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Risk Factors, Etiologies, and Screening Tools for Sepsis in Pregnant Women: A Multicenter Case-Control Study

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Abstract

Background—Given the significant morbidity and mortality of maternal sepsis, early identification is key to improve outcomes. This study aims to evaluate the performance characteristics of the systemic inflammatory response syndrome (SIRS), quick sequential organ failure assessment (qSOFA), and maternal early warning (MEW) criteria for identifying cases of impending sepsis in parturients. The secondary objective of this study is to identify etiologies and risk factors for maternal sepsis, and assess timing of antibiotics in patients diagnosed with sepsis.

Methods—Validated maternal sepsis cases during the delivery hospitalization from 1995 to 2012 were retrospectively identified at seven academic medical centers in the US and Israel. Control patients were matched by date of delivery in a 1:4 ratio. The sensitivity and specificity of SIRS criteria, qSOFA, and MEW criteria for identifying sepsis were calculated. Data including potential risk factors, vital signs, laboratory values, and clinical management were collected for cases and controls.

Results—Eighty-two sepsis cases during the delivery hospitalization were identified and matched to 328 controls. The most common causes of sepsis were the following: chorioamnionitis 20 (24.4%), endometritis 19 (23.2%), and pneumonia 9 (11.0%). *Escherichia coli 12* (14.6%), other gram negative rods 8 (9.8%), and Group A streptococcus 6 (7.3%) were the most commonly found pathogens. The sensitivities and specificities for meeting criteria for screening tools were: 1) SIRS (0.93, 0.63); 2) qSOFA (0.50, 0.95); and 3) MEW criteria for identifying sepsis (0.82, 0.87). Of 82 women with sepsis, 10 (12.2%) died. The mortality rate for those who received antibiotics

within one hour of diagnosis was 8.3%. The mortality rate was 20% for the patients who received antibiotics after more than one hour.

Conclusions—Chorioamnionitis and endometritis were the most common causes of sepsis, together accounting for about half of cases. Notable differences were observed in the sensitivity and specificity of sepsis screening tools with the highest to lowest sensitivity being SIRS, MEW, and qSOFA criteria, and the highest to lowest specificity being qSOFA, MEW, and SIRS. Mortality was doubled in the cohort of patients who received antibiotics after more than one hour. Clinicians need to be vigilant to identify cases of peripartum sepsis early in its course and prioritize timely antibiotic therapy.

Introduction

Sepsis is an important cause of maternal morbidity and mortality. According to the most recent estimate from the Centers for Disease Control and Prevention, sepsis is the third leading cause and accounts for approximately 12.7% of pregnancy-related deaths.[1] It has been estimated that for each maternal death, there are 50 women with life-threatening morbidity from sepsis.[2] In North Carolina, United Kingdom, and Michigan maternal mortality reviews, deaths due to sepsis were reportedly 43%, 47% and 73% preventable, respectively.[3–5] Early identification and prompt treatment of patients with sepsis have been shown to improve outcomes.[6] However, diagnosing sepsis during pregnancy and the postpartum period can be challenging as physiologic changes of pregnancy can mimic the signs of sepsis.[7]

Given the potential preventability of and significant morbidity and mortality associated with sepsis, early identification of sepsis is paramount, and many screening tools exist. The quick Sequential [Sepsis-related] Organ Failure Assessment (qSOFA) criteria are currently recommended as the screening tool for sepsis outside of the intensive care unit (ICU);[8] previously, the Systemic Inflammatory Response Syndrome (SIRS) criteria were used.[9] The Maternal Early Warning (MEW) criteria provides a screening tool to identify women with heightened risk for multiple causes of maternal morbidity and mortality (Table 1).[10] While not developed specifically for patients with an infection, the parameters comprising MEW criteria have been adjusted particularly for pregnancy.

The performance characteristics of these screening tools (SIRS, qSOFA, and MEW criteria) for the identification of sepsis in pregnancy are currently unknown and it is unclear which screening criteria should be used for maternal sepsis. Therefore, the primary objective of this multicenter case-control study was to evaluate the performance characteristics of the SIRS, qSOFA, and MEW criteria for identifying cases of impending sepsis during the delivery hospitalization. The secondary objectives were to characterize the etiologies, risk factors, and to assess the timing of antibiotics in patients diagnosed with sepsis.

Methods

Institutional review board approval was obtained at each of the seven participating centers: University of Michigan Health System [UMHS] (Ann Arbor, Michigan), Brigham and Women’s Hospital [BWH] (Boston, Massachusetts), Massachusetts General Hospital

[MGH] (Boston, Massachusetts), Northwestern Memorial Hospital [NM] (Chicago, Illinois), Beaumont Health [BH] (Royal Oak, Michigan), Intermountain Healthcare [IH] (Salt Lake City, Utah), Shaare Zedek Medical Centre [SZMC] (Jerusalem, Israel). As this was a retrospective chart review, informed written consent was waived. This manuscript adheres to the applicable STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines.

Delivery hospitalization (defined as a hospitalization in which both sepsis and delivery occurred) admissions were screened for sepsis. International Classification of Diseases Ninth Revision (ICD-9) codes indicating sepsis, severe sepsis, or septic shock were searched using one of the following methods: 1) delivery admissions were identified and then administrative claims were screened for ICD-9 codes consistent with sepsis, severe sepsis, septic shock, or other severe infection codes (UMHS 1995–2012, IH 1997–2012); or 2) delivery admissions were searched for ICD-9 codes indicating sepsis, severe sepsis, septic shock, and other severe infection codes (BWH and MGH 1997–2012, NM 2007–2012, BH 2000–2012, SZMC 1994–2012). Each chart identified by screening was manually reviewed to verify that the patient met the defined clinical criteria for severe sepsis: sepsis along with organ failure, hypotension, or hypoperfusion, which was the definition in use during the period when patients included in the study were hospitalized.[9]

To evaluate risk factors, sensitivity, and specificity of screening criteria, the delivery hospitalization patient group was matched to healthy control patients. Controls for delivery hospitalization cases were matched by date of delivery and hospital in a 1:4 ratio to maximize power.[11] Four controls were selected for the delivery date from the available pool of patients using a random number generator. Vital signs were collected for sepsis cases for the 24-hour period prior to and including the time of diagnosis. Time of diagnosis was defined by the earliest time any one of the following criteria was met: 1) time of initiation of broad-spectrum antibiotics or broadening of existing antibiotic regimen, 2) time of documentation of sepsis in the chart, or 3) time of transfer to the intensive care unit for sepsis. For controls, vital signs for controls were collected for the 24-hour period corresponding with the sepsis patient's diagnosis in relation to delivery (e.g., if the sepsis patient was diagnosed on postpartum day one, then the vital signs and white blood cell count for the matched control patients were collected for the 24-hour period on postpartum day one). The vital signs and daily laboratory values were collected at the same time point relative to delivery for cases and controls to account for the dynamic physiological changes (heart rate, white blood cell count, respiratory rate) occurring during delivery and the postpartum period.[7]

Data were collected that were expected to be routinely documented in both controls and cases; thus, not all diagnostic criteria for the MEW criteria scoring system were collected (urine output and oxygen saturation, as these are not routinely collected for parturients in the postpartum period). For modified MEW criteria, data regarding systolic blood pressure, respiratory rate, heart rate, and neurological changes were collected and analyzed. The MEW criteria parameters inconsistent with the physiology of sepsis (systolic blood pressure >160 mmHg, diastolic blood pressure >100 mmHg, heart rate <50, and respiratory rate <10) were not included in the analysis. For qSOFA and modified MEW criteria, neurological

changes were collected for the sepsis cases and were assumed to have occurred at the time of diagnosis; it was assumed that none of the control patients exhibited neurological changes. Data were collected by chart review and placed into REDCap™ (Research Electronic Data Capture). Data collected at each site were screened by the coordinating center (University of Michigan) for any inconsistencies or outlying values. In those instances, the primary site was contacted to verify the data through chart review.

Medical records, including documentation pertaining to prenatal care, labor and delivery records, and the intensive care unit (ICU) admission charts were reviewed. Laboratory data and medication administration records were also reviewed. Demographic information, medical comorbidities, obstetric variables, vital sign data, microbiology results, white blood cell count values, hospital course, antibiotics types ordered, time from diagnosis until antibiotic administration, and details of infection type and treatment were collected.

Statistical Analysis

The discriminatory capability of SIRS, qSOFA, and modified MEW criteria were assessed by calculating sensitivity and specificity for each individual criterion and combinations of multiple criteria. Cases and matched controls with vital signs and laboratory values for the various criteria were included in the analysis. All analyses were performed using SAS software v9.4 (SAS Institute, Care, NC).

Descriptive statistics summarized the type of infection, organism type, and clinical course for sepsis cases and were reported in n (%). Patient demographic, obstetric, and medical comorbidity characteristics were compared for sepsis cases and matched controls. To account for the small sample size and matching of cases and controls, exact conditional logistic regression estimated the association between each potential risk factor and the outcome of sepsis; exact unadjusted odds ratios (OR) and 95% confidence intervals (CI) were calculated.

Patients who developed sepsis prior to the time of delivery were excluded from the risk factor analysis for only the specific variables examining cesarean delivery, preterm delivery, stillbirth, induction of labor, and corticosteroid administration, in order to respect temporality in the analysis of risk factors (e.g., cesarean delivery cannot cause sepsis prior to delivery). However, they were included in all other variables for the risk factor analyses.

The primary objective of evaluation of screening tools and secondary objectives of descriptive clinical characteristics, defining risk factors, and antibiotic timing were determined a priori. During data collection the MEW and qSOFA criteria were published. While it was planned a priori to collect and evaluate vital signs for the identification of sepsis, it was then determined ad hoc to group by screening tools for presentation purposes only. The sample size was a convenience sample with all centers reporting all available data from cases and matched controls during the study period indicated.

Missing Data—If there were missing values for a covariate, it was excluded from the exact logistic regression model to calculate the unadjusted odds ratio for that variable. Missing data regarding the screening tool analysis were handled as follows: 1) for sepsis case

patients missing all vital sign and laboratory information (e.g., not available since the diagnosis was made at an outside hospital and subsequently transferred), the case and four matched controls were excluded from the screening tool analysis (n=8 sepsis cases and 32 controls); 2) if all control patients were not admitted to the hospital at the same time point relative to delivery that the case developed sepsis (e.g., several days prior to or after delivery), the case and four matched controls were excluded from the screening tool analysis (n= 92 controls and 23 sepsis cases); and 3) if vital signs were missing for one or more of the control patients, those particular controls were excluded from the analysis (n=15 controls).

Results

Eighty-two cases of sepsis during hospitalization for delivery and 328 controls were identified. A flowchart of patient selection and controls for the tables is indicated in Figure 1. The cases reported from each center are the following: UMHS (13 cases), BWH (17 cases), IH (18 cases), MGH (5 cases), BH (10 cases), NM (12 cases), and SZMC (7 cases). A description of organisms, type of infection, and severity of infection is presented in Table 2. The most common type of infection associated with the development of maternal sepsis was chorioamnionitis 20 (24.4%). The types of infection designated as “other” contained mostly patients who presented with disseminated infections with an unclear primary source. The most common organism type identified was *Escherichia coli* 12 (14.6%). Out of 82 women with sepsis, 10 (12.2%) died, and 6 (7.7%) were discharged to an extended care facility. Of note, among patients for whom the timing of the administration of antibiotics was available, n=56, [24 (29.3%) exact timing not available], 4 (57.1%) of non-survivors, 16 (32.7%) of survivors, and 20 (35.7%) of all sepsis cases (both survivors and non-survivors) received antibiotics more than one hour after diagnosis. The mortality rate for those who received antibiotics within one hour was 8.3% (95% CI 1.2% to 22.5%). The mortality rate was 20% (5.7% to 43.7%) for the patients who received antibiotics after more than one hour.

Fifty-one cases and 189 controls were included in the screening tool analysis. All screening criteria (SIRS, qSOFA, and modified MEW criteria) and corresponding sensitivities and specificities are listed in Table 3 for each criterion separately and also grouped according to meeting criteria and combinations of criteria met. Two SIRS criteria and two qSOFA criteria are required to meet criteria for sepsis, while one MEW criterion is required to indicate a positive trigger. SIRS criteria had a sensitivity of 0.93 (95% CI 0.81 to 0.99) and a specificity of 0.63 (95% CI 0.55 to 0.71). The qSOFA criteria had a sensitivity of 0.50 (95% CI 0.33 to 0.67) and a specificity of 0.95 (95% CI 0.91 to 0.98). The modified MEW criteria had a sensitivity of 0.82 (95% CI 0.66 to 0.92) and specificity of 0.87 (95% CI 0.81 to 0.91).

Characteristics that were evaluated as potential risk factors for development of sepsis with corresponding unadjusted OR and 95% confidence intervals (CI) are presented in Table 4. Risk factors for sepsis with point estimates of 5 or greater and significant confidence intervals were the following: cesarean delivery-in labor (OR 20.9, 95% CI 5.1 to 128.3), cesarean delivery-not in labor (OR 15.6, 95% CI 4.2 to 87.2), PROM > 24 hours prior to labor (OR 8.9, 95% CI 2.5 to 39.4), stillbirth (OR 15.4, 95% CI 2.3 to infinity), preterm delivery (OR 6.1, 95% CI 2.4 to 16.8), retained products of conception (OR 12.9, 95% CI

2.4 to 128.1), multiple gestation (OR 5.7, 95% CI 1.8 to 19.5), congestive heart failure (OR 9.7, 95% CI 1.2 to infinity), chronic renal disease (OR 9.7, 95% CI 1.2 to infinity), and chronic liver disease (OR 15.4, 95% CI 2.3 to infinity).

Discussion

In our retrospective cohort of pregnant or recently postpartum women hospitalized for delivery, 59% of sepsis cases were caused by chorioamnionitis, endometritis, and pneumonia. *Escherichia coli,* other gram negative rods, and Group A streptococcus were the most common pathogens. We observed notable differences in the sensitivity and specificity of the three most commonly used screening tools for impending sepsis (i.e., SIRS, qSOFA, and MEW criteria) in this population.

Few screening tools for sepsis have been applied to the pregnant and immediately postpartum periods, and comparisons between available tools are lacking. A novel aspect of this report is that notable differences in the sensitivity and specificity of sepsis screening tools in a multicenter parturient population were observed, with the highest to lowest sensitivity being SIRS, MEW, and qSOFA criteria, and the highest to lowest specificity being qSOFA, MEW, and SIRS. This is similar to the findings of a recent meta-analysis evaluating the sensitivity and specificity of SIRS and qSOFA in a general population of sepsis patients. That study reported SIRS as superior for sensitivity and qSOFA as superior for specificity.[12] The Sepsis in Obstetrics Score is not a screening tool for sepsis in all pregnant women, rather it is a scoring system to predict the need for ICU admission in patients with a known or suspected infection. Therefore, it was not assessed in this study as we limited our analyses specifically to screening tools for sepsis.[13]

Our study provides further insight into the causes (i.e. chorioamnionitis, endometritis and pneumonia) and specific organisms commonly associated with sepsis in pregnant women, [2,14] and highlighted the importance of initiating early therapy. The Surviving Sepsis Campaign recommends administration of an appropriate broad-spectrum antibiotic therapy within the first hour of diagnosis[15], something that was not achieved in 35.7% of our sepsis cases; in these cases, mortality was 20% compared with 8.3% for those receiving antibiotics within one hour of diagnosis. With each hour of antibiotic therapy delay in a general population with sepsis, mortality increases by 7.6%.[16] Our data suggest a similar pattern occurs in pregnancy with increased mortality when antibiotics are delayed more than one hour. Strategies to encourage early antibiotic treatment include placing broad spectrum antibiotics in automated medication dispensing systems on labor and delivery (avoiding pharmacy delays), requiring providers to close the loop of communication that prioritizes antibiotic administration (by triaging multiple orders with the nursing staff), ensuring early and adequate intravenous access, and administering antibiotics immediately while awaiting transfer to another part of the hospital (many patients did not receive antibiotics until they arrived in the ICU despite orders written several hours prior).

The strengths of this study are the detailed information obtained from chart review including vital signs, timing of antibiotic administration, and temporal relation between sepsis and risk factors (allowing the evaluation of risk factors without potential bias due to reverse

causality). This study also includes data from seven large academic centers with differing practice patterns and patient populations leading to the generalizability of the results.

Because sepsis during pregnancy and the peripartum period is rare, our data are limited in statistical power to define the significance of some potential risk factors for sepsis. We were unable to compute a multivariable logistic regression model due to the limited sample size. Sepsis was defined using the operant definition at the time the patients were hospitalized. Verifying sepsis diagnosis using sepsis-related SOFA scoring at the time of diagnosis would have been difficult because many criteria are not routinely documented in pregnant women (bilirubin level, PaO2, specific Glasgow coma scores) and creatinine levels do not correlate to the scoring system since they are much lower during pregnancy at baseline. In addition, for the purposes of this study, urine output and SpO_2 values were not collected; however these variables may be abnormal in septic patients and could enhance the sensitivity of the MEW criteria. There were also a substantial number of patients excluded from the screening tool analysis because it was essential to have both controls and patients at the same time period in relation to delivery to account for the physiological changes occurring peripartum. If the sepsis cases occurred many days prior or after delivery, it was not always possible to match controls because women with uneventful deliveries are generally discharged quickly. An additional limitation is the frequency with which complete vital sign data were missing in the patients' charts, necessitating exclusion of some patients from the analysis of the performance characteristics of the scoring systems. This finding is consistent with previous reports indicating the often incomplete and infrequent evaluation of vital signs in obstetric patients.[17] Without proper measurement and recording of vital signs, physiological abnormalities are unlikely to be identified in a timely manner; this is an important area for future quality improvement projects. As an example, although respiratory rate has been correlated with outcomes in septic patients, it is very poorly recorded in medical charts.[5,18] Ancillary staff should be educated about the importance of respiratory rate in detecting potentially significant metabolic derangement.

In conclusion, although MEW criteria demonstrated a sensitivity of 82% and a specificity of 87%, if adopted, potentially 18% of patients would not be identified. SIRS criteria demonstrated a sensitivity of 93%, but with a specificity of 63%. SIRS criteria would identify more patients, but at the potential expense of alarm fatigue. The qSOFA criteria, with a sensitivity of 50% could potentially miss 50% of patients with sepsis. Clinical, physiologic, and laboratory features should be more robustly investigated to determine if additional or altered criteria should be employed in this population of patients. Obstetric care units should be encouraged to obtain timely and complete vital sign information for all patients to readily identify patients with sepsis and to facilitate providing prompt antibiotic treatment.

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Conflicts of Interest

BTB is an investigator for grants supported by Lilly, Pfizer, GSK, Pacira, and Baxalta for unrelated projects. BTB also serves as a consultant to Optum, Inc. SE has several patents with Oridion/Medtronic and has received funding for travel from Medtronic, Zoll, Diasorin and Laerdal all for unrelated projects. All other authors declare no disclosures.

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"Key Points" Summary

- **Question:** Which of the screening tools (SIRS, qSOFA, MEW criteria) best identifies impending sepsis in pregnant or recently postpartum women?
- **Findings:** Notable differences were observed in the sensitivity and specificity of sepsis screening tools with the highest to lowest sensitivity being SIRS, MEW, and qSOFA criteria, and the highest to lowest specificity being qSOFA, MEW, and SIRS.
- **Meaning:** An ideal screening tool for maternal sepsis has yet to be identified.

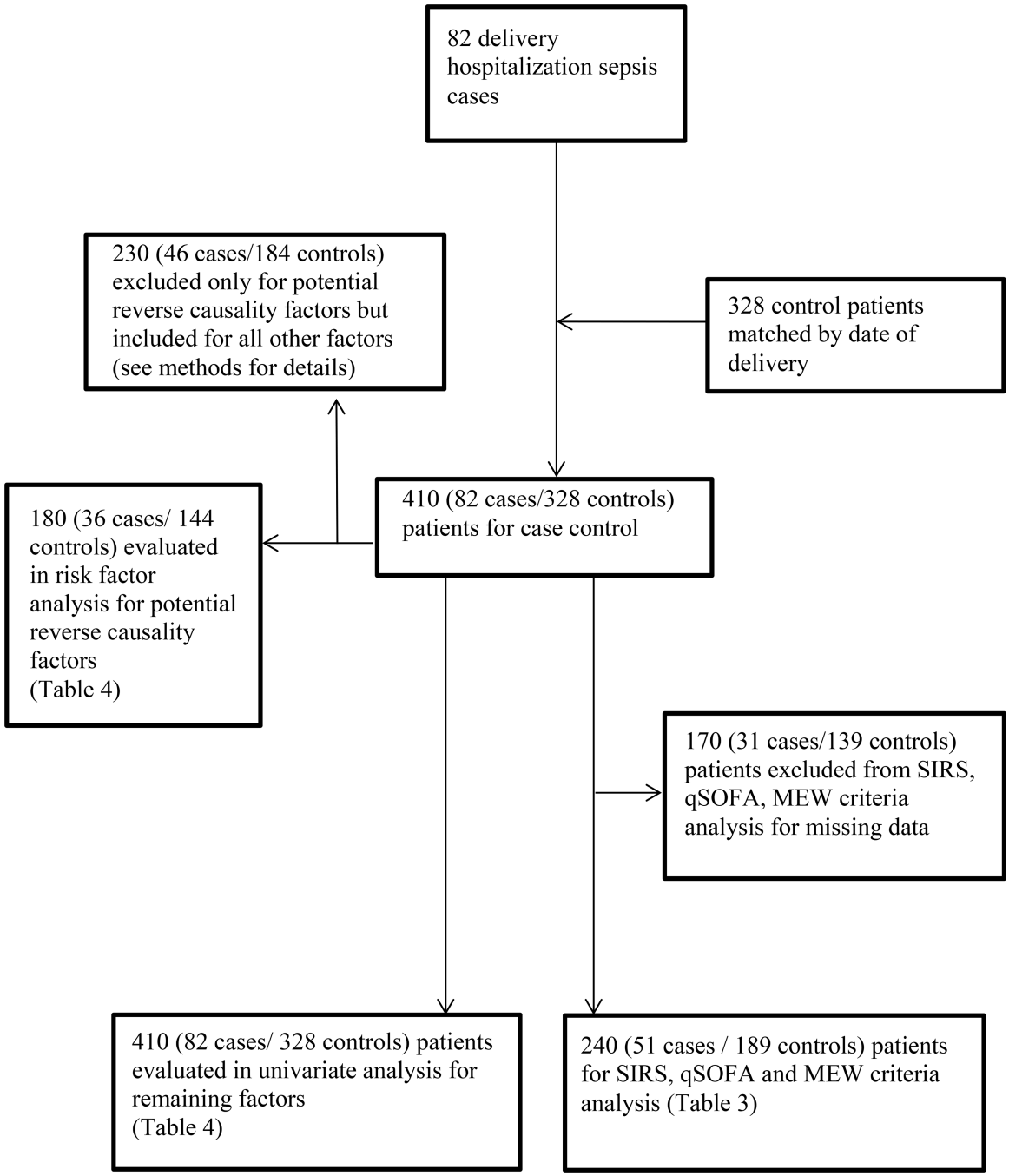

Figure 1.
Flowchart for patient selection

Table 1.

Definitions of Systemic Inflammatory Response Syndrome (SIRS) criteria, quick Sequential [Sepsis-related] Organ Failure Assessment (qSOFA) criteria, and Maternal Early Warning (MEW) criteria

Term	Definition
SIRS[a]	Two or more of the following: Temperature > 38°C or < 36°C Heart rate > 90 beats per minute Respiratory rate > 20 breaths per minute or $PaCO_2$ < 32 mm Hg White blood cell count < 4×10^9/L or > 12×10^9/L
qSOFA[b]	Two or more of the following: Respiratory rate ≥ 22 breaths per minute Altered mentation Systolic blood pressure ≤ 100 mm Hg
MEW[c]	One or more of the following: Systolic blood pressure < 90 or > 160 mm Hg Diastolic blood pressure > 100 mm Hg Heart rate < 50 or > 120 beats per minute Respiratory rate < 10 or > 30 per minute Oxygen saturation on room air, at sea level < 95% Oliguria, <35 mL/hour for ≥ 2 hours Maternal agitation, confusion, or unresponsiveness; Patient with preeclampsia reporting a non-remitting headache or shortness of breath

[a]Bone RC, Balk RA, Cerra FB, et al: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest* 1992 Jun; 101(6):1644–1655.

[b]Singer M, Deutschman CS, Seymour CW, et al: The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016 Feb 23; 315(8):801–810.

[c]Mhyre JM, D'Oria R, Hameed AB, et al: The maternal early warning criteria: a proposal from the national partnership for maternal safety. *Obstet Gynecol* 2014 Oct; 124(4):782–786.

Table 2.

Clinical characteristics of women with sepsis during the delivery hospitalization

Clinical Characteristic	Delivery Hospitalization Cases N=82
	n(%)
Type of Infection[a]	
Chorioamnionitis	20 (24.4)
Endometritis	19 (23.2)
Pneumonia	9 (11.0)
Wound infection	7 (8.5)
Genitourinary infection	5 (6.1)
Endocarditis	3 (3.7)
Pyelonephritis	3 (3.7)
Meningitis	2 (2.4)
Central line associated blood stream infection	2 (2.4)
Mastitis	0
Other	17 (20.7)
Unknown	6 (7.3)
Organism Identified	
Escherichia coli	12 (14.6)
Group A streptococcus	6 (7.3)
Other streptococcus	2 (2.4)
Staphylococcus	5 (6.1)
Other gram negative rods	8 (9.8)
Multiple organisms	6 (7.3)
Other	6 (7.3)
Unknown	37 (45.1)
Clinical Course	
Died	10 (12.2)
Discharged to an extended care facility[b]	6 (7.7)
Antibiotic timing not available	24 (29.3)
Antibiotic administration more than one hour after order	20 (35.7)
Survivors[c]	16 (32.7)
Non-survivors[d]	4 (57.1)
Intensive care unit admission	71 (86.6)
Mechanical ventilation	54 (65.9)
Hemodialysis	9 (11.0)
Neurological changes[b]	32 (44.4)
Vasopressor/inotropic support	38 (46.3)
Enteral feeding	20 (24.4)

Clinical Characteristic	Delivery Hospitalization Cases N=82
	n(%)
Timing of sepsis in relation to delivery	
Antepartum	14 (17.1)
Intrapartum	32 (39.0)
Postpartum	36 (43.9)

[a] More than one type of infection may have been present

[b] Missing values are the following: neurological changes=10, discharged to an extended care facility=4

[c] Survivors (n=49) for which antibiotic timing was available, (n=2) excluded due to already on broad spectrum antibiotics at the time of diagnosis

[d] Non-survivors (n=7) for which antibiotic timing was available

Table 3.

Sensitivity and specificity of criteria for sepsis

Criteria	N (%) Sepsis Cases	N (%) Controls	Sensitivity (95% CI)	Specificity (95% CI)
SIRS[a]				
WBC< 4 or >12	38 (74.5)	62 (41.1)	0.75 (0.60, 0.86)	0.59 (0.51, 0.67)
HR>90	49 (96.1)	104 (55.3)	0.96 (0.87, 1.00)	0.45 (0.37, 0.52)
RR>20	28 (62.2)	18 (9.9)	0.62 (0.47, 0.76)	0.90 (0.85, 0.94)
T<36°C or T>38°C	33 (68.7)	52 (28.7)	0.69 (0.54, 0.81)	0.71 (0.64, 0.78)
[T>38 or <36] and [HR>90]	33 (68.8)	33 (18.2)	0.69 (0.54, 0.81)	0.82 (0.75, 0.87)
[T>38 or <36] and [RR>20]	23 (53.5)	7 (4.0)	0.53 (0.38, 0.69)	0.96 (0.92, 0.98)
[T>38 or <36] and [WBC>12 or<4]	27 (56.3)	14 (9.8)	0.56 (0.41, 0.71)	0.90 (0.84, 0.95)
[HR>90] and [RR>20]	28 (62.2)	15 (8.3)	0.62 (0.47, 0.76)	0.92 (0.87, 0.95)
[HR>90] and [WBC>12 or <4]	36 (70.6)	32 (21.3)	0.71 (0.56, 0.83)	0.79 (0.71, 0.85)
[RR>20] and [WBC>12 or <4]	20 (44.4)	6 (4.2)	0.44 (0.30, 0.60)	0.96 (0.92, 0.98)
Any 2 SIRS	40 (93.0)	51 (36.7)	0.93 (0.81, 0.99)	0.63 (0.55, 0.71)
qSOFA[a]				
RR≥22	28 (62.2)	17 (9.4)	0.62 (0.47, 0.76)	0.91 (0.85, 0.94)
SBP≤100 mmHg	26 (55.3)	76 (40.4)	0.55 (0.40, 0.70)	0.60 (0.52, 0.67)
Neurological changes	17 (37.8)	0	0.38 (0.24, 0.53)	1.00 (0.98, 1.00)
[RR≥22] and [SBP≤100 mmHg]	14 (33.3)	9 (5.0)	0.33 (0.20, 0.50)	0.95 (0.91, 0.98)
Any 2 qSOFA	19 (50.0)	9 (5.0)	0.50 (0.33, 0.67)	0.95 (0.91, 0.98)
Modified MEW[a]				
SBP< 90 mmHg	17 (36.2)	13 (6.9)	0.36 (0.23, 0.51)	0.93 (0.88, 0.96)
HR>120	30 (58.8)	12 (6.4)	0.59 (0.44, 0.72)	0.94 (0.89, 0.97)
RR>30	14 (31.1)	0	0.31 (0.18, 0.47)	1.00 (0.98, 1.00)
Neurological changes	17 (37.8)	0	0.38 (0.24, 0.53)	1.00 (0.98, 1.00)
Any MEW trigger	31 (81.6)	24 (13.3)	0.82 (0.66, 0.92)	0.87 (0.81, 0.91)

WBC=white blood cell (10^9/L), HR=heart rate (beats per minute), RR= respiratory rate (breaths per minute), T= temperature (°C)

[a]Missing for each variable was the following: WBC< 4 × 10^9/L or >12 × 10^9/L =38, HR>90=1, RR>20=14, T<36°C or T>38°C =11, T<36°C or T>38°C and HR>90 =11, T<36°C or T>38°C and RR>20=20, T<36°C or T>38°C and WBC< 4 × 10^9/L or >12 × 10^9/L =49, HR>90 and RR>20=15, HR>90 and WBC< 4 × 10^9/L or >12 × 10^9/L =39, RR>20 and WBC< 4 × 10^9/L or >12 × 10^9/L =52, RR≥22=14, SBP<100 mmHg=5, Neurological changes=6, RR≥22 and SBP≤100 mmHg=18, SBP< 90 mmHg =5, HR>120=1, RR>30=14, Any modified MEW trigger=22, Any 2 SIRS=58, Any 2 qSOFA=22

Table 4.

Demographic, obstetric, and maternal risk factors for sepsis

	Characteristic	Delivery Hospitalization Cases n=82 (%)	Controls n=328 (%)	Unadjusted Odds Ratio 95% CI
Patient Demographics	Age			
	≤24 years old	17 (20.7)	65 (19.8)	Reference
	25 to 34 years old	48 (58.5)	200 (61.0)	0.9 (0.5, 1.8)
	≥35 years old	17 (20.7)	63 (19.2)	1.0 (0.4, 2.3)
	Race/Ethnicity[a]			
	White (non-Hispanic)	41 (52.6)	230 (74.2)	Reference
	African American (non-Hispanic)	16 (20.5)	28 (9.0)	4.0 (1.7, 11.3)
	Native American /Alaska Native	1 (1.3)	0 (0)	4.0 (0.2, Infinity)
	Asian	9 (11.5)	15 (4.8)	4.0 (1.4, 11.5)
	Native Hawaiian /Pacific Islander	2 (2.6)	1 (0.3)	9.3 (0.5, 563.4)
	Other	3 (3.8)	2 (0.6)	6.8 (0.8, 82.3)
	Hispanic	6 (7.7)	34 (11.0)	0.8 (0.2, 2.5)
Obstetric Variables	Nulliparous[a]	45 (55.6)	131 (40.3)	1.8 (1.1, 3.1)
	Type of delivery[b]			
	Spontaneous Vaginal	8 (22.2)	102 (70.8)	Reference
	Operative Vaginal	0 (0)	9 (6.3)	1.4 (0, 8.7)
	Cesarean delivery (in labor)	14 (38.9)	16 (11.1)	20.9 (5.1, 128.3)
	Cesarean delivery (not in labor)	14 (38.9)	17 (11.8)	15.6 (4.2, 87.2)
	Cerclage[a]			
	None	77 (95.1)	323 (98.8)	Reference
	Rescue	1 (1.2)	1 (0.3)	4.0 (0.1, 314)
	Prophylactic	3 (3.7)	3 (0.9)	4.0 (0.5, 29.9)
	PROM > 24 hours prior to labor[a]	10 (12.7)	6 (1.8)	8.9 (2.5, 39.4)
	Stillbirth[b]	3 (8.3)	0 (0)	15.4 (2.3, Infinity)
	Preterm delivery (<37 weeks)[b]	16 (44.4)	16 (11.1)	6.1 (2.4, 16.8)
	Retained products of conception[a]	7 (8.5)	3 (0.9)	12.9 (2.4, 128.1)
	Steroids during pregnancy[a,b]			
	None	26 (74.3)	134 (93.1)	Reference
	Maternal indication	1 (2.9)	2 (1.4)	2.4 (0, 215.6)
	Fetal indication	8 (22.9)	8 (5.6)	4.7 (1.4, 16.7)
	Induction of labor[a,b]	7 (24.1)	45 (33.6)	0.6 (0.2, 1.9)
	Multiple gestation	9 (11.0)	7 (2.1)	5.7 (1.8, 19.5)

	Characteristic	Delivery Hospitalization Cases n=82 (%)	Controls n=328 (%)	Unadjusted Odds Ratio 95% CI
	GBS positive[a]	13 (33.3)	47 (17.7)	2.3 (1.0, 5.2)
Maternal comorbidities	BMI≥40[a]	14 (19.7)	20 (7.4)	3.7 (1.4, 9.6)
	Congestive heart failure[a]	2 (2.5)	0 (0)	9.7 (1.2, Infinity)
	Chronic renal disease[a]	2 (2.5)	0 (0)	9.7 (1.2, Infinity)
	Chronic liver disease[a]	3 (3.7)	0 (0)	15.4 (2.3, Infinity)
	Diabetes Mellitus			
	Type 1	0 (0)	1 (0.3)	4.0 (0, 76.0)
	Type 2	2 (2.4)	3 (0.9)	2.7 (0.2, 23.3)
	GDM	7 (8.5)	11 (3.4)	3.1 (0.9, 10.8)
	None	73 (89.0)	313 (95.4)	Reference
	Malignancy	1 (1.2)	0 (0)	4.0 (0.2, Infinity)
	Smoking	15 (18.3)	26 (7.9)	2.7 (1.2, 5.8)

PROM= Premature rupture of membranes, GBS=Group B streptococcus, BMI=Body mass index, GDM=gestational diabetes mellitus

[a]Missing for each variable was the following: Race/ethnicity=22, Nulliparous=4, cerclage=2, PROM>24 hours prior to labor=4, Retained products of conception=1, Steroids during pregnancy=1, Induction of labor=17, GBS positive=105, BMI≥40kg/m^2=68, Congestive heart failure=7, chronic renal disease =6, chronic liver disease=6

[b]Data for patients with sepsis prior to delivery were excluded for specific variables of the analysis due to potential for reverse causality (46 sepsis cases, 184 controls)