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Maternal Deaths Due to Sepsis in the State of Michigan, 1999–2006

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Abstract

Objective—To identify maternal deaths due to sepsis in the state of Michigan, review the events leading to diagnosis, and evaluate treatment to identify areas for improvement.

Methods—A case series was collected for maternal deaths due to sepsis from a cohort of maternal deaths in the state of Michigan. The study period was 1999–2006 and included deaths during pregnancy and up to 42 days postpartum. Cases were identified using Maternal Mortality Surveillance records from the Michigan Department of Community Health. Each case was reviewed by all authors.

Results—Maternal sepsis was the cause of death in 14.6% (22/151) of pregnancy-related deaths. Of 22 deaths, 13 women presented to the hospital with sepsis, two developed sepsis during hospitalization, and seven developed sepsis at home without admission to the hospital for care. Review of available hospital records (n=15) revealed delays in initial appropriate antibiotic treatment occurred in 73% (11/15) of patients. Delay in escalation of care also occurred and was identified in 53% (8/15) of patients.

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Conclusion—Common elements in these deaths illustrate three key delays that may have contributed to the deaths: in recognition of sepsis, in administration of appropriate antibiotics, and in escalation of care.

Introduction

Sepsis remains an important cause of maternal mortality. Deaths due to maternal sepsis increased in the United States from 1998 to 2008.(1) The Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the UK (MBRRACE-UK) report for 2009–2012 indicated almost 25% of all maternal deaths were due to sepsis.(2) The diagnosis of sepsis requires a source of infection and that the criteria for the Systemic Inflammatory Response Syndrome(SIRS) be met.(3) The diagnosis of sepsis in pregnancy is challenging because many healthy pregnant women will manifest some component of the SIRS criteria (except temperature) in the absence of infection. .(4)

Little is known about pregnant and postpartum women who died of maternal sepsis in the United States. Although maternal deaths due to sepsis are rare, they are potentially preventable with early recognition and treatment: mortality in severe sepsis and septic shock has been found to increase 7.6% for each hour delay in appropriate antibiotic treatment.(5) The aims of this study are to identify maternal deaths due to sepsis in the state of Michigan from 1999 to 2006, review the events leading to diagnosis, and evaluate treatment to identify areas for improvement.

Materials and Methods

The Institutional Review Board for the Michigan Department of Community Health approved this study. The Institutional Review Boards of William Beaumont Health System and the University of Michigan Health System declared this study not regulated since all subjects are deceased.

In this case series from a cohort of maternal deaths, all maternal deaths reported in the state of Michigan 1999–2006 during pregnancy and up to one year postpartum were identified with Maternal Mortality Surveillance records from the Michigan Department of Community Health. This study period was chosen based on availability of records from the Michigan Department of Community Health. The definition of maternal death due to sepsis during pregnancy and up to 42 days postpartum was the presence of any of the following: 1) sepsis listed on the death certificate as the cause of death; 2) determination that sepsis was the cause of death by consensus of the Maternal Mortality Medical Surveillance Committee; or 3) identification of a specific source of infection leading to organ failure, consistent with the accepted definition of severe sepsis by the American College of Chest Physicians and Society of Critical Care Medicine.(3) “Maternal sepsis contributing deaths” were defined as deaths from another cause, but with sepsis as a contributing factor. After identification, data were collected by an obstetric anesthesiologist (MB) and double checked by an obstetrician (FA). Data collected for each chart included demographic information, details of presentation upon admission, unresolved issues from delivery hospitalization if applicable, antibiotic selection throughout hospitalization, culture results, vital signs at presentation,

vital signs at time of escalation of care, laboratory results, case narrative, contributing causes leading to death, cause(s) of death, and findings from the Michigan Maternal Mortality Surveillance review process. All cases were reviewed by all authors and disagreements were resolved by discussion. De-identified record summaries were provided to an infectious disease specialist (KR) for determination of whether initial and eventual antibiotic choices were appropriate based on the clinical scenario and recommended guidelines the year the case occurred. For example, ampicillin/sulbactam was an appropriate choice for an intra-abdominal process in the early 2000s; however, with the emergence of resistance among organisms, especially *Escherichia coli*, it is currently not recommended.(6) Delay of care was defined as 1) not providing timely appropriate antibiotics (within 1 hour of evidence of sepsis); or 2) failure to escalate care to an ICU or tertiary care center after it appeared by chart review that the patient was critically ill based on meeting objective parameters for admission to an intensive care unit as defined by the ACOG Practice Bulletin on Critical Care in Pregnancy(7).

Michigan Maternal Mortality Surveillance identifies maternal deaths in the following manner: voluntary reporting of maternal deaths (since inception in 1950), screening death certificates for causes of death specific to pregnancy (starting in 1950), matching death certificates of women of reproductive age (10 to 45 years old) with live birth certificates (1990-) and fetal death certificates (2004-) of the current year and previous year, and checking a box on the death certificate indicating the patient was either pregnant or pregnant within one year at the time of death (2004-).(8) The new changes in 2004 brought an increase in reporting of maternal deaths. The Michigan Department of Community Health uses the American College of Obstetricians and Gynecologists (the College)/Centers for Disease Control (CDC) definitions to classify maternal deaths. Pregnancy-associated deaths are defined as the death of a woman while pregnant or within one year of pregnancy, irrespective of cause. Pregnancy-related deaths are defined as the death of a woman while pregnant or within one year of termination of pregnancy, irrespective of the duration and site of the pregnancy, from any cause related to or aggravated by her pregnancy or its management, but not from accidental or incidental causes.(9) Every pregnancy-associated death in the state of Michigan is reviewed by an expert review committee, and a final cause of death and a determination about pregnancy relatedness is made for each case.

All results were reported as proportions. If data for a particular element was missing, it was reported as indeterminate when evaluating a clinical situation and was excluded from the numerator and denominator for categorical data.

Results

From 1999–2006 there were 1,047,857 live births in the State of Michigan and 558 pregnancy associated deaths (53.3 deaths/100,000 live births) . Of these, 151 (14.4 deaths/100,000 live births) were pregnancy related deaths (10). (In email personal communication to Sarah Lyon-Callo, MA, MS from the MDCH on June 11, 2015 the previously unpublished maternal mortality ratios for 2005 and 2006 were confirmed.) Maternal sepsis was the cause of death in 4% (22/558) of pregnancy-associated deaths reviewed during the time period and 15% (22/151) of all pregnancy-related deaths. Sepsis contributing deaths

comprised another 1% (8/558) of pregnancy associated deaths for a total of 5% (30/558) of pregnancy associated deaths and 20% (30/151) pregnancy related deaths. No cases were excluded due to differences in interpretation. The rate of maternal deaths due to sepsis was 2.1/100,000 live births., and the rate of maternal death due to sepsis and sepsis-contributing deaths was 2.9/100,000 live births. There was an increase in maternal deaths due to sepsis at home starting in 2004 with the addition of the pregnancy check box on the death certificate.

The mean maternal age of the 22 women who died from sepsis was 27 years range of 13 to 40 years of age (Table 1). The clinical details of each case are presented in the Appendix, available online at <http://links.lww.com/xxx>.

Of the women presenting to the hospital with sepsis in Table 2, 75% (9/12) demonstrated one or more of the following vital sign derangements at presentation: HR>120, RR>30, SBP<90 mmHg, SpO2 <95% on room air (Maternal Early Warning Criteria or MEWC).(11) Only 18% (2/11) of septic women were febrile on presentation and 25% (3/12) never developed a fever during hospitalization. The clinical details of each case are presented in the Appendix, available online at <http://links.lww.com/xxx>.

Delays of care were found in the majority of cases. Initial antibiotics with inadequate coverage based on the clinical situation were identified in 11/15 (73%) of patients who received hospital care for sepsis; in 2/15 (13%) cases whether appropriate antibiotics were used was indeterminate. Only 2/15 (13%) patients received appropriate initial antibiotics. Once infectious disease consultation or critical care consultation was obtained and antibiotics were changed, in 67% (10/15) subsequent antibiotic care was appropriate for the clinical situation, 20% (3/15) of women did not live long enough for subsequent therapy, and in 13% (2/15) of cases the appropriateness of therapy could not be determined. Of patients who presented to the hospital for care, delay of escalation of care was found in 53% (8/15), no delay was found in 33% (5/15), and whether timing was delayed could not be determined in 13% (2/15). Seven patients died at home or were dead on arrival, and it could not be determined whether they sought medical care prior to death.

The most common organism was *Streptococcus pyogenes* in 29% (4/14) of women with an identified organism.

Discussion

Common elements in the maternal deaths due to sepsis illustrate three key delays that may have contributed to the deaths: in recognition of sepsis, in administration of appropriate antibiotics, and in escalation of care.

The majority of women who died of maternal sepsis were afebrile on presentation and did not develop a fever for hours or days, and 25% (3/12) did not develop a fever at all. Although a temperature of less than 36°C or greater than 38°C is one of the criteria for systemic inflammatory response syndrome (SIRS), it is not required for the diagnosis of sepsis. Sepsis should be considered in critically ill women regardless of temperature. Although MEWC was not a recommendation at the time period for which the data were collected, it is reassuring that 75% of women had one or more criteria for MEWC upon

presentation and would have triggered the system had it been in place. The National Partnership for Maternal Safety recommends that all women who meet any of the MEWC receive prompt bedside evaluation by a physician or other clinician with the ability to activate resources in order to initiate emergency diagnostic and therapeutic interventions as needed. MEWC screens for multiple types of possible maternal morbidity through a simple bedside assessment.(11)

Delay in diagnosis may have been due to incomplete data available for decision making. Many records demonstrated incomplete assessments. Pulse oximetry was the most common missing assessment. The majority of women with a pulse oximetry reading documented at admission would have triggered MEWC. Record reviews suggest that respiratory rate measurements may have been inaccurate. Of 11 women with respiratory rate recorded, eight had measurements of 18, 20, or 24. Upon review, the pH and lactate levels taken shortly after decompensation and respiratory rate documentation depicted a state of metabolic acidosis so severe that a normal respiratory rate would not likely have been possible. Although respiratory rate is poorly documented in clinical settings, it has been shown to correlate with severity of sepsis in the general population.(12)

For cases with sufficient records for a determination, the majority were found to have delays in care. MBRACE-UK recommends early consultation with an infectious disease specialist in cases of maternal sepsis.(2) Each hour delay of appropriate antibiotics in patients with severe sepsis or septic shock is associated with an increase in mortality of 7.6%.(5) For treatment of postpartum endometritis, a combination of clindamycin and gentamycin with the addition of ampicillin in refractory cases is recommended by the College and is the most common regimen used.(13) A recent meta-analysis showed more treatment failures occurred with the use of a penicillin and gentamycin compared with gentamycin and clindamycin.(14) Clindamycin was underutilized in this population, and was not given to any patient who died of Group A Streptococcal infection. Clindamycin, a protein synthesis inhibitor shown to inhibit toxin production, is beneficial because the efficacy is not decreased by the stage of growth, and has been shown to decrease mortality in Group A Streptococcal infection.(15–17) While our study highlights delay of appropriate antibiotics during 1999 to 2006, we were unable to determine whether there was improvement in the timing and antibiotic selection after the publication of Surviving Sepsis Campaign Guidelines over time.(18) However, in this case series antibiotic selection was not improved in 2004, 2005, or 2006 after publication of the first set of guidelines. It is unlikely that more current data would have shown changes in clinical management; delay in recognition led to delay in treatment for the majority of cases.

The limitations of this study include that it is a case series of women rather than a study including controls. Although our cases are limited to 22 women who died of sepsis, given the rarity of maternal deaths due to sepsis, this study represents a large number of maternal deaths due to sepsis in the United States. It is possible that there are cases that may have not been identified during the years of 1999 through 2006 because the state of Michigan does not have mandatory reporting of maternal deaths. Our records were also limited to the records where the death occurred. Prenatal records, delivery records, and records from transferring hospitals were unavailable in some cases. Due to inadequate granularity of the

data available, we were unable to fully assess whether early goal directed therapy or Surviving Sepsis Campaign Guidelines were followed to provide more specific areas for improvement.(19,20)

Although maternal deaths due to sepsis are rare, early diagnosis and treatment could potentially make them preventable. Observations from this study lead to the following suggestions: 1) Consider maternal sepsis in critically ill women even in absence of a fever; 2) Administer early appropriate antibiotic therapy and utilize consultation (maternal fetal medicine, infectious disease, critical care) early if there is marked derangement in vital signs or an inadequate response; 3) Vital sign derangement should be investigated, closely monitored, and if severe should prompt escalation of care; 4) Vital signs should be accurately taken at appropriate intervals consistent with the maternal condition. If further studies reveal a similar rate of maternal deaths at home due to sepsis and postpartum deaths after discharge, there may be a role for improving patient education concerning when to seek medical attention, timing of postpartum visits, and utilization of home visits.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Bauer ME, Bateman BT, Bauer ST, Shanks AM, Mhyre JM. Maternal sepsis mortality and morbidity during hospitalization for delivery: temporal trends and independent associations for severe sepsis. *Anesth Analg*. 2013; 117(4):944–950. [PubMed: 24023020]
2. Knight, M.; Kenyon, S.; Brocklehurst, P.; Neilson, J.; Shakespeare, J.; Kurinczuk, JJ. Saving Lives, Improving Mothers' Care - Lessons learned to inform future maternity care from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2009–2012. Oxford: National Perinatal Epidemiology Unit, University of Oxford; 2014.
3. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, 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; 101(6):1644–1655. [PubMed: 1303622]
4. Bauer ME, Bauer ST, Rajala B, MacEachern MP, Polley LS, Childers D, et al. Maternal physiologic parameters in relationship to systemic inflammatory response syndrome criteria: a systematic review and meta-analysis. *Obstet Gynecol*. 2014; 124(3):535–541. [PubMed: 25162253]
5. Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med*. 2006; 34(6):1589–1596. [PubMed: 16625125]
6. Paterson DL, Rossi F, Baquero F, Hsueh PR, Woods GL, Satishchandran V, et al. In vitro susceptibilities of aerobic and facultative Gram-negative bacilli isolated from patients with intra-

- abdominal infections worldwide: the 2003 Study for Monitoring Antimicrobial Resistance Trends (SMART). *J Antimicrob Chemother.* 2005; 55(6):965–973. [PubMed: 15849262]
7. ACOG Practice Bulletin No. 100: Critical care in pregnancy. *Obstet Gynecol.* 2009 Feb; 113(2 Pt 1):443–450. [PubMed: 19155919]
8. Mhyre JM, Riesner MN, Polley LS, Naughton NN. A series of anesthesia-related maternal deaths in Michigan, 1985–2003. *Anesthesiology.* 2007; 106(6):1096–1104. [PubMed: 17525583]
9. Berg, CDI.; Atrash, H.; Zane, S.; Bartlett, L., editors. Strategies to reduce pregnancy-related deaths: from identification and review to action. Atlanta: Centers for Disease Control and Prevention; 2001.
10. Michigan Maternal Mortality Surveillance (MMMS) 1999–2004 Report. 2006. Available at: http://www.michigan.gov/documents/mdch/MDCH_MCH_Epi_VG_MMMSReport2006_220171_7.pdf. Retrieved June 3, 2015
11. Mhyre JM, D'Oria R, Hameed AB, Lappen JR, Holley SL, Hunter SK, et al. The maternal early warning criteria: a proposal from the national partnership for maternal safety. *Obstet Gynecol.* 2014; 124(4):782–786. [PubMed: 25198266]
12. Kenzaka T, Okayama M, Kuroki S, Fukui M, Yahata S, Hayashi H, et al. Importance of vital signs to the early diagnosis and severity of sepsis: association between vital signs and sequential organ failure assessment score in patients with sepsis. *Intern Med.* 2012; 51(8):871–876. [PubMed: 22504241]
13. American Academy of Pediatrics, The American College of Obstetricians and Gynecologists. Guidelines for Perinatal Care. 7th ed. Washington, DC: The American College of Obstetricians and Gynecologists; 2012.
14. Mackeen AD, Packard RE, Ota E, Speer L. Antibiotic regimens for postpartum endometritis. *Cochrane Database Syst Rev.* 2015; 2:CD001067. [PubMed: 25922861]
15. Mulla ZD, Leaverton PE, Wiersma ST. Invasive group A streptococcal infections in Florida. *South Med J.* 2003; 96(10):968–973. [PubMed: 14570340]
16. Carapetis JR, Jacoby P, Carville K, Ang SJ, Curtis N, Andrews R. Effectiveness of clindamycin and intravenous immunoglobulin, and risk of disease in contacts, in invasive group a streptococcal infections. *Clin Infect Dis.* 2014; 59(3):358–365. [PubMed: 24785239]
17. Stevens DL, Bisno AL, Chambers HF, Dellinger EP, Goldstein EJ, Gorbach SL, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2014; 59(2):e10–e52. [PubMed: 24973422]
18. Dellinger RP, Carlet JM, Masur H, Gerlach H, Calandra T, Cohen J, et al. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. *Crit Care Med.* 2004; 32(3):858–873. [PubMed: 15090974]
19. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med.* 2001; 345(19):1368–1377. [PubMed: 11794169]
20. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med.* 2013; 41(2):580–637. [PubMed: 23353941]

Table 1

Maternal characteristics

Characteristic	Frequency n (%)
Age	
24 years of age	9/22 (41%)
25 to 34 years of age	10/22 (45%)
35 years of age	3/22 (14%)
Race/ethnicity	
Caucasian	8/22 (36%)
African American	12/22 (55%)
Other race/ethnic group	2/22 (9%)
Insurance	
Private	9/22 (41%)
Public	8/22 (36%)
Unavailable	5/22 (23%)
Body mass index >30 kg/m ²	10/22 (45%)
Stage of pregnancy	
Antepartum	7/22 (32%)
Hospitalization for Delivery	2/22 (9%)
Postpartum	13/22 (59%)
Presentation	
Presented with sepsis	12/22 (55%)
Died during hospital transfer	1/22 (5%)
Developed during hospitalization	2/22 (9%)
Home death	7/22 (32%)
MEWC*	
One or more triggering signs at presentation	9/12 (75%)
Heart rate>120 bpm	5/11 (45%)
Respiratory rate>30	3/11 (27%)
Systolic blood pressure<90mmHg	2/11 (18%)
Pulse oximetry less than 95%	5/9 (56%)
Temperature at presentation	
Normal range	8/11 (73%)
Temperature>38°C	2/11(18%)
Temperature<36°C	1/11(9%)
Never developed a fever during hospitalization	3/12(25%)
Coagulation dysfunction (day of presentation or day of development of sepsis in hospitalized patients)*	
INR 1.4	8/12 (67%)
Platelet count<150 ×10 ⁹	6/14 (43%)

Characteristic	Frequency n (%)
White blood cell count $<4 \times 10^9$	5/14 (36%)
Type of infection	
Pneumonia	6/22 (27%)
Peritonitis	5/22 (23%)
Intrauterine infection	4/22 (18%)
Endocarditis	1/22 (5%)
Central line associated blood stream infection	1/22 (5%)
Bacteremia	1/22 (5%)
Unspecified	4/22 (18%)

* Denominators differ based on missing data

Maternal Early Warning Criteria are the following: Systolic blood pressure <90 or >160 mmHg, Diastolic blood pressure >100 mm Hg, Heart rate <50 or >120 beats per minute, Respiratory rate <10 or >30 breaths per minute, Oxygen saturation on room air, at sea level, $<95\%$, Oliguria <35 ml/hr for 2 hours, Maternal agitation, confusion, or unresponsiveness; Patient with preeclampsia reporting a non-remitting headache or shortness of breath (11)

Specific Maternal Early Warning Criteria and Temperature Findings of Patients Who Presented to the Hospital with Sepsis

Table 2

Patient number	MEWC triggered	Heart rate>120 BPM	Respiratory rate>30bpm	Systolic blood pressure<90mmHg	SpO2>95%	Temperature>38°C or<36°C (not part of MEWC)
1	+	n/a	n/a	n/a	+	n/a
2	+	+	-	-	n/a	-
3	+	-	+	-	n/a	-
4	+	-	-	+	+	+
5	+	+	-	+	-	-
6	-	-	-	-	-	-
7	-	-	-	-	n/a	+
8	+	+	+	-	+	-
9	+	+	-	-	+	+
10	-	-	-	-	-	-
11	+	+	+	-	-	-
12	+	-	-	-	+	-

* n/a=not available

Maternal Early Warning Criteria are the following: Systolic blood pressure <90 or >160 mmHg, Diastolic blood pressure <10 or >30 breaths per minute, Oxygen saturation on room air, at sea level, <95%, Oliguria <35 ml/hr for 2 hours, Maternal agitation, confusion, or unresponsiveness; Patient with preeclampsia reporting a non-remitting headache or shortness of breath (11)