Sex Differences in Sepsis

Date created: August 27, 2013
Author: Traci Madsen, MD

Overview

Sex and gender affect the epidemiology, treatment, and outcome of sepsis. This case illustrates some of the known sex differences in sepsis and postulates the influence sex and gender may have on the presentation of patients with sepsis

HPI

EL is a 44-year-old woman with a history of paraplegia, neurogenic bladder, and nephrolithiasis who presented to the Emergency Department (ED) with abdominal pain, back pain, and dysuria that began the night prior to presentation. She reported seven episodes of vomiting and chills but no objective fevers. Her review of systems was negative for chest pain, shortness of breath, and changes in her bowel movements. EL reported similar symptoms with kidney infections in the past.

Medical History

- Transverse myelitis
- Paraplegia
- Neurogenic bladder
- Nephrolithiasis
- Uterine fibroids
- Lupus

Social History

Negative for tobacco and alcohol use

Prescribed Medications

- Plaquenil
- Methotrexate
- Fosamax
- Pentoxifylline
- Acetaminophen
- Prednisone
- Baclofen
- Lasix
- Detrol

ED Course

Following her initial assessment, EL waited in triage for approximately 2 hours. While waiting in triage she received one hydrocodone/acetaminophen pill for pain. She was initially tachycardic

at 118 but normotensive with a blood pressure of 148/90. She was afebrile with a temperature of 99.5. The rest of her initial vitals were unremarkable. EL was then triaged to a treatment room, where she was alert, awake, and initially appeared comfortable. On exam by the physician, she was found to be moderately tender in the lower abdomen bilaterally and tender over her right costovertebral angle. On CT of the abdomen and pelvis she was found to have a 1.2-centimeter obstructing right ureteral calculus, hydronephrosis, hydroureter, and perinephric stranding. Urology was consulted. Shortly after into her ED course, her blood pressure began trending down, first with systolic values in the 90s and rapidly descending with values in the 70s and 80s. She was persistently tachycardic with heart rates in the 120s. After becoming hypotensive, EL was transferred to the critical care area of the ED, and Early Goal Directed Therapy (EGDT) was initiated for septic shock. She received a total of 4 liters of normal saline in addition to Ceftriaxone and ampicillin. She required norepinephrine through a central line for her hypotension. ScvO2 was 68%.

From the ED, she was taken emergently to the operating room for surgical decompression and right ureteral stent placement.

Pertinent Labs

- Urinary Analysis: Cloudy in appearance, 2+ blood, negative nitrites, 2+ LE, WBC 101, RBC 17, few bacteria
- CBC Initial: 7.6/9.9/32.4/261, 1% Bands
- CBC 8 hours later: 14.7/8.2/27.4/219, 10% Bands
- Urine Culture: > 100,000 Enterobacter, > 100,000 E. coli
- Blood culture: > 100,000 Enterobacter, > 100,000 E. coli
- Venous blood gas: 7.34/ 33/ 39/ 68 / 18

Hospital Course

In the OR, EL was found to have purulent material draining from the ureteral stent. Post-operatively her antibiotics were switched to meropenem in order to cover resistant organisms growing in both the urine and blood cultures. Her post-operative course was complicated by a clostridium difficile infection. Following initiation of treatment for clostridium difficile as well as a stent exchange, she was discharged to home with intravenous antibiotics for pyelonephritis and clostridium difficile.

Discussion

As severe sepsis and septic shock are high mortality conditions, it is important to understand how sex and gender affect these patients in order to improve both short-term and long-term outcomes. Gender differences in sepsis include differences in the epidemiology, infectious source, treatment, and outcomes.

First, the effect of gender on the epidemiology of sepsis is influenced by factors including age, source of infection, and comorbidities.[1] For example, consistent with other data, one large epidemiological study found that women have lower age-specific incidence rates of severe

sepsis when compared to men.[1,2] In this study, mortality from severe sepsis was also lower for women but this gender difference was explained by age, comorbidities, and site of infection.[1] Specifically, men are more likely to have pulmonary sources of infection while women are more likely to have urinary sources of infection.[1,3] However pulmonary infections are the most common cause of sepsis in both women and men.

Studies regarding the outcomes of severe sepsis and septic shock in humans have reached conflicting conclusions. One study using a large, national dataset found that women with severe sepsis or septic shock were about 10% more likely to die compared to men, a finding supported by multiple smaller observational studies.[3,4,5] Other literature, however, shows either no gender difference in mortality or higher mortality rates in men,[6,7,8,9,10] which would be more consistent with theories from animal data suggesting that female sex hormones are protective in infectious and inflammatory disease processes.[3,11] Inconsistencies in study design and study settings may be contributing to conflicting results, and further research needs to be conducted to clarify the effect of sex on sepsis mortality.

In terms of treatment of those meeting criteria for EGDT, some literature has shown that women are less likely to be treated with EGDT. Mikkelsen et al. (2010) showed that even after adjusting for illness severity, comorbidities, and various organizational factors, women were 62% less likely than men to have EGDT initiated.[12] These findings are consistent with investigations of critically ill patients showing that overall, women are less likely to receive invasive measures of care including mechanical ventilation and hemodialysis catheters even after adjusting for factors such as age and illness severity.[3,10,13] Unpublished data from the authors of this case report suggests that women are less likely to receive timely antibiotics and reach the target ScvO2 for severe sepsis or septic shock, but these findings need to be confirmed in future studies. Of note, in our case, EL did not receive her antibiotics within three hours of arrival, and her documented ScvO2 was below the target of 70%.

It is unknown whether women with sepsis present differently from men. Specifically, clinicians use the Systemic Inflammatory Response System (SIRS) criteria, which includes cut-off values for vital signs and white blood cell count, to identify patients at risk for severe sepsis. To meet criteria for sepsis, a patient must have two of four SIRS criteria plus a suspected infection. In our case, EL met only one SIRS criteria (for her elevated heart rate) at the time of triage. Her lack of SIRS criteria in addition to her non-toxic appearance may have delayed her placement in a treatment room and thus her evaluation by a physician. No studies to date have evaluated gender differences in SIRS criteria among septic patients. Some literature, though, has shown that women tend to have lower illness severity scores, which have some overlapping components with the SIRS criteria.[4]

Conclusions

Data on the gender-specific incidence and mortality rates for sepsis are complicated due to confounding factors and differences in research study designs. Known epidemiological differences in sepsis include a gender difference in source of infection with women being more likely than men to have a urinary source. Consistent with literature from other subspecialties

indicating that women are treated less aggressively for disease processes such as myocardial infarction and stroke, current sepsis data suggest that women are less likely to receive Early Goal Directed Therapy, a standard-of-care treatment guideline for patients with sepsis. Gender differences in frequency of SIRS criteria at presentation among those with severe sepsis and septic shock are unknown but provide an area for future research.

About the Author: Tracy Madsen, MD, Fellow, Women's Health in Emergency Care at the Alpert Medical School of Brown University, Providence, RI

References:

1. 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. Jul 2001;29(7):1303-1310.
2. Annane D, Aegerter P, Jars-Guincestre MC, Guidet B. Current epidemiology of septic shock: the CUBRea Network. American journal of respiratory and critical care medicine. Jul 15 2003;168(2):165-172
3. Pietropaoli AP, Glance LG, Oakes D, Fisher SG. Gender differences in mortality in patients with severe sepsis or septic shock. Gender medicine. Oct 2010;7(5):422-437.
4. Nachtigall I, Tafelski S, Rothbart A, et al. Gender-related outcome difference is related to course of sepsis on mixed ICUs: a prospective, observational clinical study. Crit Care. 2011;15(3):R151.
5. Eachempati SR, Hydo L, Barie PS. Gender-based differences in outcome in patients with sepsis. Arch Surg. Dec 1999;134(12):1342-1347.
6. Mahmood K, Eldeirawi K, Wahidi MM. Association of gender with outcomes in critically ill patients. Crit Care. May 22 2012;16(3):R92.
7. Schroder J, Kahlke V, Staubach KH, Zabel P, Stuber F. Gender differences in human sepsis. Arch Surg. Nov 1998;133(11):1200-1205.
8. Wichmann MW, Inthorn D, Andress HJ, Schildberg FW. Incidence and mortality of severe sepsis in surgical intensive care patients: the influence of patient gender on disease process and outcome. Intensive care medicine. Feb 2000;26(2):167-172.
9. Adrie C, Azoulay E, Francais A, et al. Influence of gender on the outcome of severe sepsis: a reappraisal. Chest. Dec 2007;132(6):1786-1793.
10. Valentin A, Jordan B, Lang T, Hiesmayr M, Metnitz PG. Gender-related differences in intensive care: a multiple-center cohort study of therapeutic interventions and outcome in critically ill patients. Critical care medicine. Jul 2003;31(7):1901-1907.
11. Zellweger R, Wichmann MW, Ayala A, Stein S, DeMaso CM, Chaudry IH. Females in proestrus state maintain splenic immune functions and tolerate sepsis better than males. Critical care medicine. Jan 1997;25(1):106-110.
12. Mikkelsen ME, Gaieski DF, Goyal M, et al. Factors associated with nonadherence to early goaldirected therapy in the ED. Chest. Sep 2010;138(3):551-558.
13. Fowler RA, Sabur N, Li P, et al. Sex-and age-based differences in the delivery and outcomes of critical care. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne. Dec 4 2007;177(12):1513-1519.

Key Words: Emergency Medicine, infections, inflammatory diseases, sepsis