Male Gender Is a Risk Factor for Major Infections After Surgery

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**Background:** Accumulating clinical and epidemiologic evidence suggests significant gender differences in the incidence of and outcome following major infection. In a rodent model of hemorrhagic shock, investigators have shown that males manifest depressed cell-mediated immunity that is reversed by castration or pharmacologic testosterone receptor blockade. Female rats, in contrast, show enhanced immune function that is reduced to male levels by testosterone administration. This sexual dimorphism is believed responsible for the improved outcome in female mice following septic challenge.

**Hypothesis:** Male gender is a risk factor for major infections following severe injury.

**Design:** Five-year prospective cohort study ending October 1998.

**Setting:** Urban level I regional trauma center.

**Patients and Methods:** A total of 545 trauma patients older than 15 years with an Injury Severity Score greater than 15 and survival more than 48 hours were prospectively identified and studied. Collected data included age, injury mechanism, and Injury Severity Score. Major infections, defined as pneumonia, abdominal and pelvic abscess, wound infection requiring operative debridement, and meningitis, were tabulated. The occurrence of major infections in males and females was compared using multiple logistic regression analysis.

**Main Outcome Measure:** Postinjury major infectious complications.

**Results:** Of the 545 patients, 135 (24.8%) were female and 410 (75.2%) were male. Major infections occurred in 219 (40.2%) patients. Logistic regression confirmed that male gender is an independent risk factor for major infections (\( P = .04 \)) after controlling for age and Injury Severity Score. Males had a 58% greater risk of developing a major infection (odds ratio, 1.58; 95% confidence interval, 1.01-2.48).

**Conclusions:** Male gender is associated with a dramatically increased risk of major infections following trauma. This effect is most significant following injuries of moderate severity (Injury Severity Score 16-25) and persists in all age groups.

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Despite improvements in technology and critical care, sepsis and subsequent multiple organ failure (MOF) continue to be the most common cause of late postinjury death in the surgical intensive care unit (SICU). Several studies have documented depressed cell-mediated and humoral immune function following trauma and hemorrhage. This immune suppression may, in part, reflect a compensatory anti-inflammatory response attempting to control potentially destructive postinjury hyperinflammation. Recently, experimental studies have documented hormonal influences on the immune response in animals as well as in humans. Females have been observed to have more prominent hormonal and cell-mediated immune responses compared with males. Angele et al have implicated high testosterone and low estradiol levels in the pathogenesis of immune suppression following trauma and hemorrhage using their well-established rodent model.

See Invited Critique at end of article

Several clinical and epidemiological studies have corroborated better outcome from sepsis in females compared with males. Most recently, Schroder et al observed a marked reduction in hospital mortality among female patients with surgical sepsis (26% vs 70% in males). The purpose of this study was to determine if gender differences exist in the occurrence of major infections following severe mechanical trauma using our prospective database. We hypothesized that males are at greater risk for postinjury major infections compared with females.

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PATIENTS AND METHODS

PATIENT POPULATION

During the 5-year period ending October 31, 1998, data from 545 trauma patients admitted to the trauma SICU at Denver (Colo) Health Medical Center who met inclusion criteria were entered into our prospective MOF database. Inclusion criteria included an Injury Severity Score (ISS) greater than 15, age older than 15 years, and survival greater than 48 hours. Patients transferred from another facility were excluded if the transfer was made more than 24 hours after injury. The care of these patients was directed by existing protocols and supervised by 5 general surgeons with expertise in trauma and critical care. All patients were prospectively followed up until hospital discharge or death.

PRIMARY OUTCOME

Patients were monitored for the development of infectious complications, which were categorized as either major or minor. Major infections included pneumonia, empyema, lung abscess, abdominal and pelvic abscess, extensive wound infection, meningitis, and other major infections. Pneumonia was diagnosed based on the following criteria: (1) infiltrate on plain radiograph persistent for more than 48 hours, (2) temperature greater than 38°C, (3) sputum Gram stain showing many polymorphonuclear leukocytes, (4) leukocytosis (white blood cell count >12.0 x 10^9/L) or leukopenia (white blood cell count <4.0 x 10^9/L), (5) blood culture positive for the same pathogen noted on sputum culture, (6) bronchoalveolar lavage quantitative culture with pathogen growth of more than 10^9 colony-forming units per milliliter, and (7) histopathologic diagnosis (autopsy or open lung biopsy). Pneumonia was defined as one of the following combinations of these criteria: 1 + 5; 1 + at least two of 2, 3, or 4; 1 + 6 + at least one of 2, 3, 4, or 7. Pneumonia was excluded if there was clinical resolution without antimicrobial therapy or when an alternative diagnosis was established (clinically or at autopsy). Lung abscess was diagnosed on the basis of clinical and radiographic evidence. Empyema and abdominal abscesses were defined as purulent fluid collections requiring drainage. Major wound infections were those that required operative debridement. Meningitis was diagnosed using Centers for Disease Control and Prevention criteria. Other infections were classified as major if they were associated with septic shock (eg, urosepsis).

STATISTICAL ANALYSIS

The MOF database is maintained on an IBM PC using Microsoft Access 97 software (Microsoft, Inc, Redmond, Wash). Statistical analysis was performed using SPSS for Windows 9.0 software (SPSS Inc, Chicago, Ill). Univariate analysis was performed using the \( \chi^2 \) test with Yates correction or Fisher exact test for categorical data and Student t test for continuous variables. \( P<.05 \) was considered significant.

Because infection risk is possibly related to injury severity as well as the hormonal milieu (which changes with age), data were analyzed following stratification by both age and ISS. Multiple logistic regression analysis was performed to assess gender as an independent risk factor for postinjury infectious complications after controlling for age and ISS.

RESULTS

During the 5-year study period, 545 patients were identified. There were 410 male and 135 female patients. Demographic and outcome data are presented in Table 1.

Female patients were older, more severely injured, and had a higher incidence of blunt injury. Major infections occurred in 41% of males compared with 37.8% of females. There were no significant gender differences in base deficit, early transfusion requirement, frequency of MOF, or mortality. Similarly, hospital and SICU lengths of stay were not significantly different in men and women.

The frequency (percentage of patients) of major infections stratified by age and gender is summarized in the following tabulation.

In moderately injured patients (ISS 16-25), males experienced nearly double the rate of major infection compared with females. This effect was consistent across all age categories. In severely injured patients (ISS >25), infection rates were similar regardless of gender and age category.

Multiple logistic regression analysis was performed with age, ISS, and gender as independent risk factors for major infections (Table 2). Each of the variables was a significant independent risk factor. Males were noted to have a 58% greater risk of developing a major infection compared with females (odds ratio, 1.58; \( P = .04 \)). There was no significant interaction between age and gender. In addition, mechanism of injury was not a significant risk factor for postinjury infections.

COMMENT

Immunosuppression following trauma has been well described and increases susceptibility to sepsis and subsequent MOF. Although the exact order of mechanistic events is not known, it is clear that some aspects of the immune system are stimulated while others are depressed. Moreover, dysfunctional immune response involves virtually every known participating cell line. We have demonstrated neutrophil priming for superoxide release within 6 hours of injury that returns to baseline by 24 hours. Subsequently, neutrophil superoxide production is decreased below baseline for up to 5 days. Elas-
tase release, however, is preserved during this period. The result is that neutrophil oxidative defense mechanisms are impaired, placing the patient at risk for invasive infection. The capacity for neutrophil-mediated tissue injury via elastase release, however, is intact. Monocytes and macrophages demonstrate immediate excessive release of proinflammatory cytokines followed by substantial paralysis of certain cellular responses. In a well-established model of hemorrhagic shock, Wichmann and colleagues have shown impaired production of splenocyte interleukin (IL) 2 and IL-3 in response to concanavalin A, and reduced IL-1 and IL-6 production by lipopolysaccharide-stimulated peritoneal and splenic macrophages. The depressed splenocyte IL-2 and IL-3 response is consistent with a decrease in the ratio of type I (TH1) and type 2 (TH2) helper T cells. Such a change in the relative contributions of TH1 (proinflammatory cytokine release) and TH2 (immunosuppressive cytokine release, such as IL-4 and IL-10) subpopulations would be expected to shift the balance toward immunosuppression. In fact, the authors have previously implicated IL-4 and IL-10 in the immunosuppression secondary to hemorrhagic shock. Similarly, Mack et al reported depressed IL-2 and augmented IL-4 and IL-10 production from splenocytes isolated from mice subjected to hemorrhagic shock and femoral fractures. Recently, Lyons et al documented exaggerated IL-10 release from peripheral blood mononuclear cells harvested from patients 7 to 10 days following mechanical or thermal injury, and confirmed the pivotal role of IL-10 in predisposition to infection in a murine burn model. Much attention has also focused on the excessive release of prostaglandin E2 and down-regulation of monocyte class II major histocompatibility complex HLA-DR. The impaired release of IL-6 from tissue macrophages is intriguing, particularly considering that the same environmental conditions induce a shift to the TH2 helper T cell that responds with enhanced IL-6 production. Moreover, Faist et al reported that peripheral blood mononuclear cells from severely injured patients had enhanced IL-6 release but impaired IL-1 following lipopolysaccharide exposure. The precise role of IL-6 in regulating local and/or systemic inflammation remains unclear. Interleukin 6 is recognized as an integral mediator of the acute-phase response, but excessive or prolonged increases of circulating IL-6 concentration have been associated with infectious complications and MOF in patients after trauma, burns, or elective surgery.

Several clinical studies suggest gender differences in the incidence and outcome from sepsis. In an epidemiological study of bacteremia, McGowan et al noted a higher incidence of sepsis in males compared with females. In a pediatric population with severe burn injury, Barrow and Herndon noted increased mortality in boys compared with girls. Bone retrospectively reviewed 4 severe sepsis studies and noted a predominance of male patients (60%-65%). Most recently, Schröder et al prospectively observed 52 patients (19 female, 33 male) with surgical sepsis admitted to a university hospital SICU. The male and female patients were well matched for age, cause of sepsis, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, and multiple organ dysfunction score. Male patients experienced a significantly higher mortality rate (70% vs 26%; P < .008). The authors did not comment on the incidence of sepsis in these patients.

Our prospective study adds documentation that males are at increased risk for developing major infections following injury. The male and female patients in

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>Odds Ratio (95% Confidence Interval)</th>
<th>P</th>
</tr>
</thead>
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<tr>
<td>Age</td>
<td>0.0159</td>
<td>1.02 (1.001-1.03)</td>
<td>.008</td>
</tr>
<tr>
<td>Injury Severity Score</td>
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<td>1.09 (1.06-1.11)</td>
<td>&lt;.001</td>
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<tr>
<td>Male sex</td>
<td>0.4590</td>
<td>1.58 (1.01-2.48)</td>
<td>.04</td>
</tr>
</tbody>
</table>

*Data are given as mean ± SEM or percentage of patients. ISS indicates Injury Severity Score; RBC, red blood cell; MOF, multiple organ failure; and SICU, surgical intensive care unit.
our study were well matched for transfusion requirements and early base deficit. Mortality, MOF, and hospital and SICU lengths of stay were not affected by gender. Although female patients were older and more severely injured, multivariate analysis confirmed the increased risk in males after adjusting for these differences. The lack of a difference in severely injured patients (ISS >25) is not unexpected. Severely injured patients with massive soft tissue injury are at such high risk of infectious complications that gender differences become less important. We were surprised, however, that the increased risk of infection in males persisted in the postmenopausal age group, when hormonal differences were believed to be less operative. An explanation for this unexpected finding may be provided by Schröder et al, who noted increased estradiol levels in both men and postmenopausal women with sepsis. The source of estradiol in these patients was postulated to be from conversion of testosterone or decreased hepatic estrogen catabolism related to sepsis.

In summary, we have shown that males are at increased risk of infection following trauma. This sexual dimorphism has therapeutic implications and must be taken into account when evaluating and planning interventional sepsis trials.


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17. Faist E, Storch M, Huettner L, et al. Functional analysis of monocyte (Ma) activity via synthesis patterns of interleukin 1, 6, 8 (IL-1, IL-6, IL-8) and neopterin in surgical intensive care patients. Surgery. 1992;112:562-572.


you tell us whether the infection case mix was equal between your groups?

How did you construct your multivariate model to evaluate 3 independent variables only? Why was blunt trauma mechanism excluded when it was highly significant in the univariate analysis? What was the univariate P value for the incidence of major infections that were, in fact, more than 20% more common in your male patients? If that P value was .15 or less, many would have included it in the multivariate model as well. Inclusion of another significant independent variable might change your result, considering that the number of independent variables examined was only 3.

Dr Offner: Your first question regarding our increased incidence of infections: This is due to the fact that we have a highly selective patient population, with a fairly severely injured patient population, compared with other studies, which include a greater range of injury severity in their patient population.

Our pneumonia definition has been used in a variety of subsequent studies. As far as independent validation, that has not actually been done; however, I do think it is a fairly standard definition based on a number of facets as elucidated in the presentation. I didn’t present all infections; however, I did analyze all infections. Male gender is still a risk factor for all infections, including minor infections as well.

As for the infection case mix, I assume you mean whether or not it was pneumonia vs intra-abdominal abscess, etc. Those data are available, however, because of the nature of how our database is constructed. I have had great difficulty actually sorting that out. I can tell you that the predominant major infection that we do have in our intensive care unit is pneumonia, and again, that definition of pneumonia is equally applied to men and women; it is equally applied to all patients in that SICU.

And finally, as far as a logistic regression model, more variables than those that were shown in the presentation were included; however, they were not significant, and that includes mechanism of injury, among others, that in the interest of time I chose not to present.

Edwin Deitch, MD, Newark, NJ: This will relate to your outcome data. We know that it is very difficult to tie mortality to infection in the ICU patient, because some patients are very severely injured and will die whether or not they get infected, while in others with more moderate injuries, the infection may in them one way or the other. Your data show that it’s in the intermediate level of injury that there is an association with a reduction in infection. You didn’t show any data in that subgroup about the effect of infection on outcome or survival, so your survival studies were just the entire populations.

In the subgroup of patients with ISSs between 16 and 25, where infection was reduced, did you see a concomitant improvement in outcome?

Secondly, as a related question, people die of different things. Have you stratified your data to look at infectious death vs noninfectious death to determine if there is a difference between the sexes?

And lastly, although we think it is androgens, some of your patients were postmenopausal and therefore they had different hormonal milieu. How do you account for that in your results?

Dr Offner: We did not do subgroup analysis within the strata in terms of a statistical analysis. I did look at the numbers, and they would not be statistically significant. You are right, a subgroup analysis would be appropriate in that subgroup that appears to have the potential effect.

Jan K. Horn, MD, San Francisco, Calif: I was wondering about the use of antibiotics in your patients. Can you assure us, for instance, that they all have the same preinfection regimen of antibiotics? That would have a significant impact on the incidence, since you did have a higher rate of infection.

Dr Offner: That is a very good point, and I cannot document that with any surety. What I can tell you is that the care of the patients in the ICU is done on a fairly rigid protocol basis under the direction of a few surgeons who think alike, so most of these patients are taken care of in a uniform fashion, with rounds made on a daily basis by us in order to assure that that is being done.

Mark A. Malangoni, MD, Cleveland, Ohio: You had a group of patients that would consist of older men and postmenopausal women who had the same infection risk differences as your younger groups of patients. We are looking for an explanation as to why that same relative risk exists in that group of people.

In addition, your relative risk 95% confidence intervals overlap. You have got a few decimal points out there that aren’t convincing, and I wonder if you could comment on how much you believe these statistics?

Can you tell us about the incidence of penetrating injuries in these patients, or, for that matter, contaminated injuries? I would expect that one of the things that your data may show is that men may be more likely to have injuries that result in some degree of contamination and perhaps it is the contamination that leads them to develop later infection.

Dr Offner: Let me try to address the first question first before I forget it. We were surprised when we found that the infection risk in the moderately injured patients was persistent through all age groups, because we expected that if this was related to hormonal differences, we would not see a difference when we reached that postmenopausal age group. So we were surprised by that. I don’t have a good explanation for it except if you go back to the report by Schroder that was presented here last year, they documented elevated estradiol levels in both men and women in that postmenopausal age group and surmised that it was either related to septic-related hepatic dysfunction or some other factor.

There was also an epidemiologic study of postmenopausal women that was performed about 10 years ago and published in the American Journal of Epidemiology that looked at hormone levels, and what they found was hormone levels could not be predicted by age, rather, they seemed to be affected by other factors, such as obesity, whether someone smoked or not, and other concurrent problems. That may potentially explain some of these differences.

The reason why we don’t see an effect in the more severely injured patients is that it is possible that at some threshold of injury severity, tissue injury effects outweigh any gender effects that occur.

There was a significant difference in penetrating injuries between the men and women; however, in the logistic regression analysis, a variable that included mechanism of injury was included and was not found to be significant in that regard. However, I did not individually look at penetrating injuries and the body region of injury to see if there was a difference in that regard; it is probably a good thing to do.

David D. Dunn, MD, Minneapolis, Minn: This paper obviously deflates many of our societal and personal views regarding testosterone, unfortunately. Having said that, I would like to challenge your conclusion regarding whether this is the important variable in sepsis and infection, and point out that there are probably 3 other important papers that have appeared in the last 4 to 5 years—one telling us that tumor necrosis factor polymorphism is critical, another telling us that the IgG response to anticoag antibody, coupled with IL-6, is important, and another telling us that resistant organisms are
associated with higher mortality. What is the right answer here, and do you plan to measure other variables, as Dr Barie mentioned?

Dr Offner: Clearly, this is a complicated area, and there probably are other effects that aren’t accounted for, including genetic effects, as you mentioned. We are currently trying to collate some data on neutrophil function between men and women, as well as cytokine levels, but that is in progress, and really we have few patients right now. Hopefully, we will have more as time progresses.

Irshad H. Chaudry, MD, Providence, RI: With regard to the lack of difference in survival rates between the males and females, can you tell us about the state of the menstrual cycle in the females? In this regard, our experimental studies have shown that females in the proestrus state tolerate trauma and sepsis better than males. However, the tolerance to trauma and sepsis was not different between male and females in the metestrus cycle. It is important to subgroup female patients in the different states of menstrual cycle and determine whether the different cycle states provide any difference in tolerance to trauma and sepsis.

My second question deals with the older postmenopausal female patients. Could you please tell us if any of them were receiving estrogen replacement therapy? Did you stage the female patients with regard to what cycle?

Dr Offner: These are essentially the same questions you asked Dr Schroder a year ago. Unfortunately, I don’t have a good answer. When these major injured patients come in, we usually don’t try to get a menstrual history from them, and it is not something that we typically put in our database, so we really don’t have a good idea as far as where they were in their cycle, nor do we have a good idea as to whether or not they were taking estrogen replacement. We try to take a good medical history on these patients, but, unfortunately, it is not one of the fields that we include in our database, and so I don’t have that information for you.

Invited Critique

Offner and associates, by way of a retrospective review of trauma patients, have attempted to add to the evidence that sex hormones affect the immune response. There is relatively strong and increasing evidence in experimental animals for differences between the sexes with respect to immune responsiveness. The authors provide a nice review of that accumulated evidence. They also review the somewhat less convincing studies to date suggesting clinically significant sex differences in immune responsiveness in humans.

The study is well conceived and well done. It is important to note, however, that there were no differences with respect to clinical outcome parameters (mortality, intensive care unit or hospital length of stay) between males and females despite a significant difference in major infection rates. The rates of multiple organ failure were also similar between male and female patients, perhaps surprising given that major infection is one of the stimuli that can lead to multiple organ failure. A type II error is one potential explanation for the absence of differences in clinical outcome. Another possibility is that major infection as defined by the authors (particularly the definition of pneumonia) was not restrictive enough to select patients in whom infection affected outcome. Finally, it is also possible that immunosuppression is not always detrimental after major trauma; a vigorous immune response can injure the host as much or more than the inciting insult.

The authors’ use of multiple logistic regression to control for age and Injury Severity Score is appropriate. They chose, however, not to control also for mechanism of injury, a variable that proved to be highly significant by univariate analysis. It is not beyond the realm of possibility that penetrating injury is as important as male sex in predisposing to major infection (especially abdominal abscess) after trauma. Further studies like this one ideally should control for more potential variables.

David Wisner, MD
Sacramento, Calif