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Maternal sepsis: a comprehensive review from definition to treatment

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ABSTRACT

Maternal mortality is a worldwide alarming concern, and sepsis is the third most frequent cause for its occurrence. Pregnancy and the postpartum period are an intrinsically vulnerable period during women's life, which may make the mothers more susceptible to develop sepsis, due to the physiological and immunological changes that regulate host capacity to counteract pathogens infection, such as bacteria, viruses, fungi, and protozoa. The physiological adaptations of pregnancy could additionally mask signs and symptoms of infection and limit the sensitivity and specificity of the available scores. On this basis, the obstetric-modified quick SOFA and the Modified Early Warning System were proposed to overcome these issues. Early recognition and treatment are vital to prevent mortality. Nevertheless, the evidence guiding the current management of maternal sepsis are derived from the general population and do not take into account the physiological changes of pregnancy. In pregnant women early fluid resuscitation should be carefully addressed, and the management of the source of infection may require expedite delivery, making the management of sepsis particularly challenging during gestation. Further studies are needed to establish pregnancy-related diagnostic criteria and therapeutic protocols for sepsis and septic shock in the obstetrical population.

SOMMARIO

La mortalità materna è indubbiamente un problema di rilevanza globale e la sepsi ne rappresenta la terza causa per frequenza. Durante la gravidanza e nel post-partum la donna è più suscettibile allo sviluppo della sepsi, in quanto i cambiamenti fisiologici e immunologici modulano la capacità dell'ospite di contrastare le infezioni da agenti patogeni, come batteri, virus, funghi e protozoi, rendendo le madri più vulnerabili. Questi adattamenti fisiologici possono inoltre mascherare segni e sintomi di infezione e limitare la sensibilità e la specificità degli score diagnostici disponibili, motivo per il quale è stato proposto il quick-SOFA ostetrico e il Modified Early Warning System. Il riconoscimento e il trattamento precoce sono vitali per ridurre la mortalità legata alla sepsi. Tuttavia, le evidenze su cui si basa la gestione della sepsi materna sono ricavate dalla popolazione generale, che non tiene conto del cambiamento fisiologico della gravidanza, quando la rianimazione emodinamica precoce deve essere affrontata con attenzione e la gestione della fonte di infezione può richiedere l'espletamento in tempi brevi del parto, rendendo particolarmente difficile la gestione della sepsi in ostetricia. Pertanto, sono necessari ulteriori studi per definire chiaramente i criteri diagnostici e i protocolli terapeutici per la sepsi e lo shock settico nella popolazione ostetrica.

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INTRODUCTION

According to the latest declaration of the World Health Organization (WHO), maternal mortality still represents a an alarming issue worldwide (1). Maternal mortality is defined as the death of a woman by any cause related to or aggravated by pregnancy or its management, during pregnancy or within 42 days from delivery or termination of pregnancy. Deaths from incidental or accidental causes are excluded (2).

From 1990 to 2015, the global maternal mortality rate of 43.9% declined with a 2.3% annual reduction rate. In particular, the most relevant reduction of maternal mortality rate has been observed in Eastern Asia, while in the Caribbean the slowest decrease was registered. The only exception to this trend is represented by the United States (US), where a concerning 75% increase in maternal mortality was recorded in the last 25 years (3–5). In terms of deaths per livebirth, the lowest rate of maternal deaths occurred in developed countries, while the highest in sub-Saharan countries (1). More than 99% of the women who die from pregnancy-related complications are in low and middle-income countries (6).

The causes of maternal death are historically classified in direct (obstetric complications of pregnancy) and indirect (disease previously existing or developed during pregnancy, that are aggravated by the physiological effects of pregnancy) causes, leading to give lower attention to indirect causes of maternal death than direct ones (7). Nevertheless, in 2006 the first systematic review of the literature showed that the main cause of global maternal deaths in developing countries was haemorrhage (which accounted for 27% of maternal deaths), followed by hypertensive disorders (8–10), and sepsis (14% and 7% respectively) (11,12).

Sepsis is an indirect cause and is defined as a clinical syndrome caused by the excessive activation of immune and coagulation systems by infections (13). Infection is currently the leading indirect cause of maternal death in the United States and the second leading cause in the United Kingdom. In detail, pregnancy-associated severe sepsis (PASS) increased by 236% from 2001 to 2010 and still represents a problem of global concern (14). Therefore, the early recognition and treatment of maternal sepsis, such as any other pregnancy-related infection, should become a priority for obstetricians and for every health practitioners (15).

In the last years there were many attempts to find consensus about a new definition of maternal sepsis, with the aim to provide an easier and earlier diagnosis and a consequent more accurate management of patients.

The purpose of this review is to evaluate and compare the most recent definitions and guidelines for obstetric sepsis, trying to provide a global overview improving early diagnosis and adequate management. In addition, we describe the most important risk factors for sepsis in pregnancy and puerperium.

DEFINITIONS AND NEW GUIDELINES FOR DIAGNOSIS

The historical definition of sepsis by the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) from the early nineties appears nowadays obsolete (16,17) (**table I**).

In 2001, a group of experts revised the 1992 sepsis-consensus definition and found that, apart from expanding the list of signs and symptoms related to sepsis, there was no evidence to support any change in this classification. In addition, the PIRO scheme for hypothesis-guided diagnosis of sepsis was introduced. The intention was to stratify patients considering their predisposing conditions, the nature of the original cause (infection), the nature and level of the host response, and the degree of concomitant organ dysfunction (18).

In 2013, the SCCM and the European Society of Intensive Care Medicine (ESICM) organised a task force to assess revised definitions, that were published at the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) (19). The consequence was the elimination of the terms "sepsis syndrome", "septicaemia", and "severe sepsis". The underlining reason was that, according to the new definitions, sepsis was triggered by infection. This pathophysiological consideration lead to remove the systemic inflammatory response syndrome (SIRS) from the classification of sepsis, since a number of conditions other than infection may cause SIRS. Consequently, according to the latest Sepsis-3 statements, sepsis was defined as a life-threatening organ dysfunction due to a dysregulated host response to infection (20). Therefore, the Sepsis-3 definition of "sepsis" corresponded to severe sepsis contained in previous

Table I. *Historical and most recent definitions of sepsis.*

Society	Year	Definitions
ACCP/SCCM	1992	• Systemic inflammatory response syndrome (SIRS): inflammatory response to severe clinical insult defined by the presence of two or more of the following symptoms: • Temperature >38 °C or <36 °C • Heart rate >90/min • Respiratory rate >20/min or PaCO2 <32 mmHg • White blood cells count >12000/dL or <4000/dL or >10% immature forms • Sepsis: SIRS with evidence of infection • Severe sepsis: Sepsis with signs of organ dysfunction, hypoperfusion or hypotension • Septic shock: Sepsis with persistent hypotension despite adequate fluid resuscitation or need for inotropic or vasopressor agents
SCCM/ESICM/ACCP/ATS/SIS	2001	No essential change in definitions. PIRO scheme for guiding diagnosis with expanded list of signs and symptoms
SCCM/ESICM – Sepsis-3	2014-2015	• Sepsis: a life-threatening organ dysfunction due to a dysregulated host response to infection. Severity of organ dysfunction is assessed using SOFA score. • Septic shock: Sepsis with persistent hypotension requiring vasopressors to maintain mean arterial pressure (MAP) ≥ 65 mmHg and a serum lactate level >2 mmol/L (18 mg/dL)
WHO	2016	Maternal sepsis is a life-threatening condition defined as organ dysfunction which occurs during pregnancy or postpartum

ACCP: American College of Chest Physicians. SCCM: Society of Critical Care Medicine. ESICM: European Society of Intensive Care Medicine. ATS: American Thoracic Society. SIS: Surgical Infection Society. WHO: World Health Organization.

consensus statements, as well as septic shock was described as sepsis with persistent hypotension needing vasopressors to maintain a mean arterial pressure (MAP) ≥ 65 mmHg, and a serum lactate level >2 mmol/L (18 mg/dL).

The most recent sepsis definition is provided by WHO in 2016 (21). These new guidelines are in line with previous definition from Sepsis-3, but with the goal to point the attention to a more time effective and appropriate antimicrobial therapy and fluid support. Moreover, the perspective to include laboratory tests among the diagnostic criteria seems to offer new possibilities for the future definitions.

As a result of the lack of gold-standard laboratory tests for sepsis diagnosis, the Sequential (Sepsis-related) Organ Failure Assessment (SOFA) score was introduced to better describe severity of organ dysfunction and to predict in-hospital mortality (22) (**table II**). The SOFA score was introduced in 1994 during the ESICM conference in Paris, with the intention not to predict outcome but to describe a sequence of complications. According to the Sepsis-3 new statements, organ dysfunction is determined by an acute change in total SOFA score of 2 points, resulting from the disseminating infection. Furthermore, unless patient has a pre-existing organ dysfunction, baseline SOFA score should be assumed to be zero.

Since calculating SOFA score outside of the Intensive Care Unit (ICU) may be not simply, the quick SOFA (qSOFA) was created to have a faster and easier method of evaluation (23,24). However, the qSOFA score does not define sepsis; it is intended to rapidly recognise those patients at high risk for developing severe complications and who need a more robust treatment. The qSOFA score evaluates altered mental status, tachypnoea and hypotension, and it ranges between 0 and 3 points (**table III**). A total score of 2 points in infected patients is predictive of a greater risk of poor outcome, especially if calculated outside the ICU. Among non-ICU patients with suspected infection, qSOFA has a predictive validity for in-hospital mortality that is greater than the one related to the full SOFA score and to SIRS definition (area under the receiver operating characteristic curve -AUROC- 0.81 for qSOFA vs AUROC 0.79 for SOFA score vs AUROC 0.76 for SIRS). Otherwise, in the ICU the predictive validity for in-hospital mortality is lower if qSOFA and SIRS definition are used, compared to the full SOFA score (AUROC for qSOFA 0.66 vs AUROC for SIRS 0.64 vs AUROC for SOFA score 0.74) (25).

Considering that neither the existing sepsis definitions nor the current scores account for the typical physiologic changes of pregnancy, in 2017 the Society of Obstetric Medicine Australia and New Zealand (SOMAZ) proposed an obstetric-modified qSOFA (omqSOFA) (26). Because gestation influences some variables of the full SOFA score and of the qSOFA score, such as systolic blood pressure (which usually decreases of 5-10 mmHg during pregnancy), respiratory frequency, and creatinine level (which is significantly lower during pregnan-

Table II. *SOFA score.*

SOFA SCORE	+ 0	+1	+2	+3	+4
Respiration PaO2/FiO2, mmHg	≥ 400	< 400	< 300	< 200 with respiratory support	< 100 with respiratory support
Coagulation Platelets x 10^3/mm^3	≥ 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 Hypotension	MAP ≥ 70 mmHg	MAP < 70 mmHg	Dopamine ≤ 5 or dobutamine (any dose) *	Dopamine > 5 or epinephrine ≤ 0.1 or norepinephrine ≤ 0.1	Dopamine > 15 or epinephrine > 0.1 or norepinephrine > 0.1
Central nervous system Glasgow Coma Score	15	13 – 14	10 - 12	6 - 9	< 6
Renal Creatinine, mg/dl (µmol/L) or urine output	< 1.2 (< 110)	1.2 - 1.9 (110 - 170)	2.0 - 3.4 (171 - 299)	3.5 - 4.9 (300 - 440) or < 500 ml/day	> 5.0 (> 440) or <200 ml/day

* Adrenergic agents administered for at least 1 h (doses given are in µg/kg/mamin).

Table III. *Quick SOFA score.*

Clinical signs	Score
Respiratory rate ≥ 22 breaths per minute	+1
Systolic Blood Pressure (SBP) ≤ 100 mmHg	+1
Any change in mental status (GCS <15)	+1

GCS: Glasgow Coma Scale.

Table IV. *Obstetric-modified qSOFA (omqSOFA).*

Clinical signs	Score 0	Score +1
Respiratory rate	< 25 breaths per minute	≥ 25 breaths per minute
Systolic Blood Pressure (SBP)	≥ 90 mmHg	< 90 mmHg
Altered mental status *	Alert	Not alert

* GCS is not typically assessed as part of routine clinical management in obstetric wards.

cy), the omqSOFA includes parameters adapted for the pregnant status. According to this modified score, maternal sepsis should be considered when 2 or more abnormal parameters are present, like systolic blood pressure <90 mmHg, respiratory rate ≥ 25/min, and altered mental status (**table IV**). Moreover, SOMANZ guidelines also include some changes in laboratory test ranges of the full SOFA score (for example, creatinine level is considered abnormal above a cut off of 1.02 mg/dL). The effort of SOMANZ guidelines is to reduce the rate of false-positive diagnosis caused by overlapping ranges between normal and abnormal parameters in pregnancy, and to avoid the underestimation of sepsis signs.

EPIDEMIOLOGY

Sepsis is a very threatening occurrence during pregnancy worldwide (27–29). Since there is no global agreement about its diagnosis and definition, the incidence and prevalence of sepsis provided by different studies and societies seem inaccurate (30,31). Moreover, lack of data from low-income countries makes the incidence in that regions even more difficult to be determined (32).

What is unquestionable is that sepsis mortality is currently still increasing, especially and surprisingly, in developed countries like UK and The Netherlands, where deaths caused by sepsis have nearly doubled over the past decade due to increasing infections caused by invasive group A streptococcus (33). In particular, UK absolute risk of death from maternal sepsis is relatively low (2.0/100 000 pregnancies), but the total amount of severe morbidity is nearly 50 times higher (34). The UK Obstetric Surveillance System (UKOSS), that retrieves data from obstetric departments about maternal deaths occurring in the ICUs (35), reports that sepsis represents the cause of 2-6% of maternal ICU admissions, confirming the great impact of infections and their consequences in maternal morbidity (36,37). Nevertheless, recent studies have shown an under-reporting of sepsis-related maternal deaths, due to the lack of clinical audit or confidential enquiries (34). Actually, only few countries have such a monitoring system acting

as a maternal mortality surveillance method and providing essential statistical data. Other than the UK, clinical auditing after every adverse event is offered also in Finland, France, the Netherlands, Slovenia, Australia and South Africa (38).
Furthermore, it is important to point out that 37.5%, 25.5% and 24.1% of pregnancy-associated sepsis happen during hospitalization for labour and delivery, the antepartum period and the postpartum, respectively (30).

RISK FACTORS FOR MATERNAL SEPSIS

Pregnancy and postpartum represent an intrinsically vulnerable period during women's life, which may make mothers more susceptible to develop sepsis. Physiological and immunological changes during pregnancy have an impact on the immune response (especially T-cell mediated immunity), modifying the host capacity to counteract pathogens infection, such as bacteria, viruses, fungi, and protozoa (as in the case of dengue, yellow fever, Ebola, and malaria) (39–42). Moreover, physiological adaptations to pregnancy, such as plasma volume expansion, tachycardia, blood hypercoagulation, and lower oxygen reserve could mask signs and symptoms of infection, thus delaying sepsis diagnosis (43).
Onset of labour is known to alter physical antimicrobial barriers and caesarean section has frequently been shown to be a major risk factor for maternal morbidity, increasing the risk of developing severe infection such as endometritis (44–48). Indeed, endometritis, in association with pyelonephritis and chorioamnionitis, is the most significant cause of septic shock in pregnancy (49).
In developed countries, well-known risk factors for sepsis are prolonged rupture of membranes, retained placenta or conception products, preterm labour, history of pelvic or other infection, interventions like cerclage or multiple vaginal examinations, diabetes, and anaemia (50,51). Maternal age over 35 years (52) and assisted reproductive techniques (53,54) can also increase risk of sepsis-related morbidity (17). Obesity, defined as a body mass index (BMI) > 30, is as well an established risk factor for surgical-site and nosocomial infections; it seems to negatively influence pregnancy-related outcome and to have substantial effects on immune surveillance (55,56). It is usually associated with poor wound healing, mainly after caesarean section, and genitourinary and uterine infections (57,58). What is alarming is that obesity rate is rapidly increasing in UK and in other developed countries, affecting also young women. In the mid-2000s, nearly 20% of pregnant women in UK were obese, and among extremely obese patients, almost 50% underwent caesarean sections. It is important to underline that 33% of maternal deaths correlated to sepsis occurring in UK between 2003 and 2005 were in obese pregnant women (59). At the same time, new studies revealed that bariatric surgery represents a risk for pregnant women who underwent this kind of operation before gestation. For example, previous gastric bypass, which is the most performed procedure in US, has been demonstrated to increase the risk of gastrointestinal complications which could led to sepsis during the antepartum period. In addition, whilst bariatric surgery is not itself an indication for caesarean section, rates of caesarean delivery seem higher than average in women who had prior bariatric surgery, similarly to other extensive bowel surgeries (60–62).
By contrast, analysing the literature about maternal mortality from sepsis in low-income countries, the most relevant independent risk factor is poverty. Indigence results in a lack of healthcare facilities and appropriate resources, such as antibiotics and medications, and makes women give birth to their children in unhygienic conditions and without proper obstetrics assistance. Immunosuppression caused by HIV and chronic infections like tuberculosis also play a key role in increasing the risk of severe superinfections during the postpartum period. As a result of these data, targeting the interventions towards the most vulnerable populations appears essential, as well as monitoring governments' actions to reduce the disparity of maternal death (50,63).

MANAGEMENT

The diagnosis and management of sepsis are particularly challenging during gestation and the postpartum period due to the physiological changes induced by pregnancy. The increase in blood volume and consequently in stroke volume and heart rate, as well as the increment in tidal volume (more evident in the first trimester) and in systemic vasodilatation, allow pregnant women to longer compensate before clinical deterioration become evident.

Changes in coagulation, fibrinolysis and blood cells count also play a key role in sepsis diagnosis retardation (49,64). On the other hand, the reduction in the expiratory reserve volume and functional residual capacity, and the decreased venous blood return (mainly occurring in the last trimester), reduce the ability of pregnant women to cope with chronic and acute stress deriving from sepsis (65).

Recently, many societies tried to provide early score systems to facilitate timely recognition of septic disease, such as Modified Early Warning System (MEWS) (66). Unfortunately, these scoring systems were found unsuitable to be applied in the obstetric population, because they do not consider maternal physiological changes which can mimicry sepsis initial signs (67). Between 2003 and 2005, the triennial Confidential Enquiry into Maternal and Child Health (CEMACH) report strongly recommended the routine use of the Modified Early Obstetric Warning System (MEOWS), a scoring system adapted for the obstetric population (68–71). Meanwhile MEOWS was introduced in UK, in the US the National Council for Patient Safety proposed the use of the maternal early warning criteria (MERC) (72), another scoring system dedicated to obstetrics population, as well as the Maternal Early Warning Trigger (MEWT) screening, a pathway-specific tool that supported the recommendations from The Joint Commission and other relevant societies (73). MEWT system differs from MEOWS and MERC because it was developed to recognize the 4 major causes of maternal mortality which are sepsis, cardiovascular disease, preeclampsia and haemorrhage. Even if many were the efforts from different societies and working groups to develop and refine the maternal early warning scores, no universally scoring system has currently been validated, and no clinical trial has still assessed the impact of the use of such scoring systems on mortality reduction (74). Actually, these scores need further implementation to improve their capacity to early detect signs of early sepsis and consequently identify the risk of women clinical deterioration.

In the past decades, the Society of Critical Care Medicine and the European Society of Intensive Care Medicine proposed a collaboration which resulted in 2002 in the institution of the Surviving Sepsis Campaign (SSC) (75). The goal was the reduction of sepsis mortality rate by 25% in five years. In doing so, according to the most recent available evidence, the SSC periodically published guidelines with the newest updates and recommended the use of care bundles in the clinical practice (76). Sepsis care bundles are a group of the best evidence-based interventions that, when implemented, provide an impact greater than any single intervention alone and give maximum outcome benefit (77). The Royal College of Obstetricians and Gynaecologists (RCOG) endorses the use of the care bundles in the management of sepsis, showing evidence of greater survival rate following this guidance (78,79). In the US, sepsis bundles approach showed also a substantial cost saving, since the hospitals could save up to $5000/patient using these kind of interventions (80).

The first Surviving Sepsis Campaign (SSC) guideline was published in 2004 and later revised in 2008, in 2012 and updated in 2016. Lastly, in 2018 a revised "hour-1 bundle" was settled (75,81-84). According to the first bundles from 2004, each recommendation carries a level of evidence (grades A, B, C, or D) that represents a grade of recommendations, assessment, development, and evaluation (GRADE). Initially, two sets of bundles were described: the group of the resuscitation bundles and the management ones, which were to be respectively accomplished within 6 hours and 24 hours from patient presentation (75,85) (**table V**).

The intent of the first bundles is to provide cardiorespiratory resuscitation and slow down the spread of infection. Resuscitation necessitates the use of intravenous fluids and vasopressors, and the use of oxygen therapy and mechanical ventilation, if necessary (86). The following SSC guidelines revised bundles criteria so that they at present include part of the original 6 hours bundles divided into two groups, the first is to be completed within 3 hours, the second one within 6 hours. The original 24 hours-management bundles were no longer recommended (85,87). In 2018, the latest SSC-bundles' revision combined the 3 hours and the 6 hours bundles into a single "hour-1 bundle"; the intention was the immediate starting of resuscitation and sepsis management. In this way, the concept of "time zero or time of presentation" was introduced to refer to the moment that patient access and receive triage consistent with all sepsis or septic shock's element determined through chart review (84).

Finally, it is important to mention that obstetric population was not specifically considered when establishing SSC guidelines and sepsis bundles, which refer to the general population.

Table V. *Original bundles based on the 2004-Surviving Sepsis Campaign guidelines and latest bundles from the 2016-Surviving Sepsis Campaign and 2018-revised bundles.*

2004-Surviving Sepsis Campaign Bundles:
Resuscitation Bundles (to be completed within 6 h)
· Measure serum lactate concentration
· Obtain blood cultures before antibiotic therapy administration
· Provide broad spectrum antibiotic within 3 h of emergency department (ED) admission and within 1 h of non-ED admission
· If hypotension and/or serum lactate > 4 mmol/L:
- Administer an initial minimum of 20 mL/kg of crystalloid or equivalent
- Give vasopressors for non-responsive hypotension to maintain MAP > 65 mmHg
· If persistent hypotension despite fluid resuscitation (septic shock) and/or lactate > 4 mmol/L:
- Achieve a CVP ≥ 8 mmHg
- Achieve a $ScvO_2$ ≥ 70% or mixed SvO_2 ≥ 65%
Management Bundles (to be completed within 24 h)
· Administer low-dose steroids for septic shock in accordance with a standardized ICU policy. If not administered, document why the patient did not qualify for low-dose steroids based on the standardized protocol
· Administer rhAPC in accordance with a standardized ICU policy. If not administered, document why the patient did not qualify for rhAPC
· Maintain serum glucose ≥ 70, but ≤ 150 mg/dL
· Maintain a median IPP < 30 cmH_2O for mechanically ventilated patients
2016-Surviving Sepsis Campaign Bundles:
Resuscitation Bundles (to be completed within 3 h):
· Measure lactate level
· Obtain blood cultures before antibiotic therapy administration
· Provide broad spectrum antibiotics
· Administer 30 mL/kg crystalloid over the first three hours for hypotension or lactate ≥ 4 mmol/L
Resuscitation Bundles (to be completed within 6 h)
· Give vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a MAP > 65 mmHg
· If persistent hypotension (MAP <65 mmHg) despite volume resuscitation (septic shock) or if initial lactate ≥4 mmol/L, re-evaluate volume status and tissue perfusion and document findings
· Re-measure lactate if initial lactate elevated
Management Bundles (to be completed within 24 h) no longer recommended
2018-updated Sepsis Bundles:
Resuscitation Bundles (the 3-h and 6-h bundles combined into a single 1-h bundle)
· Same bundles as previously described in 2016 by SSC

MAP: mean arterial pressure. CVP: central venous pressure. ScvO2: central venous oxygen saturation. SvO2: venous oxygen saturation. rhAPC: recombinant human activated protein C. IPP: inspiratory plateau pressure.

Lactate levels

New SSC guidelines emphasized the importance of spot and serial lactate testing and suggested that they should be extended to the inpatient setting. Hypoxia is a well-known cause of increasing lactate levels, which have been demonstrated to be associated with significant morbidity and mortality (88). The explanation in lactate increase is that, during hypoxic conditions like septic shock, mitochondrial oxidative phosphorylation fails and shifts to anaerobic glycolysis that sharply increases cellular lactate production. Usually lactate levels of less than 2 mmol/L at least 2 hours apart are considered to be normal and evidence of adequate tissue oxygenation (89). If initial lactate level is found to be > 2mmol/L, it should be repeated within 2-4 hours to guide resuscitation manoeuvre with the goal of lactate blood level normalization (90,91). Some studies report that in case of ICU's patient with lactate level at admission greater or equal to 3.0 mmol/L, its early monitoring and dropping by 20% or more per 2 hours in the first 8 hours is able to reduce ICU length of stay and overall hospital mortality (90,92).

Blood cultures before antibiotic therapy

Many studies demonstrated a significant reduction in sepsis mortality (especially in the 28-days mortality) using appropriate antibiotic therapy preceded by blood cultures (93,94). Sepsis bundles recommend obtaining blood cultures in any septic patient before the beginning of antimicrobial therapy, since only one appropriate antimicrobial dose is sufficient to sterilize cultures. Literature recommends two blood culture sets, taken from different sites at the same time. They should be collected, if possible, as soon as possible after spike of temperature. In routine practice, a set of blood culture consists of one aerobic and one anaerobic blood sample. It is important to note that, if the culture drawn through the vascular access device is positive earlier (> 2 hours) than the peripheral blood

culture, it may support the fact that the vascular access device is the source of the infection (95,96). However, it is important to avoid any potential delay of the treatments just with the aim to obtain blood cultures.

Antimicrobial therapy

Recently, many Authors confirmed that starting an effective antimicrobial therapy as soon as possible after the onset of hypotension is critical in influencing septic shock mortality (97–99). Kumar et al. established that initiation of antibiotic therapy within the first hour, defined as "the golden hour", following the onset of hypotension was associated with 79.9% survival rate. For every additional hour to delayed antimicrobial therapy initiation, survival rate were demonstrated to drop an average of 7.6% (100). Therefore an intravenous empiric broad-spectrum therapy should be started immediately for patient presenting signs of sepsis or septic shock. The initial antibiotic choice should be made in accordance with local guidelines and antimicrobial resistance profiles. Since pregnancy-related sepsis is mainly due to Group A streptococcus (GAS) and Escherichia Coli infections, empiric antibiotic coverage should include these organisms (17,26,101). Usually, standard therapy against GAS consists of high doses of β-lactam antibiotic; moreover, in association to penicillin, the new guidelines of the Infectious Diseases Society of America (IDSA) strongly recommends the combined use of the protein synthesis inhibitor like clindamycin. Patients with severe GAS infection hence should receive penicillin (2–4 million units every 4–6 hours intravenously) plus clindamycin (600–900 mg/kg every 8 hours intravenously) for at least 10–14 days. For penicillin-allergic patients, alternative protocol should include linezolid or the combination of clindamycin plus either vancomycin or daptomycin (102–104). Similarly, both clindamycin and penicillin are useful for coverage of susceptible enteric aerobic organisms, such as E. Coli.
Once specific pathogen is isolated from blood cultures, empiric antimicrobial therapy should be discontinued and antibiotic therapy with a restricted spectrum coverage should be started. Alternatively, therapy should be narrowed if patient does not have any infection. In case of patient proven to be unresponsive to first-line antimicrobial treatment, infectious disease specialist should be involved in clinical management with the aim of optimizing antibiotic therapy targeting.
In addition to antimicrobial treatment, 2016-SSC guidelines also underline the importance of the so-called "source-control", which refers to all physical and surgical measures used to control a focus of invasive infection and to restore the optimal function of the affected area. Examples of such procedures are drainage and debridement, that is the physical removal of solid necrotic tissue or of an infected device. Sometimes source control can also lead to delivery of the foetus (83,105). Recent studies about sepsis from intra-abdominal infection and correct time for surgical intervention, that is source control, advocate the need to anticipate the procedure as soon as possible, even if patient's hemodynamic status is not still optimal. However, there is no definitive answer in the literature to the question of when source control in patients with septic shock should be started (106).

Intravenous fluid

A correct fluid balance is determinant in influencing sepsis-related mortality. Many strong recommendations support the use of crystalloid fluids in the early resuscitation of patients with sepsis or hypotension and elevated lactate levels. Fluid restoration may require more than 1 hour to be completed, but initiation of resuscitation and treatment should start immediately after recognition of disease.
The 2016-SSC guidelines and the 2018-latest revised bundles endorse the use of crystalloid at an initial bolus of 30 mL/kg (83,84). This recommendation may result aggressive and potentially harmful in pregnancy, especially in patient affected by preeclampsia or pre-existing cardiac disorders or with concomitant use of oxytocin. The lower colloid oncotic pressure observed in pregnant women together with a persistent positive fluid balance can lead to fluids compartmentalization to the so-called third space, pulmonary oedema, and left ventricular diastolic dysfunction (107). For this reason, fluid resuscitation in pregnant women should be carefully managed and, after initial fluids administration, further eventual fluid therapy should be guided by dynamic measures of preload.

Vasopressors

For those patients who result non-responder to initial fluid restoration or who are not eligible for fur-

ther fluid supply, vasopressors are recommended to maintain a Mean Arterial Pressure (MAP) ≥ 65 mmHg. Targeting an individualized MAP is essential since reaching a MAP of 65 mmHg may be excessive in a previously healthy woman. The mechanism of vasopressors is based on the correction of the pathologic vasoplegia that characterizes septic shock and the maintenance of blood perfusion to organs. Although both dopamine and norepinephrine are recommended as first-line vasopressor agents in septic shock, and there is no significant difference in the outcome between patients treated with the first or with the second, SSC guidelines suggest the use of norepinephrine since it is associated with a lower number of adverse events (84,108,109). There is a lack of high-quality studies about the effects of vasopressors during pregnancy-related septic shock; however, norepinephrine has been proven to be safe in pregnancy for both the mother and the foetus (110). Epinephrine or vasopressin might also be used in pregnancy, especially when initial norepinephrine administration fails to maintain an adequate MAP. Conversely, dobutamine, which has an inotrope function, should only be infused in the setting of myocardial dysfunction or continued hypoperfusion despite fluid and vasopressor therapy (83,111).

Other interventions

In addition to the interventions above reported, other drugs and controls should be considered for the management of sepsis in pregnancy. Based on the clinical conditions, interventions such as hydrocortisone administration, blood and platelet transfusion, active glycaemic control, antithrombotic prophylaxis, and prophylaxis for gastric ulcers can be required to control the disease or prevent complications (26). Noteworthy, both pregnancy and sepsis are risk factors for venous thromboembolism, and prophylaxis with low molecular weight heparin (LMWH) has been reported effective in the prevention of venous thromboembolism in pregnancy and puerperium (112).

DELIVERY AND ANAESTHESIA CONSIDERATIONS

Appropriate timing for foetus delivery should be dictated by obstetric indications. The presence of sepsis itself is not mandatory for immediate delivery, especially if patient appropriately responds to early resuscitation treatment. Indeed, unless some conditions like chorioamnionitis or septic abortion occur, there is no evidence that prompt delivery improves maternal outcomes. Furthermore, attempting delivery in women with septic shock who are hemodynamically not stable may influence negatively both maternal and foetal mortality rates (113). For this reason, taking into account gestational age, maternal and foetal clinical conditions, stage of labour, and the presence of chorioamnionitis should be an obstetrician's priority that has to lead and justify clinical decisions.

During maternal sepsis management and treatment, foetal wellbeing has to be monitored with the most appropriate method. If the risk of preterm birth occurs, corticosteroids should be considered for foetal lung maturation, but this decision should be balanced with the need of immediate delivery (114,115). Regarding this last point, it has to be stressed that in case of maternal sepsis, antenatal corticosteroids are not contraindicated and are one of the most important antenatal therapies available to improve new-born outcomes, even in case of sepsis (116,117).

Some studies point out how septic shock is highly associated with the necessity of urgent caesarean section and that it is more frequent in those women with respiratory complications such as ARDS disease, which can lead to a rapid deterioration in both the mother and the foetus (118).

If the uterus is demonstrated to be the source of infection and surgical intervention for source control is needed, the decision whether to proceed or not ultimately depends on obstetrician's choice. The anaesthesiologist may advise whether to undergo regional or general anaesthesia, but it primarily depends on the risk and benefits of each approach, that should be evaluated case by case. To the best of our knowledge, there are no trials which have answered the question whether is better to proceed with regional or general anaesthesia in case of maternal sepsis. Regarding regional anaesthesia, underlying sepsis is a risk factor for spinal cord infective complications, like meningitis or neurological deficit secondary to abscess compression (119–121). Even if neuraxial anaesthesia is generally considered to be relatively contraindicated in case of sepsis, the American Society of Anaesthesiologists (ASA) and the American Society of Regional Anaesthesia (ASRA) advocate the possibility of using an individualized and

history-based protocol of regional anaesthesia in case of septic patients. [122] When regional anaesthesia cannot be provided in safe conditions, the guidelines suggest the use of general anaesthesia. It is important to consider that pregnancy physiologically modifies pulmonary ventilation and cardiovascular capacity; these changes imply an increased risk of gastric aspiration, difficult intubation and aortocaval compression, especially during general anaesthesia. Obstetric anaesthesiologist should not underestimate pregnancy-related risks when approaching a parturient with sepsis who necessitates anaesthesia.

NEW PERSPECTIVES

The crucial key message across all major societies' efforts is that mortality from maternal sepsis is preventable, and that early recognition and treatment is vital to achieve this outcome. To date, having large-scale randomized clinical trials (RCT) to develop guidelines for sepsis in pregnancy and puerperium results problematic, since pregnancy is an exclusion criterion for most of the studies due to obvious ethical reasons. To the present day, the available evidence for maternal sepsis management are provided from RCT conducted on the general population and for this reason do not take into account any physiological changes of pregnancy. Therefore, recommendations are to follow the current guidelines for nonpregnant women while considering the ways in which pregnancy may change the goals of management.
Further studies are needed to establish pregnancy-related diagnostic criteria for sepsis and septic shock in the obstetric population and to consequently develop specific protocols. These obstetric-specific guidelines may finally help in reducing mortality rate for sepsis and septic shock in pregnant population.

CONFLICT OF INTEREST

The authors have no proprietary, financial, professional or other personal interest of any nature in any product, service or company. The authors alone are responsible for the content and writing of the paper. All the authors conform the International Committee of Medical Journal Editors (ICMJE) criteria for authorship, contributed to the intellectual content of the study, and gave approval for the final version of the article.

REFERENCES

1. Alkema L, Chou D, Hogan D, Zhang S, Moller A-B, Gemmill A, Fat DM, Boerma T, Temmerman M, Mathers C, Say L. Global, regional, and national levels and trends in maternal mortality between 1990 and 2015, with scenario-based projections to 2030: a systematic analysis by the UN Maternal Mortality Estimation Inter-Agency Group. The Lancet, 2016; 387(10017):462–74.
2. World Health Organization. The WHO Application of ICD-10 to Deaths during Pregnancy, Childbirth and Puerperium: ICD-MM. World Health Organization, 2012.
3. Creanga AA, Syverson C, Seed K, Callaghan WM. Pregnancy-Related Mortality in the United States, 2011–2013. Obstetrics & Gynecology, 2017; 130(2):366–73.
4. Hirshberg A, Srinivas SK. Epidemiology of maternal morbidity and mortality. Seminars in Perinatology, 2017; 41(6):332–37.
5. Neggers YH. Trends in maternal mortality in the United States. Reproductive Toxicology, 2016; 64:72–6.
6. World Health Organization, United Nations Population Fund, World Bank, United Nations Population Division, United Nations Children's Fund (UNICEF). Trends in Maternal Mortality: 1990 to 2013: Estimates by WHO, UNICEF, UNFPA, The World Bank and the United Nations Population Division. World Health Organization, 2014.
7. van den Akker T, Nair M, Goedhart M, Schutte J, Schaap T, Knight M, Netherlands Audit Committee Maternal Mortality Morbidity, UK Confidential Enquiry into Maternal Deaths. Maternal mortality: direct or indirect has become irrelevant. The Lancet. Global Health, 2017; 5(12):e1181–e1182.
8. MacDonald EJ, Lepine S, Pledger M, Geller SE, Lawton B, Stone P. Pre-eclampsia causing severe maternal morbidity - A national retrospective review of preventability and opportunities for improved care. The Australian & New Zealand Journal of Obstetrics & Gynaecology, 2019.
9. Mol BWJ, Roberts CT, Thangaratinam S, Magee LA, de Groot CJM, Hofmeyr GJ. Pre-eclampsia. Lancet (London, England), 2016; 387(10022):999–1011.
10. Laganà AS, Favilli A, Triolo O, Granese R, Gerli S. Early serum markers of pre-eclampsia: are we stepping forward? The Journal of Maternal-Fetal & Neonatal Medicine, 2016; 29(18):3019–23.
11. Khan KS, Wojdyla D, Say L, Gülmezoglu AM, Van Look PF. WHO analysis of causes of maternal death: a systematic review. The Lancet, 2006; 367(9516):1066–74.
12. Say L, Chou D, Gemmill A, Tunçalp Ö, Moller A-B, Daniels J, Gülmezoglu AM, Temmerman M, Alkema L. Global causes of maternal death: a WHO systematic analysis. The Lancet Global Health, 2014; 2(6):e323–e333.
13. National Institute for Health and Care Excellence. Sepsis: Recognition, Diagnosis and Early Management. NICE, 2016.
14. Abir G, Mhyre J. Maternal mortality and the role of the obstetric anesthesiologist. Best Practice & Research Clinical Anaesthesiology, 2017; 31(1):91–105.
15. Torio CM, Andrews RM. National Inpatient Hospital Costs: The Most Expensive Conditions by Payer, 2011: Statistical Brief #160. P. in Healthcare Cost and Utilization Project (HCUP) Statistical Briefs. Rockville (MD): Agency for Healthcare Research and Quality (US), 2006.
16. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, Schein RMH, Sibbald WJ. Definitions for Sepsis and Organ Failure and Guidelines for the Use of Innovative Therapies in Sepsis. Chest, 1992; 101(6):1644–55.
17. Burlinson CEG, Sirounis D, Walley KR, Chau A. Sepsis in pregnancy and the puerperium. International Journal of Obstetric Anesthesia, 2018; 36:96–107.
18. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, Cohen J, Opal SM, Vincent J-L, Ramsay G. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference: Critical Care Medicine, 2003; 31(4):1250–56.
19. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche J-D, Coopersmith CM, Hotchkiss RS, Levy MM, Marshall JC, Martin GS, Opal SM, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA, 2016; 315(8):801–10.
20. Shankar-Hari M, Phillips GS, Levy ML, Seymour CW, Liu VX, Deutschman CS, Angus DC, Rubenfeld GD, Singer M. Developing a New Definition and Assessing New Clinical Criteria for Septic Shock: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA, 2016; 315(8):775–87.

21. Bonet M, Nogueira Pileggi V, Rijken MJ, Coomarasamy A, Lissauer D, Souza JP, Gülmezoglu AM. Towards a consensus definition of maternal sepsis: results of a systematic review and expert consultation. Reproductive Health, 2017; 14(1):67–79.
22. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, Reinhart CK, Suter PM, Thijs LG. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Medicine, 1996; 22(7):707–10.
23. Raith EP, Udy AA, Bailey M, McGloughlin S, MacIsaac C, Bellomo R, Pilcher DV, Australian and New Zealand Intensive Care Society (ANZICS) Centre for Outcomes and Resource Evaluation (CORE). Prognostic Accuracy of the SOFA Score, SIRS Criteria, and qSOFA Score for In-Hospital Mortality Among Adults With Suspected Infection Admitted to the Intensive Care Unit. JAMA, 2017; 317(3):290–300.
24. Seymour CW, Liu VX, Iwashyna TJ, Brunkhorst FM, Rea TD, Scherag A, Rubenfeld G, Kahn JM, Shankar-Hari M, Singer M, Deutschman CS, Escobar GJ, Angus DC. Assessment of Clinical Criteria for Sepsis: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA, 2016; 315(8):762–74.
25. Napolitano LM. Sepsis 2018: Definitions and Guideline Changes. Surgical Infections, 2018; 19(2):117–25.
26. Bowyer L, Robinson HL, Barrett H, Crozier TM, Giles M, Idel I, Lowe S, Lust K, Marnoch CA, Morton MR, Said J, Wong M, Makris A. SOMANZ guidelines for the investigation and management sepsis in pregnancy. Australian and New Zealand Journal of Obstetrics and Gynaecology, 2017; 57(5):540–51.
27. Galvão A, Braga AC, Gonçalves DR, Guimarães JM, Braga J. Sepsis during pregnancy or the postpartum period. Journal of Obstetrics and Gynaecology, 2016; 36(6):735–743.
28. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Critical Care Medicine, 2001; 29(7):1303–10.
29. Fernández-Pérez ER, Salman S, Pendem S, Farmer JC. Sepsis during pregnancy. Critical Care Medicine, 2005; 33(10 Suppl):S286-93.
30. Oud L, Watkins P. Evolving Trends in the Epidemiology, Resource Utilization, and Outcomes of Pregnancy-Associated Severe Sepsis: A Population-Based Cohort Study. Journal of Clinical Medicine Research, 2015; 7(6):400–16.
31. Bamfo JE. Managing the risks of sepsis in pregnancy. Best Practice & Research. Clinical Obstetrics & Gynaecology, 2013; 27(4):583–95.
32. van Dillen J, Zwart J, Schutte J, van Roosmalen J. Maternal sepsis: epidemiology, etiology and outcome. Current Opinion in Infectious Diseases, 2010; 23(3):249–54.
33. Acosta CD, Knight M. Sepsis and maternal mortality. Current Opinion in Obstetrics and Gynecology, 2013; 25(2):109–16.
34. Acosta CD, Harrison DA, Rowan K, Lucas DN, Kurinczuk JJ, Knight M. Maternal morbidity and mortality from severe sepsis: a national cohort study. BMJ Open, 2016; 6(8):e012323.
35. Acosta CD, Kurinczuk JJ, Lucas DN, Tuffnell DJ, Sellers S, Knight M, on behalf of the United Kingdom Obstetric Surveillance System. Severe Maternal Sepsis in the UK, 2011–2012: A National Case-Control Study. Fisk NM (ed). PLoS Medicine, 2014; 11(7):e1001672.
36. Timezguid N, Das V, Hamdi A, Ciroldi M, Sfoggia-Besserat D, Chelha R, Obadia E, Pallot J-L. Maternal sepsis during pregnancy or the postpartum period requiring intensive care admission. International Journal of Obstetric Anesthesia, 2012; 21(1):51–5.
37. Zwart JJ, Dupuis JRO, Richters A, Öry F, van Roosmalen J. Obstetric intensive care unit admission: a 2-year nationwide population-based cohort study. Intensive Care Medicine, 2010; 36(2):256–63.
38. Bouvier-Colle M-H, Mohangoo A, Gissler M, Novak-Antolic Z, Vutuc C, Szamotulska K, Zeitlin J, for The Euro-Peristat Scientific Committee. What about the mothers? An analysis of maternal mortality and morbidity in perinatal health surveillance systems in Europe: Maternal health in European surveillance systems. BJOG: An International Journal of Obstetrics & Gynaecology, 2012; 119(7):880–90.
39. Mor G, Cardenas I. The immune system in pregnancy: a unique complexity. American Journal of Reproductive Immunology, 2010; 63(6):425–33.
40. Mor G, Cardenas I, Abrahams V, Guller S. Inflammation and pregnancy: the role of the immune system at the implantation site. Annals

of the New York Academy of Sciences, 2011; 1221(1):80–7.
41. Mason KL, Aronoff DM. Postpartum group a Streptococcus sepsis and maternal immunology. American Journal of Reproductive Immunology, 2012; 67(2):91–100.
42. Corpolongo A, De Nardo P, Gentilotti E, Ghirga P, Maritti M, Nicastri E, Narciso P. Procedura operativa per la gestione diagnostico terapeutica della malaria. *National institute for Infectious Diseases, IRCCS "Lazzaro Spallanzani."* https://www.inmi.it/wp-content/uploads/2018/12/Protocollo_malaria_03_01_2013.pdf. Published January 3, 2013. Accessed May 3, 2020.
43. Bauer ME, Bauer ST, Rajala B, MacEachern MP, Polley LS, Childers D, Aronoff DM. Maternal Physiologic Parameters in Relationship to Systemic Inflammatory Response Syndrome Criteria: A Systematic Review and Meta-analysis. Obstetrics & Gynecology, 2014; 124(3):535–41.
44. Waterstone M, Bewley S, Wolfe C. Incidence and predictors of severe obstetric morbidity: case-control study. BMJ (Clinical research ed.), 2001; 322(7294):1089–1093; discussion 1093-1094.
45. Brace V, Penney G, Hall M. Quantifying severe maternal morbidity: a Scottish population study. BJOG: An International Journal of Obstetrics & Gynaecology, 2004; 111(5):481–84.
46. Leth RA, Møller JK, Thomsen RW, Uldbjerg N, Nørgaard M. Risk of selected postpartum infections after cesarean section compared with vaginal birth: A five-year cohort study of 32,468 women. Acta Obstetricia et Gynecologica Scandinavica, 2009; 88(9):976–83.
47. Maharaj D. Puerperal pyrexia: a review. Part I. Obstetrical & Gynecological Survey, 2007; 62(6):393–99.
48. Franchi M, Raffaelli R, Baggio S, Scollo M, Garzon S, Laganà AS, Casarin J, Zanconato G, Cromi A, Ghezzi F. Unintentional transvesical caesarean section: incidence, risk factors, surgical technique and post-operative management. European Journal of Obstetrics, Gynecology, and Reproductive Biology, 2019; 236:26–31.
49. Paruk F. Infection in obstetric critical care. Best Practice & Research Clinical Obstetrics & Gynaecology, 2008; 22(5):865–83.
50. Sriskandan S. Severe peripartum sepsis. The Journal of the Royal College of Physicians of Edinburgh, 2011; 41(4):339–46.
51. 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. Thorne C (ed). PLoS ONE, 2013; 8(7):e67175.
52. Ciancimino L, Laganà AS, Chiofalo B, Granese R, Grasso R, Triolo O. Would it be too late? A retrospective case-control analysis to evaluate maternal-fetal outcomes in advanced maternal age. Archives of Gynecology and Obstetrics, 2014; 290(6):1109–14.
53. Akhanoba F, MacDougall J, Mathur R, Hassan W. Severe systemic candidiasis following immunomodulation therapy in in vitro fertilisation-embryo transfer (IVF-ET). BMJ case reports, 2014; 2014.
54. Lee FK, Horng HC, Wang PH. Assisted reproductive technology and adverse pregnancy outcome- focus on maternal death. Journal of the Chinese Medical Association, 2018; 81(11):933–34.
55. Huttunen R, Syrjänen J. Obesity and the outcome of infection. The Lancet Infectious Diseases, 2010; 10(7):442–43.
56. Orr K, Chien P. Sepsis in obese pregnant women. Best Practice & Research Clinical Obstetrics & Gynaecology, 2015; 29(3):377–93.
57. Kramer HMC, Schutte JM, Zwart JJ, Schuitemaker NWE, Steegers E a. P, Roosmalen JV. Maternal mortality and severe morbidity from sepsis in the Netherlands. Acta Obstetricia et Gynecologica Scandinavica, 2009; 88(6):647–53.
58. Acosta CD, Bhattacharya S, Tuffnell D, Kurinczuk JJ, Knight M. Maternal sepsis: a Scottish population-based case–control study. BJOG: An International Journal of Obstetrics & Gynaecology, 2012; 119(4):474–83.
59. Knight M, Kurinczuk JJ, Spark P, Brocklehurst P, UK Obstetric Surveillance System. Extreme obesity in pregnancy in the United Kingdom. Obstetrics and Gynecology, 2010; 115(5):989–997.
60. Leal-González R, De la Garza-Ramos R, Guajardo-Pérez H, Ayala-Aguilera F, Rumbaut R. Internal hernias in pregnant women with history of gastric bypass surgery: Case series and review of literature. International Journal of Surgery Case Reports, 2013; 4(1):44–7.
61. Narayanan RP, Syed AA. Pregnancy Following Bariatric Surgery—Medical Complications and Management. Obesity Surgery, 2016; 26(10):2523–29.
62. Baggio S, Pomini P, Zecchin A, Garzon S, Bonin C, Santi L, Festi A, Franchi MP. Delivery

and pregnancy outcome in women with bowel resection for deep endometriosis: a retrospective cohort study. Gynecological Surgery, 2015; 12(4):279–85.

63. Ronsmans C, Graham WJ, Lancet Maternal Survival Series steering group. Maternal mortality: who, when, where, and why. Lancet (London, England), 2006; 368(9542):1189–200.
64. Joseph J, Sinha A, Paech M, Walters BNJ. Sepsis in pregnancy and early goal-directed therapy. Obstetric Medicine, 2009; 2(3):93–9.
65. Sibai BM, Frangieh A. Maternal adaptation to pregnancy. Current Opinion in Obstetrics & Gynecology, 1995; 7(6):420–6.
66. Subbe CP. Validation of a modified Early Warning Score in medical admissions. QJM, 2001; 94(10):521–6.
67. Lappen JR, Keene M, Lore M, Grobman WA, Gossett DR. Existing models fail to predict sepsis in an obstetric population with intrauterine infection. American Journal of Obstetrics and Gynecology, 2010; 203(6):573.e1-573.e5.
68. Cantwell R, Clutton-Brock T, Cooper G, Dawson A, Drife J, Garrod D, Harper A, Hulbert D, Lucas S, McClure J, Millward-Sadler H, Neilson J, Nelson-Piercy C, Norman J, O'Herlihy C, et al. Saving Mothers' Lives: Reviewing maternal deaths to make motherhood safer: 2006-2008. The Eighth Report of the Confidential Enquiries into Maternal Deaths in the United Kingdom. BJOG: an international journal of obstetrics and gynaecology, 2011; 118 Suppl 1:1–203.
69. Singh S, McGlennan A, England A, Simons R. A validation study of the CEMACH recommended modified early obstetric warning system (MEOWS). Anaesthesia, 2012; 67(1):12–8.
70. Swanton RD, Al-Rawi S, Wee MY. A national survey of obstetric early warning systems in the United Kingdom. International Journal of Obstetric Anesthesia, 2009; 18(3):253–257.
71. Isaacs RA, Wee MY, Bick DE, Beake S, Sheppard ZA, Thomas S, Hundley V, Smith GB, van Teijlingen E, Thomas PW, Members of the Modified Obstetric Early Warning Systems Research Group. A national survey of obstetric early warning systems in the United Kingdom: five years on. Anaesthesia, 2014; 69(7):687–92.
72. Mhyre JM, D'Oria R, Hameed AB, Lappen JR, Holley SL, Hunter SK, Jones RL, King JC, D'Alton ME. The Maternal Early Warning Criteria: A Proposal from the National Partnership for Maternal Safety. Journal of Obstetric, Gynecologic & Neonatal Nursing, 2014; 43(6):771–779.
73. Shields LE, Wiesner S, Klein C, Pelletreau B, Hedriana HL. Use of Maternal Early Warning Trigger tool reduces maternal morbidity. American Journal of Obstetrics and Gynecology, 2016; 214(4):527.e1-527.e6.
74. Paternina-Caicedo A, Miranda J, Bourjeily G, Levinson A, Dueñas C, Bello-Muñoz C, Rojas-Suarez JA. Performance of the Obstetric Early Warning Score in critically ill patients for the prediction of maternal death. American Journal of Obstetrics and Gynecology, 2017; 216(1):58.e1-58.e8.
75. 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 J-L, Levy MM, Surviving Sepsis Campaign Management Guidelines Committee. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. Critical Care Medicine, 2004; 32(3):858–73.
76. Mukherjee V, Evans L. Implementation of the Surviving Sepsis Campaign guidelines. Current Opinion in Critical Care, 2017; 23(5):412–6.
77. Levy MM, Pronovost PJ, Dellinger RP, Townsend S, Resar RK, Clemmer TP, Ramsay G. Sepsis change bundles: Converting guidelines into meaningful change in behavior and clinical outcome. Critical Care Medicine, 2004; 32(11):S595–S597.
78. Royal College of Obstetricians and Gynaecologists. Bacterial Sepsis in Pregnancy. RCOG Green-top Guideline No. 64a, 2012.
79. Royal College of Obstetricians and Gynaecologists. Bacterial Sepsis following Pregnancy. RCOG Green-top Guideline No. 64b, 2012.
80. Shorr AF, Micek ST, Jackson WL, Kollef MH. Economic implications of an evidence-based sepsis protocol: can we improve outcomes and lower costs? Critical Care Medicine, 2007; 35(5):1257–62.
81. Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, Reinhart K, Angus DC, Brun-Buisson C, Beale R, Calandra T, Dhainaut J-F, Gerlach H, Harvey M, Marini JJ, et al. Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008. Intensive Care Medicine, 2008; 34(1):17–60.
82. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL,

Douglas IS, Jaeschke R, Osborn TM, Nunnally ME, Townsend SR, Reinhart K, Kleinpell RM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. Intensive Care Medicine, 2013; 39(2):165–228.
83. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, Kumar A, Sevransky JE, Sprung CL, Nunnally ME, Rochwerg B, Rubenfeld GD, Angus DC, Annane D, Beale RJ, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Intensive Care Medicine, 2017; 43(3):304–77.
84. Levy MM, Evans LE, Rhodes A. The Surviving Sepsis Campaign Bundle: 2018 update. Intensive Care Medicine, 2018; 44(6):925–8.
85. Barochia AV, Cui X, Eichacker PQ. The Surviving Sepsis Campaign's Revised Sepsis Bundles. Current Infectious Disease Reports, 2013; 15(5):385–93.
86. Angus DC, van der Poll T. Severe Sepsis and Septic Shock. New England Journal of Medicine, 2013; 369(9):840–51.
87. Makic MBF, Bridges E. CE: Managing Sepsis and Septic Shock: Current Guidelines and Definitions. The American Journal of Nursing, 2018; 118(2):34–9.
88. Morris E, McCartney D, Lasserson D, Van den Bruel A, Fisher R, Hayward G. Point-of-care lactate testing for sepsis at presentation to health care: a systematic review of patient outcomes. British Journal of General Practice, 2017; 67(665):e859–e870.
89. Jones AE, Shapiro NI, Trzeciak S, Arnold RC, Claremont HA, Kline JA, Emergency Medicine Shock Research Network (EMShockNet) Investigators. Lactate clearance vs central venous oxygen saturation as goals of early sepsis therapy: a randomized clinical trial. JAMA, 2010; 303(8):739–46.
90. Jansen TC, van Bommel J, Schoonderbeek FJ, Sleeswijk Visser SJ, van der Klooster JM, Lima AP, Willemsen SP, Bakker J. Early Lactate-Guided Therapy in Intensive Care Unit Patients. American Journal of Respiratory and Critical Care Medicine, 2010; 182(6):752–761.
91. Armstrong BA, Betzold RD, May AK. Sepsis and Septic Shock Strategies. Surgical Clinics of North America, 2017; 97(6):1339–79.
92. Rhee C, Murphy MV, Li L, Platt R, Klompas M. Lactate Testing in Suspected Sepsis: Trends and Predictors of Failure to Measure Levels. Critical Care Medicine, 2015; 43(8):1669–76.
93. Cardoso T, Carneiro AH, Ribeiro O, Teixeira-Pinto A, Costa-Pereira A. Reducing mortality in severe sepsis with the implementation of a core 6-hour bundle: results from the Portuguese community-acquired sepsis study (SACiUCI study). Critical Care, 2010; 14(3):R83.
94. Zadroga R, Williams DN, Gottschall R, Hanson K, Nordberg V, Deike M, Kuskowski M, Carlson L, Nicolau DP, Sutherland C, Hansen GT. Comparison of 2 Blood Culture Media Shows Significant Differences in Bacterial Recovery for Patients on Antimicrobial Therapy. Clinical Infectious Diseases, 2013; 56(6):790–797.
95. Blot F, Schmidt E, Nitenberg G, Tancrède C, Leclercq B, Laplanche A, Andremont A. Earlier positivity of central-venous- versus peripheral-blood cultures is highly predictive of catheter-related sepsis. Journal of Clinical Microbiology, 1998; 36(1):105–109.
96. Patel M. Utility of blood culture in sepsis diagnostics. Journal of the academy of clinical microbiologists, 2016; 18(2):74–79.
97. Ferrer R, Martin-Loeches I, Phillips G, Osborn TM, Townsend S, Dellinger RP, Artigas 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. Critical Care Medicine, 2014; 42(8):1749–1755.
98. Seymour CW, Gesten F, Prescott HC, Friedrich ME, Iwashyna TJ, Phillips GS, Lemeshow S, Osborn T, Terry KM, Levy MM. Time to Treatment and Mortality during Mandated Emergency Care for Sepsis. New England Journal of Medicine, 2017; 376(23):2235–2244.
99. Liu VX, Fielding-Singh V, Greene JD, Baker JM, Iwashyna TJ, Bhattacharya J, Escobar GJ. The Timing of Early Antibiotics and Hospital Mortality in Sepsis. American Journal of Respiratory and Critical Care Medicine, 2017; 196(7):856–863.
100. Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S, Suppes R, Feinstein D, Zanotti S, Taiberg L, Gurka D, Kumar A, Cheang M. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Critical Care Medicine, 2006; 34(6):1589–1596.
101. Knowles SJ, O'Sullivan NP, Meenan AM, Hanniffy R, Robson M. Maternal sepsis incidence, aetiology and outcome for mother and fetus:

a prospective study. BJOG: An International Journal of Obstetrics & Gynaecology, 2015; 122(5):663–671.

102. Stevens DL, Bisno AL, Chambers HF, Everett ED, Dellinger P, Goldstein EJC, Gorbach SL, Hirschmann JV, Kaplan EL, Montoya JG, Wade JC. Practice Guidelines for the Diagnosis and Management of Skin and Soft-Tissue Infections. Clinical Infectious Diseases, 2005; 41(10):1373–1406.
103. Andreoni F, Zürcher C, Tarnutzer A, Schilcher K, Neff A, Keller N, Marques Maggio E, Poyart C, Schuepbach RA, Zinkernagel AS. Clindamycin Affects Group A Streptococcus Virulence Factors and Improves Clinical Outcome. The Journal of Infectious Diseases, 2017; 215(2):269–277.
104. Hamilton SM, Stevens DL, Bryant AE. Pregnancy-Related Group A Streptococcal Infections: Temporal Relationships Between Bacterial Acquisition, Infection Onset, Clinical Findings, and Outcome. Clinical Infectious Diseases, 2013; 57(6):870–876.
105. Marshall JC, al Naqbi A. Principles of Source Control in the Management of Sepsis. Critical Care Clinics, 2009; 25(4):753–768.
106. Azuhata T, Kinoshita K, Kawano D, Komatsu T, Sakurai A, Chiba Y, Tanjho K. Time from admission to initiation of surgery for source control is a critical determinant of survival in patients with gastrointestinal perforation with associated septic shock. Critical Care, 2014; 18(3):R87.
107. Marik P, Bellomo R. A rational approach to fluid therapy in sepsis. British Journal of Anaesthesia, 2016; 116(3):339–349.
108. De Backer D, Biston P, Devriendt J, Madl C, Chochrad D, Aldecoa C, Brasseur A, Defrance P, Gottignies P, Vincent J-L, SOAP II Investigators. Comparison of dopamine and norepinephrine in the treatment of shock. The New England Journal of Medicine, 2010; 362(9):779–789.
109. Boulain T, Runge I, Bercault N, Benzekri-Lefevre D, Wolf M, Fleury C. Dopamine therapy in septic shock: Detrimental effect on survival? Journal of Critical Care, 2009; 24(4):575–582.
110. Minzter BH, Johnson RF, Paschall RL, Ramasubramanian R, Ayers GD, Downing JW. The diverse effects of vasopressors on the fetoplacental circulation of the dual perfused human placenta. Anesthesia and Analgesia, 2010; 110(3):857–862.
111. Cordioli RL, Cordioli E, Negrini R, Silva E. Sepsis and pregnancy: do we know how to treat this situation? Revista Brasileira De Terapia Intensiva, 2013; 25(4):334–344.
112. Bain E, Wilson A, Tooher R, Gates S, Davis L-J, Middleton P. Prophylaxis for venous thromboembolic disease in pregnancy and the early postnatal period. The Cochrane Database of Systematic Reviews, 2014; (2):CD001689.
113. Sheffield JS. Sepsis and septic shock in pregnancy. Critical Care Clinics, 2004; 20(4):651–660.
114. Garite TJ, Combs CA. Obstetric Interventions Beneficial to Prematurely Delivering Newborn Babies: Antenatal Corticostetroids, Progesterone, Magnesium Sulfate. Clinics in Perinatology, 2012; 39(1):33–45.
115. Crowther CA, Brown J, Alsweiler J, Middleton P. Antenatal Corticosteroids given to Women Prior to Birth to Improve Fetal, Infant, Child and Adult Health: Clinical Practice Guidelines. Liggins Institute, 2014.
116. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics. Practice Bulletin No. 170: Critical Care in Pregnancy. Obstetrics and Gynecology, 2016; 128(4):e147-154.
117. Committee on Obstetric Practice. Committee Opinion No. 713: Antenatal Corticosteroid Therapy for Fetal Maturation. Obstetrics and Gynecology, 2017; 130(2):e102–e109.
118. Snyder CC, Barton JR, Habli M, Sibai BM. Severe sepsis and septic shock in pregnancy: indications for delivery and maternal and perinatal outcomes. The Journal of Maternal-Fetal & Neonatal Medicine, 2013; 26(5):503–6.
119. Hebl JR, Niesen AD. Infectious complications of regional anesthesia. Current Opinion in Anaesthesiology, 2011; 24(5):573–80.
120. Horlocker TT, Wedel DJ. Infectious complications of regional anesthesia. Best Practice & Research Clinical Anaesthesiology, 2008; 22(3):451–75.
121. Wedel D, Horlocker T. Regional Anesthesia in the Febrile or Infected Patient. Regional Anesthesia and Pain Medicine, 2006; 31(4):324–33.
122. Anon. Practice Advisory for the Prevention, Diagnosis, and Management of Infectious Complications Associated with Neuraxial Techniques: An Updated Report by the American Society of Anesthesiologists Task Force on Infectious Complications Associated with Neuraxial Techniques and the American Society of Regional Anesthesia and Pain Medicine. Anesthesiology, 2017; 126(4):585–601.