Gender-Based Differences in Outcome in Patients With Sepsis

Soumitra R. Eachempati, MD; Lynn Hydo, RN; Philip S. Barie, MD, FCCM, FCCS

Hypothesis: Among factors postulated to affect outcome in sepsis is the gender of the patient, with a suggestion that females may have lower mortality. This study tested the hypothesis that female patients admitted to the surgical intensive care unit with a documented infection have a lower mortality rate.

Design: Retrospective analysis of a prospectively collected data set.

Setting: Surgical intensive care unit of a university hospital medical center.

Methods: Analysis of a consecutive series of 1348 patients who had signs of systemic inflammatory response syndrome on admission to a surgical intensive care unit. A cohort of 443 patients (32.9%) admitted with documented infection—and who therefore had sepsis, severe sepsis, or septic shock—constituted the study population. For each patient, APACHE (Acute Physiology and Chronic Health Evaluation) II and III scores, systemic inflammatory response syndrome score, gender, age, and hospital mortality were recorded. \( \chi^2 \) With Fisher exact test was performed to compare mortality rates between males and females. Univariate analysis of variance was used to compare continuous variables in discrete populations. Multivariate analysis of variance was used to determine which factors independently predicted mortality.

Primary Outcome Measures: Mortality, intensive care unit length of stay, hospital length of stay, and maximal multiple organ dysfunction score. Outcomes stratified by gender.

Results: Patients had mean ± SEM age of 67 ± 1 years; mean ± SEM APACHE II and III scores of 20.1 ± 0.4 and 67.7 ± 1.0 points, respectively. There were no demographic differences between genders. Overall, 104 (23.5%) of 443 patients with sepsis died. The difference in mortality rates between female and male patients was not significant, except in octogenarians (\( P = .05 \)). Multivariate analysis of variance, APACHE III (\( P < .001 \)), maximal multiple organ dysfunction score (\( P < .001 \)), and female gender (\( P = .02 \)) predicted mortality. In females, APACHE III (\( P = .03 \)) and maximal multiple organ dysfunction score (\( P < .001 \)) predicted mortality, but age did not.

Conclusion: Female gender is an independent predictor of increased mortality in critically ill surgical patients with documented infection.

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SEXUALLY TRANSMITTED DISEASES remain a primary cause of morbidity and mortality in hospitalized patients. Among many factors postulated to affect outcome in sepsis is the gender of the patient. Females have a more active humoral and cell-mediated response than males. In 1898, Calzolari et al showed that adult male rabbits developed increased thymic mass after castration. In more recent studies, castrated animals developed thymic hypertrophy and splenic enlargement, the latter largely caused by expansion of the B-cell population.

Results of studies of the immunologic effects of sex steroids demonstrate altered production of sex steroids under stress. With a model of chronic intraperitoneal sepsis in male mice, Sharma et al showed that sepsis significantly decreased levels of testosterone at 24 and 48 hours compared with control animals. Progesterone levels were also significantly increased at 12 hours in infected and sham-operated mice but not in control (nonoperated) mice.

Androgens may have immunosuppressive effects; administration hindered the development of fatal autoimmune disease in NZB/NZW F1 hybrid mice. In a trauma-hemorrhage model, androgens had an immunosuppressive role, independent of changes in corticosterone release. In a skin allograft rejection model, Graf et al observed that female mice had significantly shorter rejection times, and the time to rejection was shortened in males after castration.

Responses to noxious agents are also gender-specific in animal models. Human females exert an increased primary and secondary antigen response to poliovirus administration. Zellweger et al found that female mice had a significantly higher survival rate after similar infectious challenge.
Methods

A retrospective review was performed of the database of a single tertiary surgical intensive care unit (ICU) between 1994 and 1998. All data were collected prospectively. Patients admitted to the surgical ICU with systemic inflammatory response syndrome (SIRS) and a diagnosis of infection were identified. All admissions were emergent; patients admitted electively for monitoring purposes were excluded from this analysis. Patients were considered to have sepsis by having a SIRS score of 2 or greater and a documented diagnosis of infection. Location of the primary infection was also recorded in 1 of 8 categories: pulmonary, central nervous system, abdominal, skin and soft tissue, blood, genitourinary, multiple sources, or other.

For each patient, APACHE (Acute Physiology and Chronic Health Evaluation) II and III scores and SIRS score were determined, based on the worst values obtained within the first 24 hours of admission to the ICU.15,16 Age and gender were recorded. Defined end points included length of stay in the ICU, length of stay in the hospital, maximal multiple organ dysfunction score,17,18 and hospital mortality. Patients were stratified by gender and by location of the primary infection. Categorical variables (eg, gender and infection site) were analyzed using a2 with Fisher exact test. Covariate variables were analyzed by univariate analysis of variance (ANOVA). Multivariate ANOVA was performed to determine factors having an independent effect on mortality. Data are expressed as mean ± SEM. Statistical significance was accepted at P = .05.

The immunosuppressive effects of androgens may be reversed by administration of antiandrogens. Angele et al13 demonstrated in a murine hemorrhage and infection model that male mice had depressed splenocyte and macrophage function. Treatment with flutamide, an androgen receptor blocker, resulted in improved splenocyte macrophage IL-1 and IL-6 release, and increased survival.

In a prospective study of 52 patients with surgical sepsis, Schröder et al14 examined gender-related differences in outcomes and certain mediator levels. Hospital mortality was 70% in males but only 26% in females. Males had higher tumor necrosis factor α levels and lower IL-10 levels than women. Lower testosterone levels occurred in male patients compared with male controls, whereas higher estradiol levels were noted in postmenopausal female patients compared with controls of similar age.

Although gender may affect the experimental septic response, it is unclear whether this biological feature is relevant to the outcome of critically ill patients. To our knowledge, no large study has analyzed gender-related outcomes after sepsis in critically ill patients. We tested the hypothesis that a gender-specific difference in morbidity and mortality, specifically, lower mortality and other improved outcomes in females, exists for critically ill patients with sepsis.

Results

During the study, 3490 consecutive patients were admitted to the surgical ICU. Of these, 1348 patients (38.6%) met the criteria for SIRS on admission (≥2 points). Of 1348 patients, 443 (32.9%) admitted with SIRS proved to have an infection and, therefore, were given a diagnosis of sepsis. Overall, 104 (23.5%) of 443 patients with sepsis died.

Descriptive statistics for the patients are presented in Table 1. Mean age was 67 ± 1 years, with no difference between males and females. Age distribution of the gender cohorts is shown in Figure 1. Patients had a SIRS score of 3.3 ± 0.1 points, an APACHE II score of 20.1 ± 0.4 points, and an APACHE III score of 67.7 ± 1.6 points;
Gender-specific mortality as a function of primary infection site is shown in Figure 3. Although there were no site-related differences in mortality between genders, the comparisons might be affected by small sample sizes (except for abdominal infections).

The interactions of age and gender with respect to mortality are depicted in Figure 4, expressed by decile of age. There was 0 mortality for patients aged 20 to 29 years so the data are omitted. There was no difference in mortality by multiple-group $\chi^2$ for males with respect to age ($P = .45$) or for females compared with males within age strata, except for higher mortality for octogenarian females ($P = .05$). Data suggest no survival advantage for female patients with sepsis and indeed, that females may be disadvantaged. Moreover, the lack of an age-related mortality effect in females implies that the effect of estrus cycle or menopausal status on mortality may be discounted.

The independence of effects of various variables on mortality was tested using multivariate ANOVA (Table 4). Within the overall cohort, independent effects on mortality were exerted only by severity of illness on ICU admission (APACHE III score, $P < .001$), degree of organ dysfunction (maximal multiple organ dysfunction score, $P < .001$), and notably, female gender ($P = .02$). Because female gender was independently associated with mortality, a multivariate ANOVA was per-

Table 2. Outcomes of the Patient Cohorts

<table>
<thead>
<tr>
<th></th>
<th>Entire Cohort</th>
<th>Males</th>
<th>Females</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>ULOS, d</td>
<td>11.6 ± 0.8</td>
<td>11.3 ± 1.1</td>
<td>11.8 ± 1.3</td>
<td>.76</td>
</tr>
<tr>
<td>HLOS, d</td>
<td>38.3 ± 1.9</td>
<td>38.2 ± 2.7</td>
<td>38.4 ± 2.7</td>
<td>.92</td>
</tr>
<tr>
<td>MMOD score</td>
<td>6.7 ± 0.3</td>
<td>7.2 ± 0.4</td>
<td>6.2 ± 0.4</td>
<td>.08</td>
</tr>
<tr>
<td>Mortality, No. (%)</td>
<td>104 (23.5)</td>
<td>45 (21.4)</td>
<td>59 (25.3)</td>
<td>.37</td>
</tr>
</tbody>
</table>

*Data are given as mean ± SEM unless otherwise indicated. ULOS indicates intensive care unit length of stay; HLOS, hospital length of stay; and MMOD, maximal multiple organ dysfunction. Statistical testing was for differences between the male and female cohorts; no differences were observed.

Table 3. Descriptive and Outcome Statistics of Survivors Compared With Nonsurvivors Irrespective of Gender

<table>
<thead>
<tr>
<th></th>
<th>Survivors</th>
<th>Nonsurvivors</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>66.2 ± 1.0</td>
<td>69.0 ± 1.4</td>
<td>.13</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>17.5 ± 0.3</td>
<td>28.3 ± 1.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>APACHE III score</td>
<td>58.2 ± 1.3</td>
<td>98.3 ± 4.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>SIRS score</td>
<td>3.1 ± 0.1</td>
<td>3.6 ± 0.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ULOS, d</td>
<td>9.3 ± 0.8</td>
<td>19.1 ± 2.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>HLOS, d</td>
<td>39.9 ± 2.2</td>
<td>33.7 ± 3.5</td>
<td>.16</td>
</tr>
<tr>
<td>MMOD score</td>
<td>4.6 ± 0.3</td>
<td>13.5 ± 0.5</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*Data are given as mean ± SEM. APACHE indicates Acute Physiology and Chronic Health Evaluation; SIRS, systemic inflammatory response syndrome; ULOS, intensive care unit length of stay; HLOS, hospital length of stay; and MMOD, maximal multiple organ dysfunction.

again, there were no differences between males and females. The distribution of infections by gender is shown in Figure 2. Abdominal infections composed two thirds of the cases, whereas multiple sites of infection were identified in 8.6% of cases. There were no differences between groups with respect to case mix.

Patient outcomes are summarized in Table 2. By univariate ANOVA, there were no differences in predefined outcomes between males and females. As expected, nonsurvivors presented with more severe illness and a higher SIRS score, irrespective of gender, spent substantially more time in the ICU, and developed significantly greater organ dysfunction ($P < .001$) (Table 3). However, age did not affect mortality.
formed for the cohort of female patients to determine concurrence with the overall model, specifically, to assess the effect of age on mortality. Whereas severity of illness (P = .03) and magnitude of organ dysfunction (P < .001) again predicted mortality, there was no impact of age on mortality in females (P = .14), lending further support to the idea that neither estrus cycle nor menopausal status affected the results in females.

Many factors affect outcome in sepsis.19-22 Noting the presence of an accentuated proinflammatory cytokine response in sepsis, investigators35 have tried adjunctive therapies for sepsis targeting several different cytokines. These strategies have not shown benefit in clinical settings.29,33 The importance of “gender-specific physiological mechanisms” has been recognized for a variety of disease states.20 In animal models, investigators26-30 have demonstrated that gender-specific differences exist in immune function. In humans, gender-specific differences have been noted for many disease processes,27-29 including gastrointestinal tract,30 psychiatric,31,32 pulmonary,33,34 and cardiac diseases.35-38

Male and female patients demonstrate different sex steroid hormone responses to infection.39-42 Fourier et al43 observed high estrogen levels in males and females with sepsis and septic shock. Schroder et al44 demonstrated that male patients had consistently lower testosterone levels than controls, and that postmenopausal female patients had higher estradiol levels than expected. Owing to the previously demonstrated immunosuppressive characteristics of androgens, several researchers12-14 have hypothesized that differences in sex steroid hormone concentrations in patients with sepsis might represent a mechanism by which male patients may have higher mortality in sepsis.

Although data from animal studies strongly suggest that male gender is a risk factor for an adverse outcome from infection, clinical data are conflicting. A meta-analysis45 of 122 trials of community-acquired pneumonia demonstrated an odds ratio of 1.3 for mortality in male patients. However, trials45 in patients with nosocomial pneumonia that acknowledged male gender as a risk factor and examined specifically for such an effect did not demonstrate the phenomenon. A review44 of 18 792 patients with blunt trauma, stratified by age, gender, and injury severity, found no relationship between gender and mortality. Female trauma patients had a higher incidence of urinary tract infection, whereas older, more seriously injured male patients had a higher incidence of pneumonia; neither difference affected outcome.44

Results of the present study suggest that critically ill female surgical patients with sepsis may have slightly increased mortality compared with their male counterparts. Similar results were observed by McLauchlan et al46 in a cohort of critically ill patients who also had predominantly intra-abdominal infection. They observed significantly higher mortality in females; the severity of illness reported was even higher in that study (mean APACHE II score, 23; incidence of shock, 80%; hospital mortality, 63%) than in ours.

In contrast, Schroder et al44 reported that mortality in male patients was higher in a small cohort of 52 patients, 45 of whom had intra-abdominal infection and only 19 of whom were male. Compared with the present study, patients studied by Schroder et al14 were younger (mean age, 54 years because patients ≥75 years were excluded) and less severely ill (mean APACHE II score, 18), but had substantially more organ dysfunction, as assessed by the Marshall score (mean, 10.4 points). Despite the careful descriptions of sex steroid hormone concentrations provided, mortality in males was implausibly high (70%, despite a mean APACHE II score of only 18), and their results are likely spurious. Moreover, Schroder et al44 did not perform a multivariate ANOVA to determine whether gender independently affected mortality in their study.

Why might female gender impart an adverse outcome from infection? Severe infection stimulates both a proinflammatory and an anti-inflammatory response.46 Recent hypotheses47 suggest that the development of organ dysfunction, which is invariably associated with death from infection, may arise from dysregulated proinflammatory and anti-inflammatory responses. Which temporal sequence and magnitude of countervailing responses are optimal for survival is a matter of conjecture because anti-inflammatory responses are difficult to quantify, especially at the bedside.

Patients in septic shock have high concentrations of the anti-inflammatory mediator IL-10. It is possible that a relative degree of immunosuppression might be advantageous in some circumstances. For example, Stroud et al46 found female gender to be an independent predictor of mortality in patients with nosocomial enterococcal bacteremia, along with severity of illness, type of antibiotic drug used for therapy, and age. Invasive enterococcal infections have a tendency to occur in debilitated, immunosuppressed patients.49

Nonimmunologic factors might contribute to worse outcomes for women during serious illness. Males might have better access to preventive health care, and maintain a superior baseline health status.50-52 A gender-related difference in access to emergency care might also exist.53 Data might also suggest that men are admitted to

<table>
<thead>
<tr>
<th>Variable</th>
<th>Entire cohort</th>
<th>$F$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>0.7</td>
<td>.42</td>
<td></td>
</tr>
<tr>
<td>Female gender</td>
<td>6.3</td>
<td>.02</td>
<td></td>
</tr>
<tr>
<td>Magnitude of SIRS</td>
<td>1.3</td>
<td>.26</td>
<td></td>
</tr>
<tr>
<td>APACHE III score</td>
<td>11.3</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Infection source</td>
<td>1.2</td>
<td>.30</td>
<td></td>
</tr>
<tr>
<td>Vasopressor therapy</td>
<td>0.1</td>
<td>.96</td>
<td></td>
</tr>
<tr>
<td>Organ dysfunction</td>
<td>103.6</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>2.2</td>
<td>.14</td>
<td></td>
</tr>
<tr>
<td>Magnitude of SIRS</td>
<td>0.1</td>
<td>.92</td>
<td></td>
</tr>
<tr>
<td>APACHE III score</td>
<td>5.1</td>
<td>.03</td>
<td></td>
</tr>
<tr>
<td>Infection source</td>
<td>0.2</td>
<td>.95</td>
<td></td>
</tr>
<tr>
<td>Vasopressor therapy</td>
<td>0.3</td>
<td>.60</td>
<td></td>
</tr>
<tr>
<td>Organ dysfunction</td>
<td>53.4</td>
<td>&lt;.001</td>
<td></td>
</tr>
</tbody>
</table>

*SIRS indicates systemic inflammatory response syndrome; APACHE, Acute Physiology and Chronic Health Evaluation.
the hospital with a less severe pattern of illness. However, studying only ICU patients, as we did, obviates that concern.

Results of the present study demonstrate that women might have worse outcomes to sepsis than men, but there are several limitations. The study is retrospective, but the data were collected prospectively. Gender cohorts were well-matched at baseline in our study, which should have minimized any pre-existing patient bias. Inclusion of only ICU patients may have omitted less severely ill patients who were destined to avoid organ failure. However, our outcome data reveal that our patients had a relatively low mortality rate for their severity of illness.

Our findings do not support the hypothesis that females are superior to males in responding to infection. Prospective multicenter studies are necessary to resolve the discrepancy. Before studies are undertaken to evaluate the effect of hormonal manipulation in patients with sepsis, clearer demonstration of the roles of sex steroid hormones in the pathogenesis of sepsis is needed. Study may be especially needed to determine whether differential signaling or other mechanisms regulate a gender-specific proinflammatory and anti-inflammatory responses in patients with sepsis.


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Robert G. Sawyer, MD, Charlottesville, Va: The authors present data suggesting that female gender is an independent risk factor for death following infection in septic surgical patients, particularly those with peritonitis. As we heard yesterday, this is an important, interesting, and controversial topic. Our group has also been interested in this question. In fact, we reported data at the most recent ICAAC meeting showing little difference in outcome after 800 consecutive infections based on gender. Interestingly, the presentation elicited no discussion from the floor, confirming my suspicion that our medical colleagues have achieved a well-evolved, X-like androgynous state, rendering this issue moot to them.

The authors have struggled, as have we, with attempts to explain these findings. Although we too believe there may be a hormonal basis for these results, I feel compelled to leave the deconvolution of this topic to our current president. On the other hand, I have some questions about the process of care.

Much of the difference in outcome for men and women with cardiovascular disease has been attributed to different levels of treatment. Have you examined these questions? Specifically, were the males and females treated with similar antibiotics for a similar duration? Were they diagnosed with equal promptness? In a related question, what percentage of these infections were nosocomial versus community acquired, since the time to diagnosis is more physician dependent and thus, subject to bias, for hospital-acquired infections?

Finally, you noted that, after age stratification, only octogenarian females had a worse outcome than males. Do you have any reason to believe that we are more likely to withdraw support from critically ill, elderly females than their male counterparts?

Dr Eachempati: In answer to the first group of questions, the males and females were treated equally. The same group of physicians, as I mentioned, treated all the patients, and there was no differentiation or perception that care was withdrawn or changed for genders.

We don’t know which patients had community-acquired or nosocomial infections. What we can only do, though, is look and see that our baseline characteristics in our patients, the APACHE IIIs and IIIs, were very similar for the males and females, and we have to base our outcomes on that initial group of data points.

And, finally, why would octogenarian women do worse? I am not sure. One thing we did do in our analysis is break down by groups and try to see if premenopausal or postmenopausal women did worse. That was not significant in our analysis, though we did not include that here.

John A. Mannick, MD, Boston, Mass: I have long held the opinion, perhaps prejudiced, that data available in the literature at the moment suggest that factors that help us resist an infectious challenge may not be the same as those that help us get over sepsis once it has gotten a hold of us or our animal models, and it seems to me that what we have seen so far can be interpreted in the same fashion, with regard to the gender question.

The data from Denver that we heard yesterday really focused on whether traumatized female patients had a lower incidence of infection than traumatized male patients when severity of injury was taken into consideration, and the answer was that, in moderate injury, female patients were better able to resist infection. Certainly, Dr Chaudry’s data can be interpreted in the same way, I think. That is, female rodents that are challenged with bacteria are able to overcome this challenge better than male rodents that are challenged with bacteria after an equal traumatic injury.

And I am not sure that this says that females, once they are septic, can survive better than males; in fact, your data would suggest the opposite may be true. But I wonder whether we are not missing a point here about what we are trying to straighten out. Perhaps what you have reported and what was reported from Denver may be completely compatible, and I would like to hear your thoughts on that.

Dr Eachempati: One feature of Dr Offner’s presentation I did enjoy was that he stratified his patients for injury severity between 16 and 25 and greater than 25. In our data, we did not break down, by different APACHE levels or outcomes, and that may be a feature we would explore later, which would give us more information.

Jorge L. Rodriguez, MD, Minneapolis, Minn: The majority of your patients were involved with an abdominal process. The underlying abdominal process is important. Do you have any data as to stratifying the patient population, based on gender, on the severity of the abdominal process, and on which specific type of abdominal process? Acute appendicitis is that ruptured in an elderly person is a little different from a dead piece of colon that you need to take out.

Dr Eachempati: That is an excellent point. Again, the APACHE score would not differentiate whether the patient had a perforated appendix or a completely dead ischemic bowel. In our group of patients (443), many of these factors would fall out, and this was done over several years. Naturally, on a prospective basis, what we could do is certainly stratify by exact diagnosis of the abdominal pathology. I want to reiterate that, for the different locations of infection, there was no difference in mortality between the males and females.

Irshad H. Chaudry, MD, Providence, RI: Another way of looking at this is again pointing out the complexity between the clinical and the experimental studies. In our studies, we did not find any survival benefit in the metestrus state or diestrus state, except in the proestrus state. And thus, it becomes difficult to determine what state of cycle the patient might have been in, since the cycle stops as soon as the injury occurs. That factor has to be taken into account.

Perhaps you can indirectly determine the cycle by measuring prolactin and/or estrogen levels to determine if there is any correlation with outcome. Unless you define the cycle, it is difficult to lump everything and say there is a difference or there is not a difference.

Dr Eachempati: One of the studies that I did not see ever done was, in patients who survived and did not survive, levels of estrogen measured in the blood for extended periods of time in survivors and nonsurvivors, seeing if there was a trend at a certain time whether the patients would have different estrogen levels. Certainly, that would be a very difficult study to undertake because some of these patients had 30- to 60-day hospital stays, but certainly that would shed, I am sure, a great deal of information on the subject.

As opposed to the proestrus state that you are referring to, we did see a trend in decreased mortality in the younger women, but this was not statistically significant.

Lenas M. Napolitano, MD, Baltimore, Md: In our study of over 18,000 patients, we were very careful to go back and look at pre-existing disease as a risk factor. Have you looked at that in this specific study?

Dr Eachempati: No, we did not look at pre-existing disease in this study except where it fell into the APACHE II and III scores, but certainly that would be a valid set of data points for the next study.

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