Research Article ISSN 2835-6276

American Journal of Medical and Clinical Research & Reviews

Sepsis

Felis S, Tirloni V, Bertoni M, De Simone A.

Obstetrics & Gynecology Department - IRCCS San Martino Hospital-Genova -Italy

*Correspondence: Felis S

Received: 21 Nov 2023; Accepted: 25 Nov 2023; Published: 05 Dec 2023

Citation: Felis S. Sepsis. AJMCRR 2023; 2(12): 1-22.

ABSTRACT

Maternal sepsis is "a life-threatening condition defined as an organ dysfunction caused by an infection during pregnancy, delivery, puerperium, or after an abortion," with the potential to save millions of lives if a proper approximation is made. Undetected or poorly managed maternal infections can lead to sepsis, death, or disability for the mother, and an increased likelihood of early neonatal infection and other adverse outcomes. Physiological, immunologic, and mechanical changes that occur in pregnancy make pregnant women more susceptible to infections than nonpregnant women and may obscure signs and symptoms of infection and sepsis, resulting in a delay in the recognition and treatment of sepsis. Prioritization of the creation and validation of tools that allow the development of clear and standardized diagnostic criteria of maternal sepsis and septic shock, according to the changes inherent to pregnancy, correspond to highly effective strategies to reduce the impact of these conditions on maternal health worldwide. After an adequate diagnostic approach, the next goal is achieving stabilization, trying to stop the progression from sepsis to septic shock, and improving tissue perfusion to limit cell dysfunction. Management protocol implementation during the first hour of treatment will be the most important determinant for the reduction of maternal mortality associated with sepsis and septic shock.

Keywords: maternal mortality; maternal sepsis; sepsis; sequential organ failure assessment.

INTRODUCTION

Despite considerable progress in diagnosis and treatment, available epidemiological studies suggest that the burden of sepsis, in terms of maternal and fetal-neonatal morbidity and mortality, remains high in all socioeconomic settings (1). Clinically, it is a complex condition that recognizes multiple causes, may affect multiple organs, and may be secondary to interactions of immune and metabolic effects that are still poorly understood.

Worldwide, sepsis is estimated to be the third most frequent direct cause of maternal death, after postpartum hemorrhage and hypertensive disorders of pregnancy (2). In Western countries, despite improved therapeutic opportunities and the availability of modern antibiotics, the incidence of sepsis

has been increased in pregnancy, at delivery, and in the puerperium (3,4,5). In fact, maternal infections that are not promptly diagnosed and managed can evolve into sepsis, death, or severe maternal morbidity, as well as an increased risk of adverse fetal and/or neonatal outcomes (6, 7). Sometimes the condition can occur even in the absence of recognized risk factors and can pose a serious challenge to clinicians. In fact, the physiological changes induced by pregnancy tend to be confused with some pathophysiological aspects associated with the septic condition (7).

NEW TERMINOLOGY AND DEFINITION OF SEPSIS

In 2016, the new definition of sepsis was published at the Third International Consensus Definitions For Sepsis and Septic Shock (Sepsis-3), and in early 2017 the new Surviving Sepsis Campaign Guidelines were published (7, 8).

- **Sepsis** is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection.
- **Organ dysfunction** can be identified as an acute change in total SOFA score (Sequential Sepsis-related Organ Failure Assessment) of 2 points due to infection (Figure 1).
- **The initial SOFA score** can be assumed to be 0 in patients for whom pre-existing organ dysfunction was not known.
- **SOFA score of 2 points** or more is associated with an in-hospital mortality greater than 10%. Patients with modest signs of dysfunction may deteriorate later, emphasizing the severity of their condition and may need prompt and appropriate intervention.
- **qSOFA** (for quick SOFA) provides simple criteria for identifying adult patients with suspected infection who have high risk of ICU admission or death.
- **Septic shock** is a subgroup of sepsis in which circulatory and cellular/metabolic changes are severe enough to result in significantly increased mortality.
- Patients with **septic shock** have clinical picture of sepsis associated with persistent hypotension requiring vasopressors to maintain PAM of 65 mmHg and having serum lactate levels > 2 mmol/l despite adequate volemic resuscitation. In-hospital mortality of these patients exceeds 40%.

With the new definition, the setting of infection with appropriate host inflammatory response (no called sepsis) is clearly distinguished from that of infection accompanied by an abnormal inflammatory response that is injurious to the organism producing it. Thus, what was previously called severe sepsis becomes sepsis, while the concept of septic shock remains unchanged.

The other fundamental change concerns the method of recognition: the introduction of SOFA as the reference score for the assessment of organ damage meets the criteria of accuracy and simplicity. Hospitalized patients with a SOFA of 2 or greater have a mortality rate of 10%, and therefore need to be managed with an appropriate level of attention and resources.

To make the recognition of the septic patient more immediate and effective, even in resource-poor conditions and in the early stages of rescue, the concept of qSOFA was introduced. It is based on the use of 3 objective parameters: altered level of consciousness (GSC < 15 or AVPU ≠ by A), systolic blood pressure (PAS) < 100 mmHg, and res-

piratory rate > 22/min. In the presence of at least two of these altered parameters in the presence of infection, sepsis is suspected; in these patients, the risk of death is high and appropriate management protocols should be implemented.

- **Suspected sepsis**: infection + qSOFA ≥ 2
- **Sepsis**: infection + SOFA ≥ 2
- **Septic shock:** sepsis + refractory infection requiring vasopressors to maintain PAM ≥ 65 mmHg and/or hyperlactacidemia > 2 mmol/l despite adequate volemic filling

Score	1	2	3	4
GCS	13-14	10-12	6-9	< 6
RESPIRATORY Pa/Fi=2 (mmHg)	< 400	< 300	< 200	< 100
CARDIOVASCULAR Hypotension	MAP < 70 mm Hg	Dopamine < 5 or Dobutamine	Dopamine > 5 o Adr < 0,1 o Noradr < 0,1	Dopamine > 15 Adrenaline > 0,1 Noradrenaline > 0,1
COAGULATION Plates (10^3/ mm^3)	< 150	< 100	< 50	< 20
LIVER Bilirubin (mg/dl)	1,2-1,9	2,0-5,9	6,0-11,9	>12
RENAL Creatinine (mg/dl) or Diuresis	1,2-1,9	2,0-3,4	3,5-4,9 o < 500 ml/24 ore	>5,0 < 200 ml/24 h

Table 1- SOFA score (repurposed by Vincent JL, Crit Care Med 1988; 26:1793-800)

Abbreviations: FiO_2, inspiratory fraction of oxygen; MAP, mean arterial pressure; PaO_2, partial pressure of oxygen.

Catecholamine doses are expressed in µg/Kg/min for at least 1 hour.

The Glasgow Coma Scale score has a range between 3 and 15: the higher the score, the better the neurological function.

In summary, the finding at Triage of a qSOFA ≥ 2 associated with suspicion of infection should prompt activation of a protocol for immediate recognition of suspected sepsis (code Yellow at Triage) and subsequent actions (blood cultures, antibiotic therapy, volemic resuscitation). The subsequent finding of a SOFA ≥ 2 will confirm the diagnostic hypothesis.

It should be noted that both scores have not been appropriately validated in the obstetric population.

DEFINITION OF SEPSIS IN THE OBSTETRIC POPULATION

According to the most recent 2017 WHO definition, maternal sepsis is a life-threatening condition defined as organ dysfunction resulting from infection arising in pregnancy, during childbirth, following abortion or in puerperium. Specific criteria for defining maternal sepsis, however, have yet to be developed. Criteria for identifying maternal sepsis should be based on the presence of suspected or confirmed infection plus signs of mild or moderate organ dysfunction (e.g., tachycardia, low blood pressure, tachypnea, altered mental status, decreased urinary output).

These criteria should be simple to assess, preferably based on identifiable clinical signs at the patient's bedside, applicable in different socioeconomic settings (9).

Figure 1 shows the rationale for the diagnosis of maternal sepsis with an infographic summary. If

we find certain or suspected infection, we must always check for the presence of organ damage to make the diagnosis of sepsis. Equally if we find organ damage that cannot otherwise be explained, we must always check for the presence of definite or suspected infection to make a diagnosis of maternal sepsis.

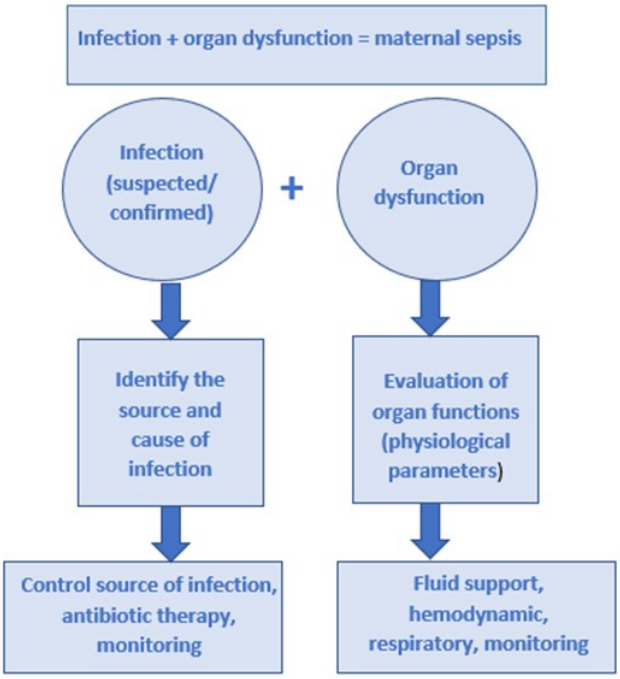

Figure 1- Approach for implement the new WHO definition of maternal sepsis (11)

About the site of infection, the concept of "puerperal sepsis" includes, according to the 2015 WHO definition, not only genital tract infections, but also all extragenital and incidental infections:

Urogenital tract infections related to labor, delivery and puerperium

- Infections from uterus and related structures (chorioamnionitis, endometritis, retention of products of conception, pelvic abscess, and perineal or abdominal wound infections)
- Infections of urological origin (lower or upper urinary tract infections)

Infection specifically related to birth, but not in the urogenital tract: breast infections (abscesses or mastitis)

Accidental infections

- Respiratory infections (exudative tonsillitis, bronchitis, pneumonia, empyema)
- Cardiovascular infections (endocarditis)
- Central nervous system infections (meningitis, encephalitis, sinusitis and brain abscesses)
- Infections of the digestive system (peritonitis, appendicitis, cholecystitis, diverticulitis)
- Infections of the integumentary system (cellulitis, wound infections and sepsis of venous accesses)

WHO has not considered it appropriate to extend the use of the SOFA score used for adult sepsis as a diagnostic aid for maternal sepsis. In fact, this score has not yet been validated for maternal sepsis, which configures a different clinical picture from the general population due to physiological changes in pregnancy. In addition, the parameters needed to assess the SOFA score are detectable only in intensive care settings. For this reason, WHO sponsored the multicenter GLOSS (Global Maternal Sepsis Study) as part of the Global Maternal and Neonatal Sepsis Initiative (10).

The project also includes among its goals the definition and validation of a set of criteria for identifying suspected and certain maternal sepsis.

EPIDEMIOLOGY

Sepsis in pregnancy is responsible for 10.7 % of maternal deaths in the world (2), and it has been estimated that approximately 6.900.000 cases of maternal sepsis occur annually worldwide (11).

A systematic review, conducted using the WHO database on maternal mortality in 115 countries between 2003 and 2009, ranks sepsis as the third leading cause of maternal death, preceded by hemorrhage (27 %) and hypertensive disorders (14%) (2).

In countries with advanced social-health systems, however, maternal sepsis appears to increase (3-5), and although the absolute risk of mortality is low, the burden due to severe maternal morbidity secondary to this dreaded obstetric complication should not be overlooked. Indeed, for every maternal death from sepsis, there are many cases of severe maternal morbidity, as reported in a population-based study conducted in the United Kingdom: this study estimated 47 cases/100.000 of severe maternal morbidity from genital tract infections compared with 0.50 cases of maternal death per 100.000 births due to the same cause (5, 6).

DIAGNOSTIC CRITERIA

Pending the development of internationally validated diagnostic criteria for maternal sepsis, we consider those adopted in the ItOSS (Italian Obstetric Surveillance System) project, which were defined by taking as reference the Sepsis-3 criteria (8) and adapted to the population of women pregnant or within 42 days of delivery (12).

The ItOSS project adopted the following diagnostic criteria for clinical diagnosis of infection and organ damage:

Clinical diagnosis of infection is based on the finding of at least one of the following signs/ symptoms:

- Fever = 38° C
- Headache and/or neck stiffness
- Respiratory symptoms (productive cough, pharyngodynia)
- Difficulty breathing (respiratory rate =20 respiratory acts/min and/or use of accessory muscles and/or hypoxemia with SpO2 <95%)
- Urinary symptoms (dysuria)
- Abdominal and pelvic pain and/or tension
- Diarrhea or vomiting
- Skin rash
- Malodorous vaginal discharge
- Preterm contractions and/or premature rupture of membranes in preterm pregnancies (pPROM)
- Malodorous and/or purulent amniotic fluid in cases of pPROM
- Signs of fetal or neonatal infection

Diagnosis of organ damage is based on the finding of at least one of the following parameters:

- Cardiovascular: systolic blood pressure <90 mmHg or mean arterial pressure <65 mmHg
- Respiratory: oxygen requirement to maintain SpO2 >95%
- Renal: creatininemia value >1.2 mg/dl
- Hepatic: bilirubinemia value >1.2 mg/dl
- Central nervous system: altered state of consciousness
- Hematologic: platelet value <100.000/mm^3 or 50% drop from usual values in pregnancy

The diagnosis of septic shock in the obstetric setting, similarly to the diagnosis in the adult population, involves the finding of a suspected or certain infection associated with hypotension with the requirement to administer vasopressors to maintain a mean arterial pressure >65 mmHg and a lactacidemia >2 mmol/l after adequate expansion of the volaemia (13).

In clinical practice, it is therefore important to look for signs/symptoms of organ damage in all patients with presumed or established infection and in all patients with organ damage that cannot otherwise be explained to look for signs/symptoms of infection to confirm or exclude the diagnosis of sepsis/septic shock. Similarly, in patients with altered vital parameters, it is important to always look for signs/symptoms of possible infection and organ damage to rule out or confirm the diagnosis of sepsis/septic shock. It should also be remembered that preterm labor is often a consequence of maternal infection and may therefore be the warning sign of maternal sepsis (14).

PREVENTION

Several different behavioral measures are recommended for the prevention of possible infections/sepsis in the obstetric population, which include (12, 15-19):

- Good personal hygiene and frequent hand washing
- Correct nutrition to avoid overweight and obesity
- Prevention and treatment of anemia
- Information about foods to avoid preventing transmission of serious infections such as listeriosis, salmonellosis, and toxoplasmosis
- Seasonal influenza vaccination (18, 20) to prevent possible complications of the disease related to pregnancy status and to prevent infection in infants
- Correct information about the signs and symptoms of possible infection

Healthcare personnel must also adhere to appropriate clinical care practices aimed at infection control such as (12, 19, 20):

- Hygiene and disinfection
- Antibiotic prophylaxis and appropriate use of antibiotics to reduce the risk of antibiotic resistance
- Protocols for bladder catheterization and management of peripheral and central venous accesses
- Use of checklists
- Implementation of clinical audits of sentinel events

In 2015, WHO published 20 evidence-based recommendations (Table 2) to promote appropriate measures to prevent maternal infections in the peripartum (21).

RECOMMENDED	NOT-RECOMMENDED
Digital vaginal examination at 4-hour intervals for routine assessment of the first stage of active labor in low-risk women	Routine perineal pubic shaving before vaginal delivery
Intrapartum antibiotic administration to women with group B streptococcus (GBS) colonization for the prevention of early neonatal GBS infection	Routine vaginal cleansing with chlorhexidine during labor to prevent infectious morbidity
Administration of antibiotics for women with preterm rupture of membranes	Routine vaginal cleansing with chlorhexidine during labor in women with group B streptococcus (GBS) colonization for prevention of neonatal GBS infection
Routine antibiotic prophylaxis for women submitted to manual placental removal	Routine antibiotic prophylaxis during the second or third trimester to all women for the purpose of reducing infectious morbidity
Routine antibiotic prophylaxis for women with third- or fourth-degree perineal laceration	Routine antibiotic administration for women in preterm labor with intact membranes
Vaginal cleansing with povidone iodine immediately before cesarean section	Routine antibiotic administration for women with premature rupture of membranes at or near term (Strong recommendation based on low-quality evidence)
The choice of an antiseptic agent and its method of application for skin preparation before cesarean section should be based primarily on the clinician's experience with that particular antiseptic agent and method of application, its cost, and local availability	Routine antibiotic administration for women with meconium-stained amniotic fluid

Antibiotic prophylaxis for women undergoing elective or emergency cesarean section: - prophylactic antibiotics should be administered before the skin incision, rather than intraoperatively after cord clamping. - a single dose of first-generation cephalosporin or penicillin should be used in preference to other classes of antibiotics	Routine antibiotic prophylaxis for women submitted to operative vaginal delivery
First-line antibiotic treatment of chorioamnionitis consists of a simple regimen such as ampicillin and gentamicin once daily	Routine antibiotic prophylaxis for women with episiotomies
A combination of clindamycin and gentamicin is indicated for the antibiotic treatment of postpartum endometritis	Routine antibiotic prophylaxis for women with uncomplicated vaginal delivery

Table 2 - Recommendations for the prevention of maternal infections in the peripartum (21)

EARLY WARNING SYSTEMS FOR RECOGNIZING THE RISK OF OBSTETRIC COMPLICATIONS

In the United States, since 2010, The Joint Commission has required hospitals to develop written criteria for identifying early warning signs in changes or deterioration in the clinical condition of pregnant patients so that further clinic-therapeutic measures can be put in place, including involving the necessary medical specialists (23).

Important are Sepsis Care Bundles: simplified schemes of recommendations that when implemented en bloc result in a better outcome than if the recommendations were implemented individually. In addition to these, in England, the Modified Early Obstetric Warning System (MEOWS) has been established specifically for the pregnant patient to check the degree of clinical instability of the pregnant patient in real time (24). Featuring good specificity (79%) and sensitivity (89%), it could be preferred to the Maternal Early Warning System (MEWS) because maternal temperature is also considered. Several advantages have been demonstrated: improved communication between obstetrical and medical staff, reduction of clinical intervention time, activation even by obstetrical staff of procedures that are essential for therapeutic success (e.g., administering oxygen, cannulation of a peripheral vein, etc.) with better results in terms of clinical framing and outcome. Figure 2 shows a modified version by Singh in 2012 (25) of the MEOWS monitoring and alerting system, which is an example of the graphical cards that should be established and shared in every maternity hospital for recording and timely verification of the set of vital parameters and their trend over time (26).

The adoption and routine use of the MEOWS alert system and its card requires shared training among gynecologists, obstetricians, and anesthesiologists combined with audits of complex clinical cases (14). The routine use of early warning cards in all physiologic pregnancies is rightly debated because in addition to presenting a critical issue related to the unavailability of sufficient human resources, it would also result in unnecessary overmedicalization (24).

For these reasons, if the woman presents a low obstetric risk during pre- and postpartum hospitalization, it is sufficient to assess the main vital parameters (e.g., blood pressure, temperature, respiratory rate) provided by the MEOWS system every 24 hours until discharge, unless otherwise prescribed

by a physician (12).

These graphical monitoring systems are based on the detection of vital parameters in a color-coded scale that allows the patient's clinical status and risk of deterioration to be quickly visualized, facilitating timely alerting of the care team.

	Date								
	Hour								
Respiratory rate/min	≥ 25								
	20-24								
	11-19								
	≤ 10								
SpO_2	96-100%								
	≤ 95%								
Temperature ° C	≥ 38								
	37.5-37.9								
	36-37.4								
	35.1-35.9								
	≤ 35								
Systolic pressure mmHg	≥ 160								
	140-159								
	100-139								
	91-99								
	≤ 90								
Diastolic pressure mmHg	≥ 100								
	90-99								
	50-89								
	41-49								
	≤ 40								
Diuresis	> 30cc/h								
	< 30 cc/h								
Level of consciousness	Vigilant								
	Voice								
	Pain								
	Not responsive								
Pain	0								
	1								
	2								
Total red parameters									
Total yellow parameters									
Name of practitioner									

Figure 2 - MEOWS for the monitoring and warning system (modified from Singh et al, 2012)

In the presence of a single markedly altered alert parameter (red) or two altered parameters at the same time but to a lesser extent (yellow), immediate medical evaluation should be activated to rule out suspected clinical deterioration risk situations including infection and/or sepsis and/or septic shock (25).

RISK FACTORS

A complete personal and obstetrical history makes it possible to assess the health status of the woman and fetus and to recognize possible risk factors for obstetrical complications. Because in cases of sepsis, prompt diagnosis and early treatment are essential elements in improving maternal/fetal outcomes (5,7), the search for and recognition of possible risk factors is particularly important for the prevention of this condition (12).

Risk factors for sepsis that should be systematically investigated in the preconceptional, prenatal, intrapartum, and postnatal periods are described next (14, 27, 28):

1. **Maternal conditions pre-existing pregnancy** such as obesity (BMI =30 kg/m2), diabetes, malnutrition, severe anemia (Hb <9 g/dl), positive history for group B streptococcus, immunodepressant conditions and/or immunodepressant therapy, positive history of pelvic infections, group A streptococcus infection in close female contact, and conditions of social deprivation.
2. **Pregnancy-related maternal conditions** such as inadequate obstetrical care, group A streptococcal infections in close contact with the

woman, bacterial vaginosis, amniocentesis and other invasive prenatal diagnostic procedures, cervical cerclage, prolonged rupture of membranes, induction of labor, and use of antibiotics in the 2 weeks before delivery.

3. **Maternal conditions related to labor and delivery** such as prolonged active stage I, excessive vaginal explorations in stage II labor (> 5), operative delivery, preterm delivery, cesarean section, episiotomy, and perineal trauma.
4. **Maternal conditions in the postnatal period** such as retention of the placenta and its manual removal, urinary tract infections, surgical wound/episiorrhaphy infections, infection of the peridural catheter insertion site, and mastitis.

Major independent risk factors for sepsis include obesity (29, 30) and cesarean section (31).

ETIOLOGY

Identification of the source and etiologic agent responsible for the infection is of paramount importance for proper antibiotic therapy setting. By frequently, infections responsible for sepsis in pregnancy affect the genital tract (39%), followed by the urinary system (37%) (32).

Table 2 shows the main sources of infection and related clinical pictures of infections that most commonly affect women in pregnancy, childbirth, or puerperium (33).

SOURCE OF INFECTION	CLINICAL PICTURES OF INFECTION
Genital system	Chorioamniositis, endometritis, wound infections (perineal suture, episiotomy, cesarean section), septic abortions
Urinary system	Lower and upper urinary tract infections, pyelonephritis
Respiratory system	Bacterial or viral pneumonia, tuberculosis
Intraperitoneal	Perforation of the appendix, acute appendicitis, acute cholecystitis, intestinal infarction
Other	Mastitis, mammary abscess, pelvic septic thrombophlebitis, necrotizing fasciitis, malaria, miliary tuberculosis

Table 3 - Sources and related obstetric infections (33)

BACTERIAL INFECTIONS

Infections in the obstetric population are often polymicrobial in nature, probably because of their frequent genital origin. The most frequently isolated bacterial microorganisms are Escherichia coli and group A streptococcus (14, 27, 28).

Escherichia coli, a Gram-negative bacterium, is the most frequent infectious agent in both the pre and postnatal periods. It can be responsible for septic miscarriages, pyelonephritis, chorioamnionitis, endometritis, and surgical wound infections after cesarean section (14, 27, 28).

Group A Streptococcus, second in frequency, is a Gram-positive bacterium responsible for severe postpartum endometritis, toxic shock syndromes, necrotizing fasciitis, sepsis and septic shock most frequently in the postnatal period (6, 14, 28).

Group A Streptococcus beta hemolyticus, known as Streptococcus pyogenes (GAS), is a potentially lethal virulent microorganism that causes a clinical picture characterized by abdominal pain, fever, and tachycardia. The infection can occur in

pregnancy or, more frequently, in the postpartum period. Women in the postpartum period have a 20 -fold increased risk of developing GAS infection compared with the non-obstetric population. Exotoxins produced by streptococcus can result in widespread tissue necrosis affecting multiple noble organs, including the kidney, and can cause toxic shock syndrome burdened by a 60 percent mortality rate (27, 34).

Group B Streptococci are often involved in chorioamnionitis.

Klebsiella is frequently responsible for upper urinary tract infections.

Staphylococcus aureus, along with other Gram-positive bacteria such as streptococci, can cause pneumonia, a source of possible obstetric sepsis (14, 27).

Listeria monocytogenes, a Gram-positive bacterium, is responsible for listeriosis, an infection classified as a foodborne disease because it generally follows ingestion of contaminated food. Very rare in Western countries, it is responsible for severe clinical pictures with high mortality rates (35).

Anaerobic bacteria are involved in necrotizing fasciitis, Chorioamniositis, endometritis, and surgical infections after cesarean section (14, 27).

VIRAL INFECTIONS

Influenza A (H1N1) and B viruses are the most common viral agents in obstetrics and can be responsible for pneumonias that are difficult to manage clinically (17).

WHO, major international agencies and the Ministry of Health recommend influenza vaccination in pregnancy. Pregnant women are in the highest priority category for vaccination both to prevent the disease in infants, for whom the vaccine is not indicated due to the unavailability of studies on its safety, and to prevent possible complications of the disease related to the pregnant state (17, 36).

Varicella zoster is less common in pregnancy and yet is associated with high mortality (37).

MYCOTIC INFECTIONS

Candida albicans, responsible for fungal sepsis, is rare in pregnancy. The onset of the disease is related to the balance of progesterone and estrogen production: a higher concentration of the former allows the body to increase the production of antibodies to Candida, and high concentrations of the latter inhibit it (39).

PSIS MANAGEMENT

Maternal sepsis poses a complex challenge for healthcare professionals both because of the need to care for the mother and the fetus at the same time and because of the physiological changes associated with pregnancy, which can confound the signs of infection (7).

Timely diagnosis and early initiation of therapeutic treatment have demonstrated a significant impact on improving survival and morbidity associated with sepsis, as evidenced by work conducted by Rivers and coworkers as early as 2001 (40) and then in 2012 (41), in which a reduction in mortality was demonstrated following adoption of the Early Goal Direct Therapy protocol.

The results of Rivers' study were then incorporated into the Surviving Sepsis Campaign Guidelines until the first draft in 2004 (42) and retained in the 2008 (43) and 2012 (44) drafts for the formulation of the 3- and 6-hour management bundles. The term bundle has Anglo-Saxon origins and refers to a group of evidence-based interventions that provide better outcomes when performed together rather than individually (45, 46).

Until trials specific to pregnant women are available, protocols for peripartum sepsis will necessarily have to be translated from those validated in the adult population with due consideration of the physiological changes in vital parameters that occur in pregnancy (12). Recent work has demonstrated the applicability and effectiveness of bundles to the obstetric population as well (47).

Given the lack of specificity and the different criteria proposed for the diagnosis of maternal sepsis, we propose a modified flow chart from the UK Sepsis Trust (https://sepsistrust.org) that assumes the routine use of the MEOWS monitoring and alerting card as a tool that can facilitate diagnostic guidance and alerting in cases of suspected maternal sepsis. However, it is necessary to mention the irreplaceable importance of clinical judgment, which integrates information about the woman's vital parameters with her medical history and clinical history, to arrive at a correct and timely diagnosis.

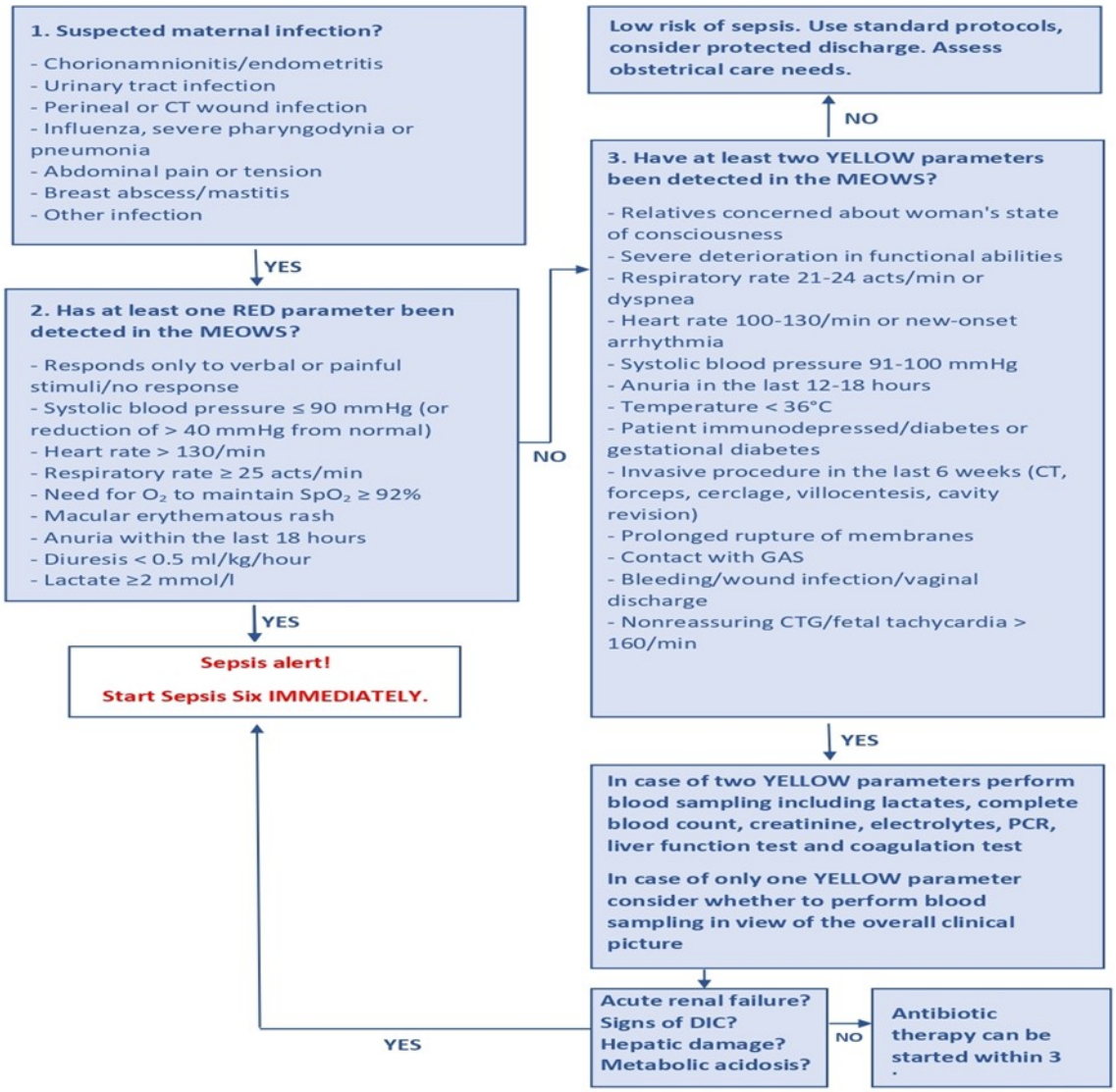

Figure 3 - Flow chart for identification of maternal sepsis and activation of Sepsis-six bundle (Six e Red Flag Sepsis UK Sepsis Trusthttps://sepsistrust.org/professional-resources/training/)

THE SEPSIS SIX BUNDLE

When maternal sepsis is diagnosed, the bundle called Sepsis-Six is recommended (12, 48).

This is a package of 6 actions to be implemented in the first hour after sepsis is suspected or confirmed. The actions are divided into three diagnostic (TAKE 3) and three therapeutic (GIVE 3) interventions described in Table 4.

THREE DIAGNOSTIC ACTIONS (TAKE 3)	1. Take blood cultures and consider source control	2. Measure serial serum lactates	3. Commence accurate urine output measurement
THREE THERAPEUTIC ACTIONS (GIVE 3)	1. Titrate oxygen to a saturation target of 94%	2. Administer empiric intravenous antibiotics	3. Start intravenous fluid resuscitation

Table 4 - The Sepsis-Six (55)

In case of suspected or certain sepsis, the use of the MEOWS alert system (12) is recommended to monitor the woman's condition and promptly identify the need for her transfer to the ICU.

The three diagnostic actions (TAKE 3)

TAKE BLOOD CULTURES AND CONSIDER SOURCE CONTROL (7, 48)

In patients with suspected sepsis or septic shock, samples for blood culture and routine microbiological culture tests should be taken before the start of antibiotic therapy, if this does not delay its initiation. If antibiotic therapy was already in progress, it is recommended that they be performed before the next drug administration (two samples per blood culture, for aerobic and anaerobic germs).

It is recommended to obtain culture examinations for all potential foci of starting infection: urinoculture, pharyngeal swab, deep wound swab and/or sampling of purulent material, sputum, lumbar puncture and/or culture examination of drains or devices and placenta, vaginal swab in case of malodorous amniotic fluid.

MEASURE SERIAL SERUM LACTATES (7, 48, 49)

In patients with suspected sepsis or septic shock, it is recommended that lactates should be checked immediately or within 30 minutes at the latest by arterial or venous blood gas analysis and some hematochemical tests to facilitate the identification of possible organ damage (complete blood count with formula, lactates, electrolytes, PT, PTT, fibrinogen, bilirubinemia, creatinemia, azotemia, PCR or PCT).

The absolute lactate value, although an indirect measure of tissue perfusion, is more accurate than the objective examination and urinary output. Its trend over time is also useful in monitoring the clinical situation and assessing the response to therapy.

A lactate value >2 mmol/l associated with severe arterial hypotension refractory to volemic load, with the need for aminic support to maintain a MAP >65 mmHg, is indicative of an evolution of sepsis into septic shock.

COMMENCE ACCURATE URINE OUTPUT MEASUREMENT (50)

In patients with suspected sepsis or septic shock, the placement of a permanent urinary catheter with hourly diuresis monitoring is recommended as a sensitive measure of renal perfusion. Oliguria/

anuria with diuresis values <0.5 ml/kg/h (MEOWS threshold >30 cc/h) is a significant indicator of a blood perfusion defect and an indirect clinical index of a worsening hemodynamic picture of the patient.

THREE THERAPEUTIC ACTIONS (GIVE 3):

TITRATE OXYGEN (7, 48)

In patients with suspected sepsis or septic shock, administration of 100% O2 oxygen therapy is recommended to maximize oxygen transport to organs and tissues and maintenance of saturation =95% (threshold value to prevent fetal hypoxia). It should be remembered that in sepsis, normal saturation levels may not ensure optimal tissue perfusion due to the increased metabolic demand for oxygen and its reduced peripheral availability and utilization capacity due to reduced transport and extraction. In case of prolonged administration of high oxygen flows, humidification is recommended to avoid dryness of tracheal and buccal mucosa.

Careful observation of respiratory rate (RF) and saturation (SpO_2) is recommended: in case of severe respiratory failure, the anesthesiologist-resuscitator will assess the need for noninvasive respiratory support or intubation and mechanical ventilation.

ADMINISTER EMPIRIC INTRAVENOUS ANTIBIOTICS (7, 48, 50, 51)

In patients with suspected sepsis or septic shock, it is recommended that administration of intravenous antibiotic therapy should begin as soon as possible and in any case within 1 hour of recognition of the condition. Timeliness of antibiotic therapy is indeed a key element for survival because in the 6 hours following the diagnosis of sepsis and/or septic shock each hour of delay is associated with a linear increase in the probability of death.

Administration of more targeted therapy is recommended only after isolation of the pathogen, identification of any resistance, and/or detection of clinical improvement.

Initial empirical antibiotic treatment (7, 48, 50, 51)

The initial empirical treatment must be defined by seeking to maximize therapeutic appropriateness. Therefore, aspects that may guide the choice of appropriate antibiotics for each individual clinical picture should be carefully and systematically assessed, such as the site of infection, the distribution of pathogens within the community and hospital, antibiotic resistance phenomena, and the immunological status of the patient.

To facilitate the choice of appropriate treatment regimens, those proposed for maternal sepsis with outbreaks starting in the genital tract, urinary tract, or surgical wound in the Sanford Guide to Antimicrobial Therapy (50) are given below.

These are four patterns involving the use of different active agents depending on the need to cover infections complicated by antibiotic-resistant bacteria and/or in the event of a positive history of penicillin allergy. The part in italics describes the conditions that require switching from one treatment schedule to the next. All antibiotics must be administered intravenously.

THE FIRST TREATMENT PLAN	Penicillin/beta-lactamase inhibitor (e.g., piperacillin/tazobactam) + aminoglycoside (e.g., gentamicin or amikacin) - Piperacillin/tazobactam at a dose of 4.5 g every 6 hours (first dose as a bolus or rapid infusion to rapidly reach therapeutic blood levels and as a prolonged infusion for 4-6 hours thereafter) - Gentamicin as a single administration at a dose of 5 mg/kg/day (or amikacin as a single administration at a dose of 15 mg/kg/day)
In the case of infection complicated by extended-spectrum beta-lactamase (ESBL)-producing bacteria, such as women with a recent microbiologically established infection with ESBL-producing bacteria, or with colonization by ESBL-producing bacteria, or with recent exposure to fluoroquinolones and/or cephalosporins, the first treatment schedule should be replaced by the second	
THE SECOND TREATMENT PLAN	A broad-spectrum Carbapenems (e.g. meropenem; imipenem/ cilastatina; ertapenem; doripenem) + aminoglycoside (e.g. gentamicin or amikacin). - Meropenem at a dose of 1 g every 8 hours - Gentamicin as a single administration at a dose of 5mg/kg/day (or amikacin as a single administration at a dose of 15 mg/kg/day)
In the case of a positive history of anaphylactic shock or severe allergic reaction to penicillin, carbapenems are contraindicated because there is an infrequent possibility of cross-reaction between penicillins and carbapenems. In these women, the third treatment regimen can be used	
THE THIRD TREATMENT PLAN	Ciprofloxacin and aminoglycoside (e.g., gentamicin or amikacin) to be combined with metronidazole to cover anaerobes - Ciprofloxacin at a dose of 400 mg every 8-12 hours - Gentamicin as a single administration at a dose of 5 mg/kg/day (or amikacin as a single administration at a dose of 15 mg/kg/day) - Metronidazole 1 g loading dose followed by 500 mg every 6 hours
In the case of Methicillin Resistant Staphylococcus Aureus (MRSA) infections, previous treatment plans are not effective. Assessment of the risk of colonization by MRSA in the obstetric population is difficult because no definite criteria are available, however it must be suspected in the case of - exposure to antibiotic therapy with fluoroquinolones, cafalosporins or carbapenems in the previous 6 months; - hospitalization or intravenous therapy in the year before delivery; - transfer from another health facility; - presence of a bladder catheter or vascular catheters on admission to hospital. In these women it is possible to use the fourth treatment schedule.	
THE FOURTH TREATMENT PLAN	Penicillin/beta-lactamase inhibitor (e.g., piperacillin/tazobactam) and aminoglycoside (e.g. gentamicin or amikacin) to which an anti-MRSA drug (e.g. vancomycin, daptomycin or teicoplanin) should be added - Piperacillin/tazobactam at a dose of 4.5 g every 6 hours (first dose as a bolus or rapid infusion to rapidly reach therapeutic blood levels and as a prolonged infusion for 4-6 hours thereafter) - Gentamicin as a single administration at a dose of 5 mg/kg/day (or amikacin as a single administration at a dose of 15 mg/kg/day) - Daptomycin in a single dose of 8 mg/kg/day or vancomycin 500 mg 4 times/day or teicoplanin 12 mg/kg 2 times/day during the first 2 days followed by 12 mg/kg/day

Table 5 - Treatment plans for maternal sepsis (12, 57)

Remember that if Candida infection is suspected, an antifungal agent may be included in the initial empirical therapy. Risk factors for Candida infection include (12):

- Immuno-compromised state (neutropenia, chemotherapy, transplant, diabetes mellitus, liver, or kidney failure)
- Prolonged use of invasive devices (hemodialysis catheter, central venous catheter)
- Parenteral nutrition
- Necrotizing pancreatitis
- Major surgery (especially if abdominal)
- Prolonged administration of broad-spectrum antibiotics
- Prolonged hospitalization/intensive care unit admission
- Recent fungal infections
- Multi-site colonization

Targeted antibiotic treatment (7)

Only after the isolation of the pathogen and the availability of an antibiogram allowing the identification of possible resistance and/or after the detection of clinical improvement can the initial empirical antibiotic treatment be modulated.

The decision to continue, modulate or discontinue broad-spectrum antibiotic therapy must be made taking into consideration clinical judgement, supported by the opinion of the infectivologist where available, and the woman's daily clinical assessment, and may be implemented if the following conditions occur:

- Clinical improvement (resolution of septic shock, reduced demand for vasopressors, etc.)
- Resolution of infection as indicated by biomarkers (especially procalcitonin)
- Predetermined duration of combination therapy+

If the laboratory does not confirm the suspicion of infection, antibiotic therapy should be discontinued immediately to minimize the risk of the woman developing resistance to the pathogen or a side effect to treatment (e.g., Clostridium difficile colitis) that would require an additional antibiotic.

Regarding the duration of antibiotic treatment, in most severe infections associated with sepsis or septic shock, 7-10 days of antibiotic therapy is adequate. Longer therapy may be considered in the case of a slow clinical response, if foci of infection cannot be drained, if a bacteremia with staphylococcus aureus has set in and requires at least 14 days' therapy, and in the case of immunodeficiency. Especially in these cases, it is recommended to consult the infectivologist. Shorter courses of treatment may be considered in cases of rapid clinical resolution, following effective control of the starting focus in intra-abdominal or urinary sepsis and in cases of uncomplicated pyelonephritis.

Table 6 shows the standard dosages for intravenous administration of the different antibiotics used to treat sepsis (50).

The dose must always be appropriate to the patient's weight and the therapy must always include intravenous administration of the antibiotics.

ANTIBIOTIC	STANDARD DOSE IN ADULTS WITH SEPSIS
Amoxicillin/ clavulanate	2.25 g every 6 h
Amikacin	15 mg/Kg/day
Ampicillin/ sulbactam	3 g every 6 h
Azithromycin	500 mg/day (single dose)
Ceftriaxone	2 g/day (single dose)
Clindamycin	900 mg every 8 h
Ciprofloxacin	400 mg every 8-12 h
Daptomycin	8 mg/Kg/day (single dose)

Gentamicin	5 mg/Kg/day (single dose)
Levofloxacin	750 mg/day (if weight >70 kg: 500 mg every 12 h)
Meropenem	2 g loading dose, then 1 g every 6-8 h (prolonged infusion of 4-6 h)
Metronidazole	15 mg/Kg loaded dose, then 7.5 mg/Kg every 6 h
Piperacillin/ tazobactam	4.5 g every 6 h (first bolus dose, then prolonged infusion of 4-6 h)
Vancomycin	25 mg/Kg loading dose, then 500 mg every 6 h

Table 6- Dosages and infusion modes of antibiotics for the treatment of sepsis (57)

START INTRAVENOUS FLUID RESUSCITATION

It is important to remember that alterations in tissue perfusion are part of the pathophysiological picture of sepsis, not least because of the physiological changes in pregnancy that complicate the clinical picture of the condition. Absolute and/or relative hypovolemia plays an important role in the genesis of tissue perfusion alterations characteristic of sepsis. Timely volemic replenishment helps to correct maternal hypovolemia and hypotension and to improve tissue hypoperfusion dangerous not only to the woman but also to the fetus because of placental vasoconstriction.

Adequate volemic resuscitation requires the administration of a volemic load of 30 ml/kg of crystalloids within the first 3 hours with the aim of restoring intravascular volume and maintaining a MAP = 65 mmHg.

During volemic resuscitation, vital parameters and lactacidemia should be closely monitored to detect the evolution of the clinical picture and identify complications early on. It is also recommended to place the woman in left lateral decubitus to rule out aorto-caval compression and to consider adding albumin to crystalloids in patients requiring large amounts of fluid. In all cases of hypoperfusion or confirmed septic shock, it is recommended to assess fetal viability. In sepsis, the hemoglobin level is also an indicator of organ and tissue oxygen perfusion. The combination of anaemia and tissue hypoxia in the hypotensive septic patient requires consideration of transfusion of hemoglobin to improve oxygen transport.

Once the volemic resuscitation protocol has been applied, if maternal hypotension persists the diagnosis of septic shock is made, if it resolves the diagnosis of sepsis is made. Septic shock must be managed by an anesthesiologist-resuscitator who also carefully monitors and records the water balance, given the risk of pulmonary or cerebral oedema in these patients.

CONTROL OF THE SOURCE OF INFECTION (7, 48)

In the case of sepsis, control of the septic focus from which the infection originates is critical to the success of treatment. It is therefore recommended to identify or exclude the presence of infection foci as early as possible by means of objective examination and, when necessary, by resorting without delay to the most appropriate imaging based on the diagnostic suspicion (12):

- Pelvic ultrasound to identify any collection or presence of material in the uterine cavity
- Abdominal ultrasound
- CT or MRI abdomen and pelvis for example to exclude pelvic abscesses or uterine microabscesses in case of endometritis

Imaging diagnostics useful for the identification of possible infections of non-obstetrical origin, such as appendicitis, pancreatic abscess, or intestinal infarction, should also be considered, without forgetting infections of respiratory origin.

It will also be necessary to promptly remove vascular access devices that could represent possible septic sources, obviously after other vascular accesses have been established.

Once the site of the septic infection has been diagnosed, procedures for its control such as evacuation of the products of conception, drainage of abscesses, delivery in cases of chorioamnionitis, hysterectomy in cases of myometrial necrosis, and wound bed clearance (debridement) in surgical wound infections should also be considered.

VENOUS THROMBOEMBOLISM PROPHYLAXIS (7, 52)

In the case of sepsis, pharmacological prophylaxis of venous thromboembolism with low molecular weight heparin (LMWH) is recommended, unless contraindicated to its use. The combination of pharmacological prophylaxis with mechanical prophylaxis (elastic stockings or intermittent pneumatic compression) is suggested. In the event of clinical contraindications to LMWH prophylaxis, mechanical prophylaxis alone is recommended (12).

The prophylactic doses of LMWH in pregnancy and in the postnatal period are as defined in the guidelines of the American College of Chest Physicians (2012), considering body mass index to adjust the dosage to body weight extremes:

- Deltaparin 5,000 IU subcutaneously every 24 hours
- Nadroparin 2,850 IU subcutaneously every 24 hours
- Enoxaparin 4,000 IU subcutaneously every 24 hours

OBSTETRICAL SURVEILLANCE OF FETAL WELL-BEING AND TIMING OF DELIVERY (14)

Maternal sepsis affects fetal well-being because of the direct effect of the infection on the fetus, the critical maternal condition, and the effects of therapies administered to the woman. The decision as to the appropriate mode and timing of delivery must be individualized and must consider the severity of the maternal condition, the viability of the fetus, the gestational age, and the duration of labour. During labour it is recommended that fetal well-being be monitored by auscultation of the fetal heart rate (FCF) with continuous cardiotocographic monitoring, especially in case of maternal fever (12, 53).

In a full-term fetus, the most reported signs on the intrapartum cardiotocographic (CTG) tracing in case of infection are:

- Mild tachycardia (160-180 bpm) with reduced variability or severe tachycardia (>180 bpm)
- Absence of cycling
- Persistently reduced or absent variability (for >50 minutes)
- Absence of antecedent decelerations that could justify tachycardia.

None of these features is specific to a picture of infection, however in fetuses with bacterial infection during labour, fetal tachycardia without decelerations is associated with an increased risk of cerebral palsy even in the absence of umbilical cord blood pressure (54).

Consequently, the finding of fetal tachycardia during intrapartum CTG, especially when associated with reduced variability, in the absence of antecedent decelerations or other signs of hypoxia should

prompt consideration of an ongoing infection (55).

The assessment of fetal heart rate must be related to expected values based on gestational age. For example, in a fetus beyond term, whose base rate should be between 110 and 130 bpm, values persistently between 150 and 160 bpm may indicate an inflammatory picture (56).

It is useful to remember that each degree increase in maternal temperature increases the baseline fetal rate by 10% (57).

For example, in cases of maternal fever due to urinary tract infection near term, it is appropriate to assess the restoration of FCF after administration of antipyretics to the mother to decide the timing and mode of delivery. Changes in baseline variability or the appearance of decelerations also require timely reassessment of early warning signs of maternal deterioration (mean arterial pressure, hypoxia and acidemia) (58).

If maternal conditions are unstable, delivery increases maternal and fetal mortality rates except in cases where the source of infection is endouterine (59). For this reason, it is recommended that maternal conditions be established prior to delivery, except in cases of endouterine infection.

SECOND-LEVEL RESUSCITATIVE INTERVENTIONS

In Table 7, we summarize the main second-level resuscitative interventions, extrapolated from the latest guidelines of the 2017 Surving Sepsis Campaign (7).

VASOPRESSORS	Noradrenaline as vasopressor of first choice Addition of vasopressin (up to 0.03 U/min) or adrenaline to increase MAP to optimal target, or addition of vasopressin (up to 0.03 U/min) to reduce noradrenaline dosage Dopamine only for highly selected patients (e.g., patients with low risk of tachyarrhythmias and absolute or relative risk of bradycardia) Dobutamine in patients with persistent hypoperfusion despite adequate fluid loading and use of vasopressor agents In all patients requiring vasopressors, have an arterial catheter in place as soon as possible
CORTICOSTEROIDS	Routine use of ev hydrocortisone is not recommended if adequate volemic resuscitation and vasopressor therapy can restore haemodynamic stability If this is not possible, ev hydrocortisone 200 mg daily is suggested
HEMODERIVATES	Transfusion of concentrated red blood cells if Hb < 7.0 g/dl (in the absence of other circumstances such as myocardial ischaemia, severe hypoxaemia or acute haemorrhage) Fresh frozen plasma to correct coagulation abnormalities in the absence of bleeding or planned invasive procedures Platelet transfusion for prophylactic purposes when the platelet count is < 10.000/mm3 (10 × 109/L) in the absence of apparent bleeding and when the platelet count is < 20.000/mm3 (20 × 109/L) if the patient is at significant risk of bleeding. Higher platelet count targets (50.000/mm3 [50 × 109/L]) in the case of active bleeding, surgical procedures, or invasive procedures
MECHANICAL VENTILATION	Tidal volume of 6 ml/Kg, plateau pressures of 30 cm H20, high PEEP values in ARDS patients Prone position and a PaO2/FIO2 ratio < 150 Neuromuscular blockers for a period ≤48 hours in patients with ARDS and a PaO2/FIO2 ratio < 150 Conservative volemic filling strategy for patients with ARDS showing no signs of tissue hypoperfusion
SEDATION AND ANALGESIA	Continuous or intermittent sedation should be minimized in mechanically ventilated septic patients, targeting specific titration endpoints
GLYCAEMIC CONTROL	Protocol approach for managing blood glucose levels by starting insulin administration when blood glucose levels are above 180 mg/dl

RENAL REPLACEMENT THERAPIES	Continuous or intermittent renal replacement therapy (RRT) in septic patients with acute renal failure Continuous therapy to facilitate fluid balance management in haemodynamically unstable septic patients
ULCER PROPHYLAXIS	Stress ulcer prophylaxis in septic patients or patients with septic shock who have risk factors for intestinal bleeding
NUTRITION	Early trophic/hypocaloric enteral feeding in critically ill patients with sepsis or septic shock

Table 7- Second Level Resuscitative Interventions (7)

Care goals and prognosis should be discussed with the patient and family members. It is also recommended that goals of care be incorporated into end-of-life treatment and care plans, using palliative care principles when appropriate. Finally, it is suggested that goals of care be addressed as early as possible, but no later than 72 hours after the patient is admitted to the ICU (7).

REFERENCES

1. Fleischmann C, Scherag A, Adhikari NKJ, et al. Assessment of global incidence and mortality of hospital-treated sepsis: current estimates and limitations. Am J Respir Crit Care Med 2016;193:259-72.
2. Say L, Chou D, Gemmill A, Tunçalp Ö, Moller AB, Daniels J, et al. Global causes of maternal death: a WHO systematic analysis. Lancet Glob Health 2014;DOI:10.1016/S2214-109X(14)70227-X.
3. Senior K. In the dark about sepsis. Lancet Infect Dis 2012;12:751-2.
4. Schutte JM, Steegers EA, Schuitemaker NW, Santema JG, de Boer K, Pel M, et al. Rise in maternal mortality in the Netherlands. BJOG 2010;117:399-406.
5. Acosta CD, Knight M, Lee HC, Kurinczuk JJ, Gould JB, Lyndon A. The continuum of maternal sepsis severity: incidence and risk factors in a population based cohort study. PLoS One. 2013;8:e67175.4.
6. Acosta CD, Kurinczuk JJ, Lucas DN, et al. Severe maternal sepsis in the UK, 2011-2012: a national case-control study. PLoS Med 2014;11:e1001672.
7. Rhodes A, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Intensive Care Med 2017; 43:304-77.
8. Singer M, Deutschman CS, et al. The Sepsis Definitions Task Force Members. The Third International Consensus Definition for Sepsis and Septic Shock (Sepsis-3). Jama. February 2016,801-810.
9. WHO Statement on Maternal Sepsis. Geneva; 2017 [http://www.who.int/reproductivehealth/publications/maternal_perinatal_health/maternalsepsis-statement/en/] Accessed 17 February 2017.
10. Bonet M, Souza JP, Abalos E, Fawole B, Knight M, Kouanda S, Lumbiganon P, Nabhan A, Nadisauskiene R, Brizuela V, Metin Gülmezoglu A. The global maternal sepsis study and awareness campaign (GLOSS): study protocol. Reprod Health 2018; DOI:10.1186/s12978-017-0437-8.
11. Dolea C, Stein C. Global burden of maternal sepsis in the year 2000. Evidence and information for policy. World Health Organization, Ginevra, 2003.
12. Donati S. Dossier “La prevenzione e gestione della sepsi materna” in: Corso di Formazione a

distanza: La prevenzione e gestione della sepsi materna – Italian Obstetric Surveillance System - Istituto Superiore di Sanità; ZADIG Editore - 0ttobre 2018
13. World Health Organization Statement on Maternal Sepsis. Ginevra, 2017.
14. Royal College of Obstetricians and Gynaecologists. Bacterial sepsis in pregnancy, Green top Guideline N. 64a –2012.
15. National Institute for Health and Care Excellence (NICE) Clinical guideline, Postnatal care up to 8 weeks after birth, 2015
16. Sistema nazionale linee guida (SNLG), Istituto superiore di sanità (ISS). Gravidanza fisiologica Linea guida 20. Roma, ISS, 2016.
17. Macias AE, et al. for the Global Influenza Initiative. The Global Influenza Initiative recommendations for the vaccination of pregnant women against seasonal influenza. Influenza Other Respir Viruses 2015;9:S31-7.
18. Ministero della Salute Dipartimento della Programmazione e dell'Ordinamento del Servizio Sanitario Nazionale Direzione Generale della Programmazione Sanitaria Ufficio III ex D.G.Prog. Manuale di formazione per il governo clinico: la sicurezza dei pazienti e degli operatori. 2012.
19. AGENAS. Linee di indirizzo per la prevenzione delle complicanze in gravidanza. Agenzia Nazionale Per i Servizi Sanitari Regionali, 2017.
20. Committee on Obstetric Practice. ACOG Committee Opinion No 732 Influenza vaccination during pregnancy Obstet Gynecol 2018; 131:e109-14.
21. World Health Organization fact sheet on influenza, WHO 2018.
22. Agenzia Italiana del Farmaco - AIFA http://www.aifa.gov.it/content/oms-nuove-linee-guida-la-prevenzione-e-il trattamento- delle-infezioni- nel- periodo- del- peripartum
23. The Joint Commission. Preventing maternal death. Sentinel Event Alert. 2010;1-4.
24. Mackintosh N, Watson K, et al. Value of a modified early obstetric warning system (MEOWS) in managing maternal complications in the peripartum period: an ethnographic study. BMJ Qual Saf. 2014; 23:26-34.
25. Singh S, McGlennan A, England A, Simons R. A validation study of the CEMACH recommended modified early obstetric warning system. Anaesthesia 2012; 67:12-18.
26. Knight M, Nair M, Tufnell D, Shakespeare J, Kenyon S, Kurinczuk JJ (Eds.) on behalf of MBRRACE-UK. Saving Lives, Improving Mothers' Care - Lessons learned to inform maternity care from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2013-15. Oxford: National Perinatal Epidemiology Unit, University of Oxford 2017.
27. Chebbo A, Tan S, Kassis C, Tamura L, Carlson RW. Maternal sepsis and septic shock. Critical Care Clinics 2016; 32: 119-135.
28. Royal College of Obstetricians and Gynaecologists. Bacterial sepsis following pregnancy, Green top Guideline N. 64b, 2012.
29. Axelsson D, Blomberg M. Maternal obesity, obstetric interventions and post-partum anemia increase the risk of post-partum sepsis: a population-based cohort study based on Swedish medical health registers. Infect Dis, London, 2017.
30. Karlsson E, et al. Review of the impact of pregnancy and obesity on influenza virus infection. Influenza Other Respir Virus 2012; 6:449e60.
31. Smaill FM, Grivell RM. Antibiotic prophylaxis versus no prophylaxis for preventing infection after cesarean section. Cochrane Database of

Systematic Reviews 2014, Issue 10. Art. No.:CD007482.

32. Lavi Oud, Pregnancy-associated severe sepsis: contemporary state and future challenges. Infect Dis Ther 2014; 3:175-89.
33. Elton RJ, Chaudhari S. Sepsis in obstetric. Continuing Education in Anaesthesia, Critical Care & Pain, 2015.
34. Palaniappan N, Menezes M, Wilson P. Group A streptococcal puerperal sepsis: management and prevention. Obstet Gynaecol 2012; 14:9-16.
35. Epicentro, 2016. http://www.epicentro.iss.it/problemi/listeria/listeria.asp
36. Burney LE. Influenza immunization: statement. Public Health Rep 1960; 75:944.
37. Lamont RF, Sobel JD, et al. Varicella-zoster virus (chickenpox) infection in pregnancy. BJOG 2011; 118:1155-62.
38. Buist S, Mapp CE. Respiratory Diseases in Women. European Respiratory Society. 2003; Vol.8: Monograph 25.
39. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001; 345:1368-77.
40. Rivers EP, Katranji M, Jaehne KA, et al. Early interventions in severe sepsis and septic shock: a review of the evidence one decade later. Minerva Anestesiol 2012; 78:712-24.
41. Dellinger RP, Carlet JM, Masur H, Gerlach H, Calandra T, Cohen J, Gea-Banacloche J, Keh D, Marshall JC, Parker MM, Ramsay G, Zimmerman JL, Vincent JL, Levy MM. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. Crit Care Med. 2004 Mar;32(3):858-73.
42. Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med. 2008;36(1):296-327.
43. Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock 2012. Critical Care Med. 2013; 41:580-637. Intensive Care Medicine. 2013; 39:165-227.
44. Levy MM, Rhodes A, Phillips GS, et al. Surviving Sepsis Campaign: association between performance metrics and outcomes in a 7.5-year study. Crit Care Med 2015; 43:3-12.
45. Arora KS, Shields LE, Grobman WA, D'Alton ME, Lappen JR, Mercer BM. Triggers, bundles, protocols, and checklists. What every maternal care provider needs to know. Am J Obstet Gynecol 2016; 214:444-51.
46. Brown KN, Arafeh JMR. Obstetric sepsis: focus on the 3-hour bundle. J Perinat Neonatal Nurs 2015; 29:213-21.
47. Robson WP, Daniels R. The Sepsis Six: helping patents to survive sepsis. Brit J Nurs 2008; 17:16-21.
48. Albright CM, Ali TN, Lopes V, Rouse DJ, Anderson BL. Lactic acid measurement to identify risk of morbidity from sepsis in pregnancy. Am J Perinatol 2015; 32:481-6.
49. Gilbert David N, Eliopoulos George M, Chambers Henry F, Saag Michael S, Pavia Andrew T (Editor). The Sanford Guide to Antimicrobial Therapy 2018 48th Edition
50. Ferrer R, Martn-Loeches I, Phillips G, Osborn TM, Townsend S, Dellinger RP, Artgas A, Schorr C, Levy MM. Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock from the first hour: results from a guideline-based performance improvement program. Crit Care Med 2014; 42:1749-55.

51. Guyat G, Akl E, Crowther M, Holger J, et all Antithrombotic therapy and prevention of thrombosis,9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines.
52. National Collaborating Centre for Women's and Children's Health. Intrapartum care: Care of healthy women and their babies during childbirth. London, RCOG Press, 2007.
53. Sameshima H, Ikenoue T, Ikeda T, Kamitomo M, Ibara S. Association of non-reassuring fetal heart rate patterns and subsequent cerebral palsy in pregnancies with intrauterine bacterial infection. Am J Perinatol 2005; 22:181-7.
54. Ugwumadu A. Understanding cardiotocographic patterns associated with intrapartum fetal hypoxia and neurologic injury. Best Pract Res Clin Obstet Gynaecol 2013; 27:509-36.
55. Ugwumadu A. Are we (mis)guided by current guidelines on intrapartum fetal heart rate monitoring? Case for a more physiological approach to interpretation. BJOG 2014; 121:1063-70.
56. Chandraharan E. Handbook of CTG interpretation: from patterns to physiology. Cambridge University Press, 2017.
57. American College of Obstetricians and Gynaecologists Commitee on Obstetric Practice. ACOG Practice Bullettin No. 100: Critical care in pregnancy. Obstet Gynecol 2009; 113:443-50.
58. Shefeld JS. Sepsis and septic shock in pregnancy. Crit Care Clin 2004; 20:651-60.