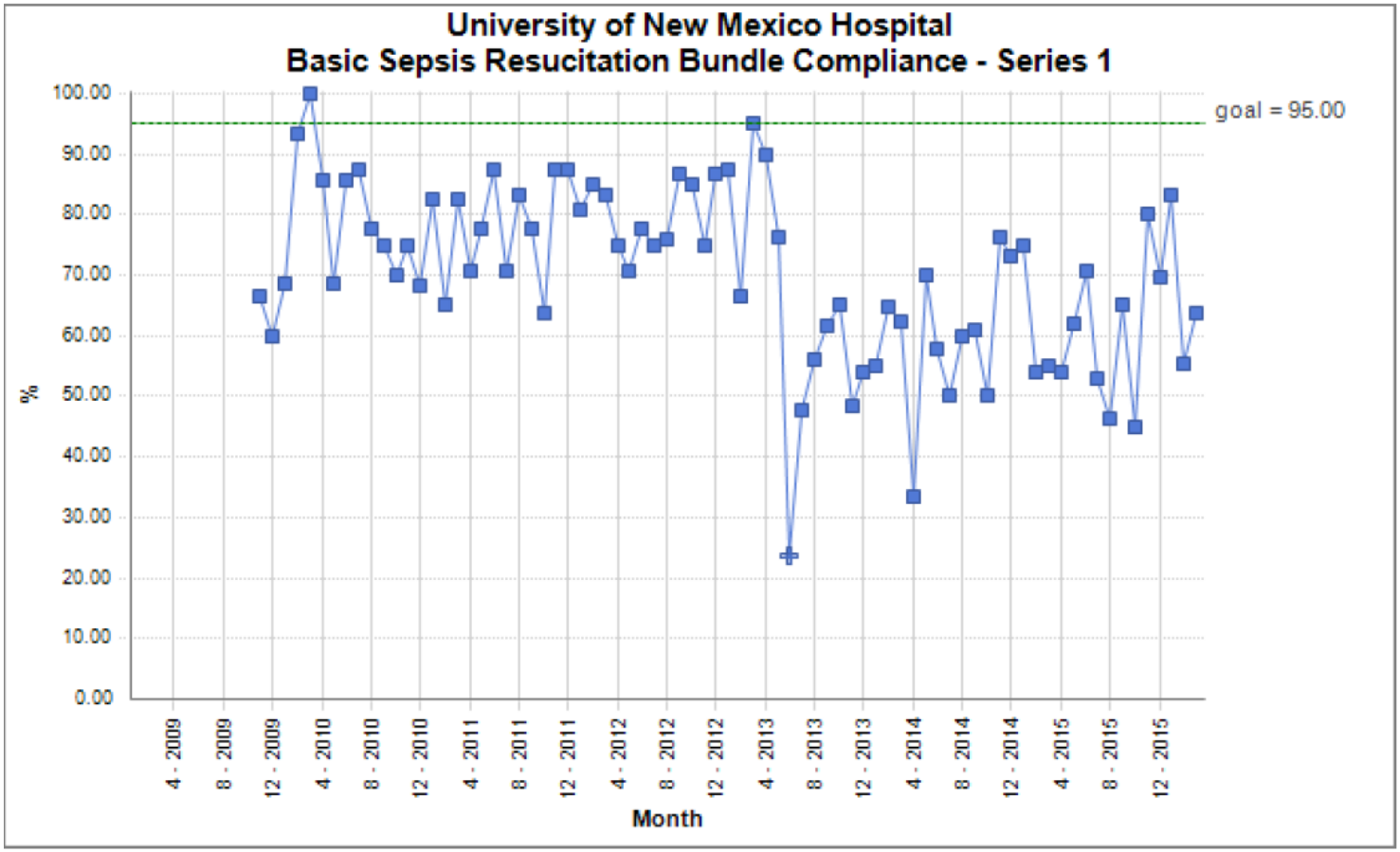
- Antibiotics Given within 1h

- Initial bolus of 3L

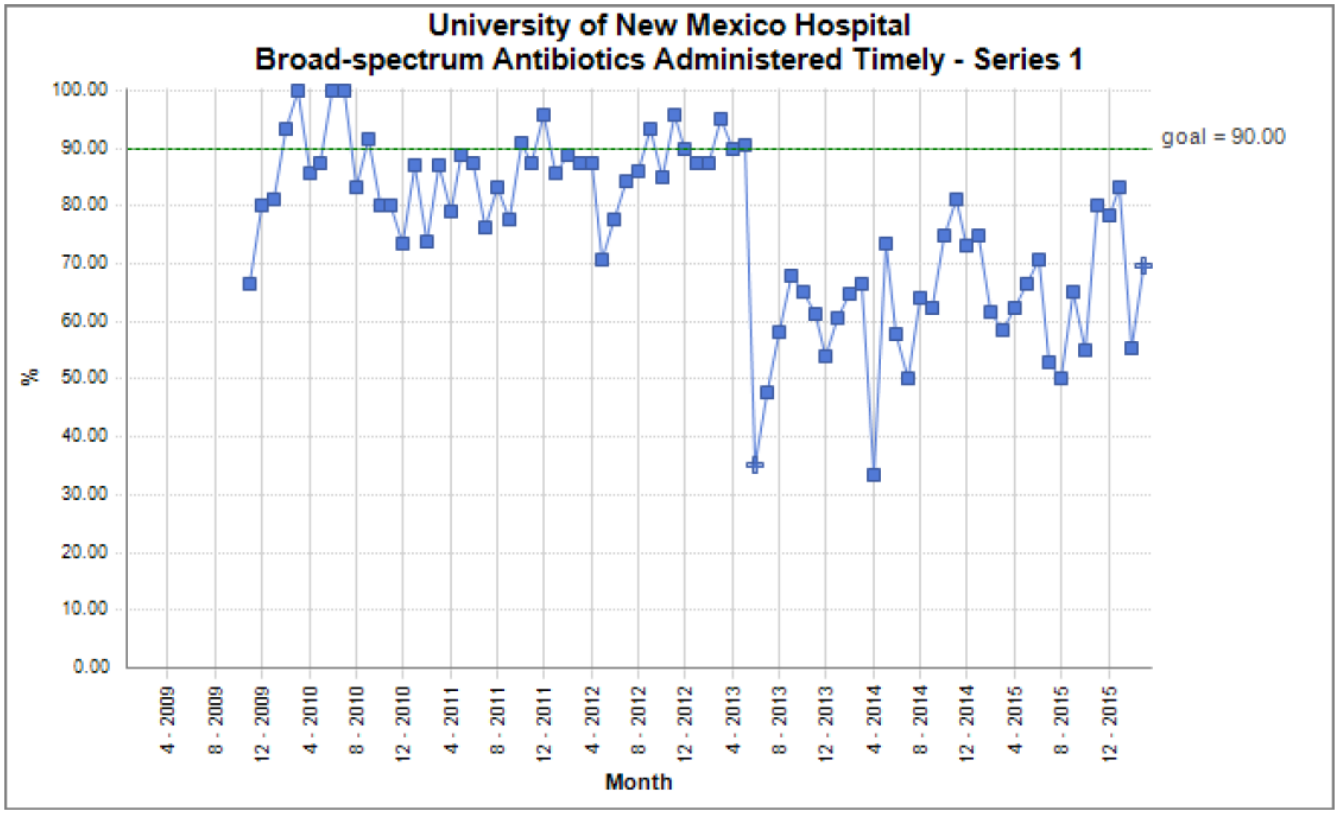
-Non-invasive Cardiac Output guided fluid resuscitation

-Pressors to keep MAP >65

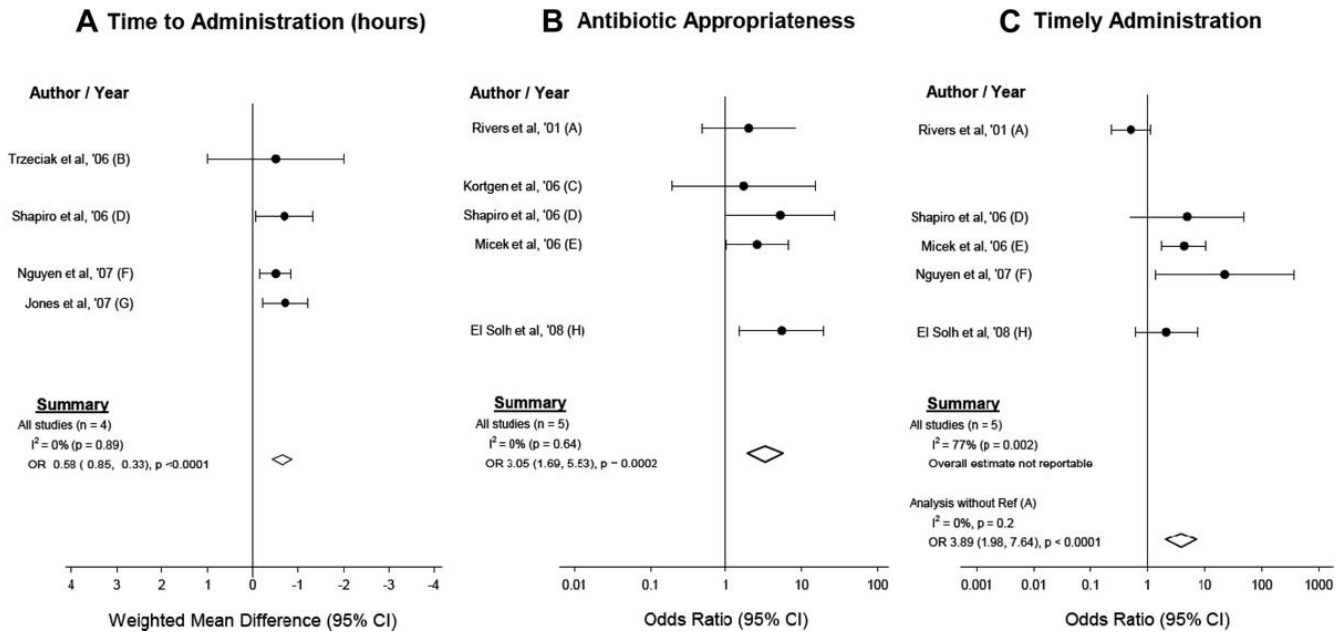
How do we do?


University of New Mexico Hospital
Basic Sepsis Resucitation Bundle Compliance - Series 1
goal = 95.00
%
100.00
90.00
80.00
70.00
60.00
50.00
40.00
30.00
20.00
10.00
0.00
4 - 2009
8 - 2009
12 - 2009
4 - 2010
8 - 2010
12 - 2010
4 - 2011
8 - 2011
12 - 2011
4 - 2012
8 - 2012
12 - 2012
4 - 2013
8 - 2013
12 - 2013
4 - 2014
8 - 2014
12 - 2014
4 - 2015
8 - 2015
12 - 2015
Month

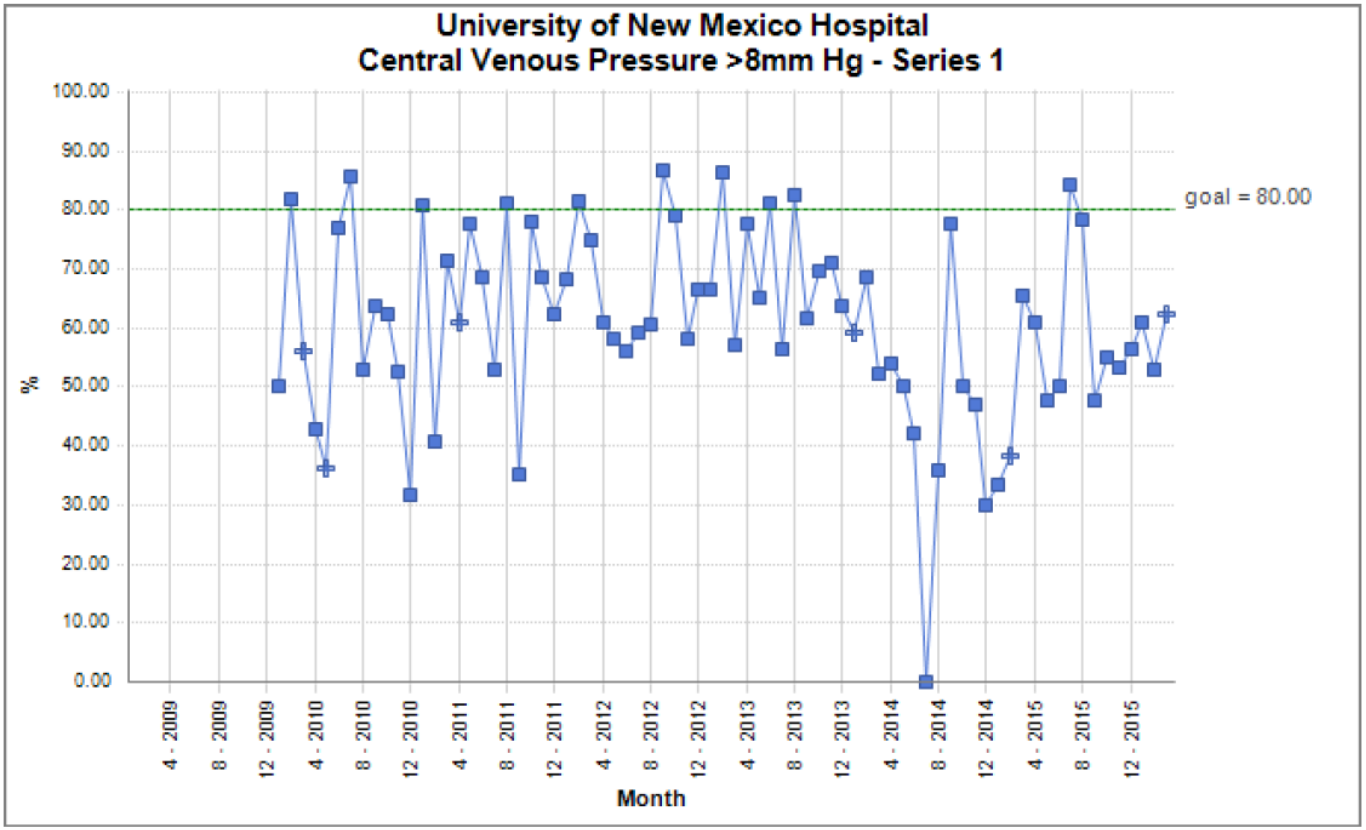
Early antibiotic administration



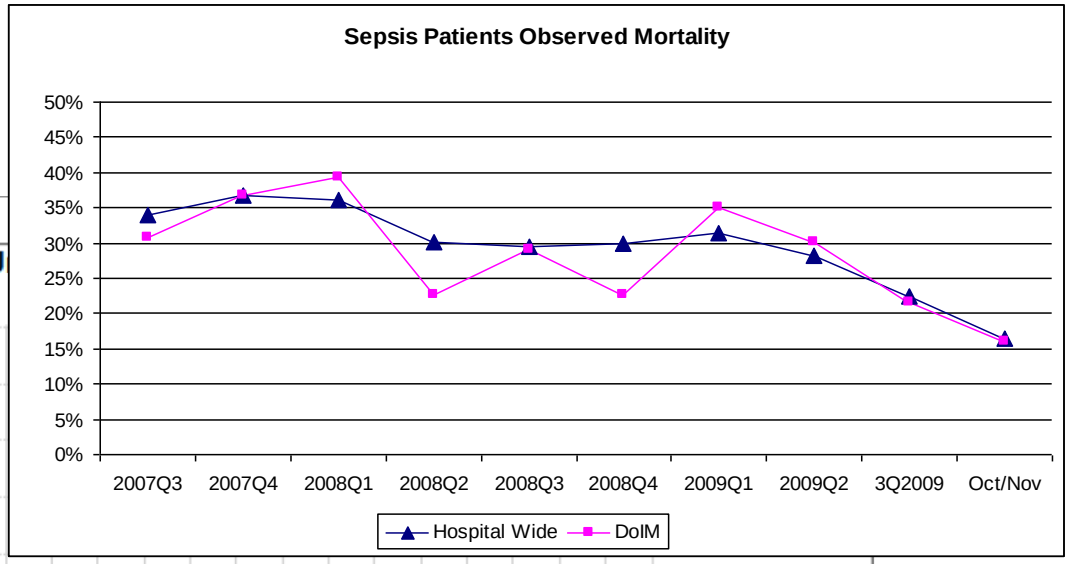
Treatment differences associated with better outcomes

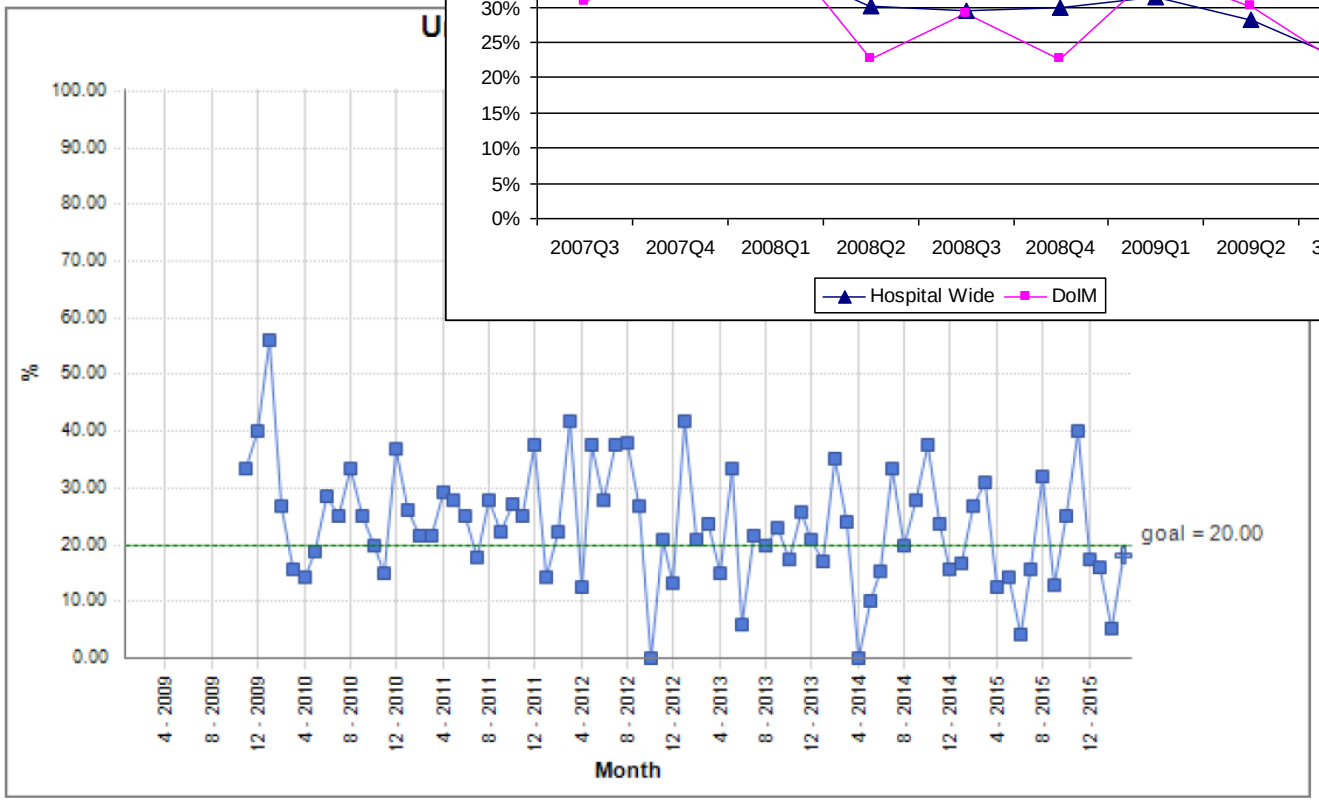


Goal-directed fluid ressus



Mortality


Sepsis Patients Observed Mortality
50%
45%
40%
35%
30%
25%
20%
15%
10%
5%
0%
2007Q3
2007Q4
2008Q1
2008Q2
2008Q3
2008Q4
2009Q1
2009Q2
3Q2009
Oct/Nov
Hospital Wide
DoIM


100.00
90.00
80.00
70.00
60.00
50.00
40.00
30.00
20.00
10.00
0.00
%
goal = 20.00
4 - 2009
8 - 2009
12 - 2009
4 - 2010
8 - 2010
12 - 2010
4 - 2011
8 - 2011
12 - 2011
4 - 2012
8 - 2012
12 - 2012
4 - 2013
8 - 2013
12 - 2013
4 - 2014
8 - 2014
12 - 2014
4 - 2015
8 - 2015
12 - 2015
Month

Controversies remaining in EGDT

- Role for CVP vs other Goals
- Dobutamine
- Transfusion of blood
- Right pressor?
- Steroids
- Lactate clearance

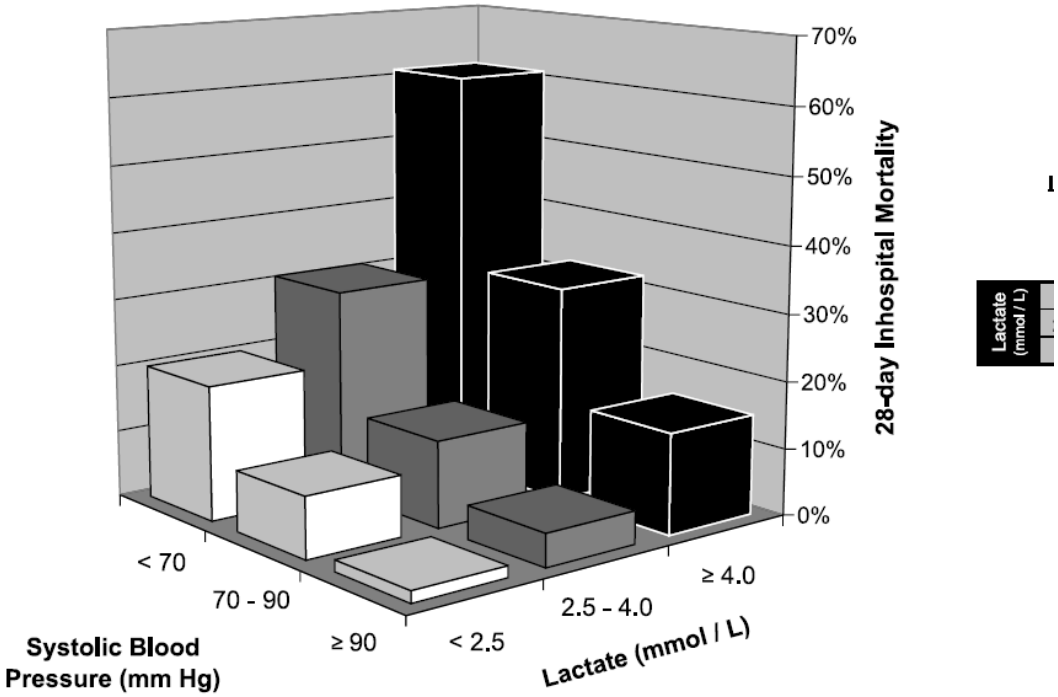


Fig. 1 28-day in-hospital mortality risk stratified by blood pressure and serum lactate level

Howell , Int care Med 2007

Lactate in pregnancy and sepsis

- Lower serum bicarbonate therefore more susceptible to metabolic acidosis

- One study looking at maternal and fetal outcomes

-Seems to be correlation, however number of very septic patients extremely small.

Table 4
Adjusted odds ratio (AOR) of adverse outcomes per unit increase in lactic acid concentration

	AOR (95% CI)
Transfer to ICU	1.72 (0.63–4.70)
Transfer to telemetry unit	2.34 (1.27–4.29)
Transfer to ICU or telemetry unit	2.34 (1.33–4.12)
Positive blood cultures	1.6 (0.83–3.08)
Positive influenza test	1.01 (0.44–2.31)
Preterm birth (< 37 wk)	1.11 (0.52–2.40)
Fetal tachycardia	0.96 (0.51–1.84)
Composite neonatal outcome	0.73 (0.31–1.72)

Abbreviations: AOR, adjusted odds ratio; BMI, body mass index; unit.

Note: AOR is adjusted for age, BMI, and race.

Pressors in Septic shock

- No good data

- Most papers recommend Norepinephrine Some Phenylephrine

- RCT for peri C-section use showed no differences Phenylephrine vs Norepinephrine in fetal outcome

- Ephedrine used for peri-operative hypotension, not practical for sepsis

- Theoretical concern for Uterine contraction with Vasopressin

- Maintenance of BP more important than concern for vasoconstriction

- After fluid resuscitation, naturally.

- Steroids for pressor resistant shock.

Causes of Sepsis

Box 1. Bacterial infections associated with septic shock in the obstetric patient

Obstetric
Chorioamnionitis
Postpartum endometritis (more common after cesarean section)
Septic abortion
Septic pelvic thrombophlebitis
Cesarean wound infection
Episiotomy infections

Nonobstetric
Appendicitis
Cholecystitis
Urinary tract infections
Pyelonephritis (perinephric abscess, renal calculi)
Pneumonia
HIV
Malaria

Invasive procedures
Necrotizing fasciitis
Infected cerclage
Postchorionic villus sampling/amniocentesis (septic abortion)

Miscellaneous
Toxic shock syndrome

Guinn et. al., Sepsis during pregnancy, Ob Glyn Clin NA, 2007

Pyelonephritis

-Hydronephrosis can be physiologic but may predispose to pyelonephritis

- Bacteremia not uncommon

-Usual GNR, or Group B strep

- ARDS may be more common in pregnant patients with pyelo

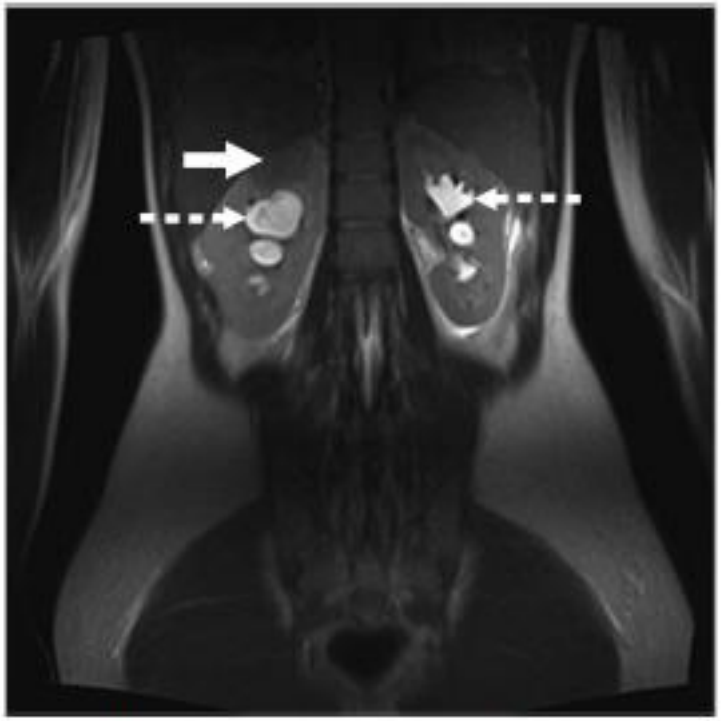


Fig. 1. Abdominal magnetic resonance imaging scan revealing substantial obstructive hydronephrosis of the kidneys (*broken arrows*), right kidney greater than left. Signal distortion in the superior portion of the right renal parenchyma suggests acute lobar nephronia (focal infection without liquefaction) and pyelonephritis (*solid arrow*).

Barton. Severe Sepsis and Septic Shock in Pregnancy. Obstet Gynecol 2012.

Parenteral regimens for empiric treatment of pyelonephritis in pregnancy

Antibiotic	Dose, interval
Mild to moderate pyelonephritis	
Ceftriaxone	1 g every 24 hours
Cefepime	1 g every 12 hours
Aztreonam*	1 g every 8 hours
Ampicillin PLUS Gentamicin¶	1-2 g every 6 hours 1.5 mg/kg every 8 hours
Severe pyelonephritis with an impaired immune system and/or incomplete urinary drainage	
Piperacillin-tazobactam	3.375 g every 6 hours
Meropenem	1 g every 8 hours
Ertapenem	1 g every 24 hours
Doripenem	500 mg every 8 hours

Doses are for patients with normal renal function.
If methicillin-resistant S. aureus (MRSA) is known or suspected, see treatment regimens outlined separately in topics addressing MRSA management.

* Alternative in the setting of beta lactam allergy.
¶ Aminoglycosides have been associated with fetal ototoxicity; this regimen should be used only if intolerance precludes the use of less toxic agents.

Graphic 56181 Version 11.0

Pneumonia

- Usual pathogens

-increased risk for H1N1

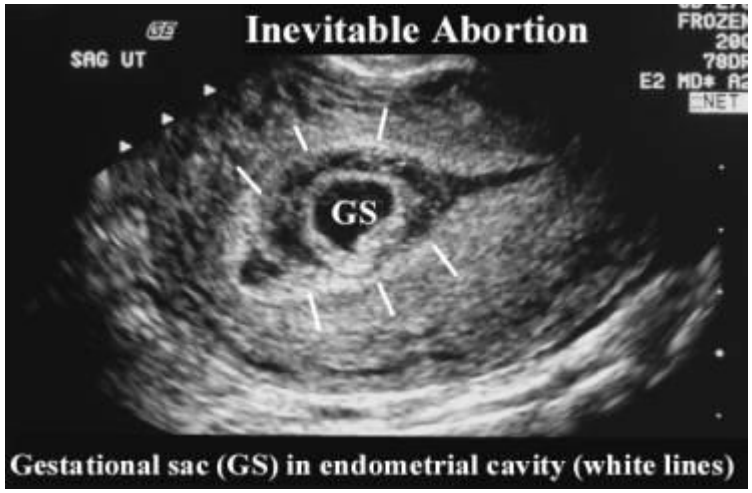
Septic Abortion

- Incomplete spontaneous miscarriage or incomplete surgical or medical abortion

-Fever , chills , cramping, foul-smelling discharge

-Antibiotics

- Uterine evacuation



Chorioamnionitis / Intramniotic infection

- Fever, vaginal discharge, change in amniotic fluid color, tachycardia

- Direct spread of cervico-vaginal flora

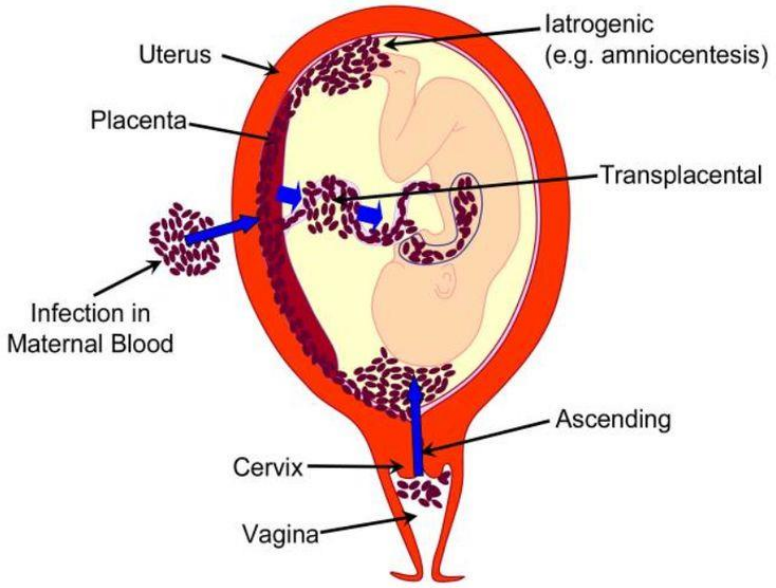
- PROM and Pre-term labor

-Amniocentesis can be helpful in complex cases

- - Polymicrobial flora normally

- Will not clear until delivery

- Significant neonatal moribidities including sepsis



Barton. Severe Sepsis and Septic Shock in Pregnancy. Obstet Gynecol 2012.

Antibiotics in IAI

- Ampicillin and Gentamycin
- Ampicillin , Gentamycin and Clindamycin (C-section)
- Ampicillin / sulbactam
-Ticacillin – clavulanate
- Cefoxitin

Endometritis

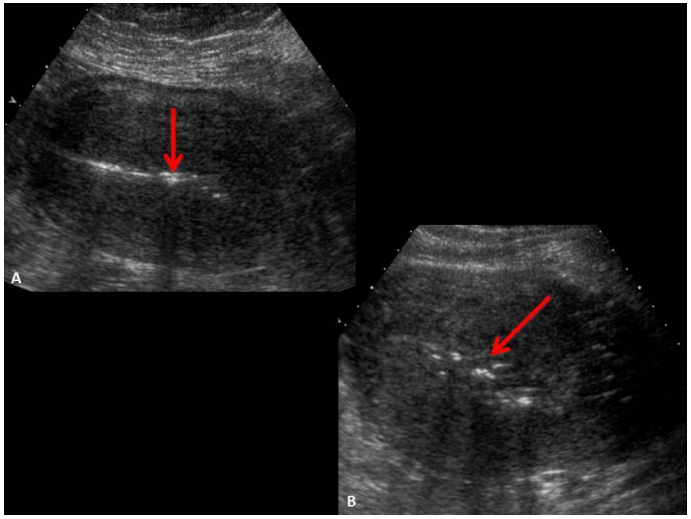
- C-section biggest risk factor

- Can evolve to necrotizing myometritis

- Abcesses or peri-uterine infection

- May have boggy, edematous uterus, may not be painful

- Can be Group A strep



Antibiotics in Endometritis

- Clindamycin 600 mg orally every 6 hours plus gentamicin 4.5 mg/kg intramuscularly every 24 hours
- Amoxicillin-clavulanic acid 875 mg orally every 12 hours
- Cefotetan 2 g intramuscularly every 8 hours
- Meropenem or imipenem-cilastatin 500 mg intramuscularly every 8 hours
- Amoxicillin 500 mg plus metronidazole 500 mg orally every 8 hours

Necrotizing Fascitis

- GP A Strep, Staph, Clostridium Perfrigens ,Polymicrobial

- Can be wound infection

-Necrotizing Vulvitis can occur at episiotomy site

Broad – Spectrum Antibiotics in Maternal Sepsis

- Pen, Clinda , Gentamycin

Vs

-Vancomycin and Piperacillin / Tazobactam

Antibiotics in Pregnancy

Table 2. Anti-Infective Agents with Concerns for Use During Pregnancy

Agent or Medication Class	Concern Avoid the following if clinical scenario permits
Aminoglycosides	Conventional dosing, as in pyelonephritis, is safe[12] Higher than conventional doses may achieve therapeutic levels in the fetus[40]; nephrotoxicity or ototoxicity could occur
Antifungals	
-Echinocandins	Less likely to cross placenta[41] Caspofungin embryotoxic in animals[12]
-Fluconazole	Doses exceeding 400 mg/d in first trimester cause concern for numerous anomalies[41,42]
-Voriconazole	Teratogenic and toxic in animals[12,41]
Colistimethate sodium/ Colistin	Embryotoxicity and malformations in animals[12]
Daptomycin	Limited data; unknown concern Second- and third-trimester exposures have not revealed harmful effects[43,44]
Fluoroquinolones	Concerning for cartilage development[12]
Linezolid	No human data; unknown effects[12]
Sulfamethoxazole	Third-trimester use and concern for kernicterus[45]
Tetracyclines (including tigecycline)	Tooth and skeletal structure incorporation and resultant discoloration starting at 14 weeks[12] Pregnancy category D
Trimethoprim	First-trimester use associated with increased risk of cardiovascular defects, neural tube defects and oral clefts[45,46]

Fetal Monitoring

- Fetal tachycardia due to Fever

- Endotoxins may lead to Uterine contraction but pre-term labor unusual

- B-agonists in setting of sepsis may increase concern for pulmonary edema

-internal vs external

Delivery

- Resuscitate mother as well as possible first

- Site of infection key

-Temperature control

-Ensure neonatal resuscitation equipment available at all times

-Emergency Cesearean in setting of CPR?

Box 6. Potential Maternal and Perinatal Indications for Delivery With Severe Sepsis or Septic Shock

Maternal

- Intrauterine infection
- Development of disseminated intravascular coagulation
- Hepatic or renal failure
- Compromised cardiopulmonary function by uterine size or peritoneal fluid, or uterine size and peritoneal fluid
  - Compartment syndrome
  - Hydramnios
  - Multifetal gestation
  - Severe adult respiratory distress syndrome or barotrauma
- Cardiopulmonary arrest

Fetal

- Fetal demise
- Gestational age associated with low neonatal morbidity or mortality

Barton. Severe Sepsis and Septic Shock in Pregnancy. Obstet Gynecol 2012.

Conclusions… What is unique to maternal sepsis?

- High level of suspicion for Maternal Sepsis with consideration of Maternal /Fetal physiology

- Prognostic factors in maternal sepsis not as well defined, caution is warranted

- Early antibiotics, lactate measurement, fluid resuscitation are keys to good outcomes (likely).

- Cooperative management with early involvement of OB team and Critical Care is critical.

-Early Consideration of surgically - treatable causes / evaluation for source control imperative when appropiate

-Fetal monitoring and consideration of delivery.