

COMMENTARY

Sex and severe sepsis

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See related research by Sakr *et al.*, <http://ccforum.com/content/17/2/R50>

Abstract

Epidemiological studies document that males are more prone than females to develop severe sepsis and this is confirmed by Sakr and colleagues in the previous issue of *Critical Care*. However, the impact of gender on prognosis of severe sepsis is a matter of debate. Sakr and colleagues report a higher mortality in septic females than in males. This puzzling result might be explained by confounding factors such as age, nosocomial infections, follow-up period, and case mix. The impact of sexual hormones in older females is less relevant. Treatments aimed at modifying sexual hormone profile are promising but need to be tested in future trials.

In the previous issue of *Critical Care*, Sakr and colleagues [1] reported an epidemiologic study they performed in 24 intensive care units (ICUs) in the Piedmont region of Italy. The study documents a lower prevalence of severe sepsis (SS) but a higher ICU mortality in females than in males.

The study's results on outcome are puzzling. Most previous studies report either no effect of gender or a protective effect of being a female. Several confounding factors might account for this result: the number of included patients with SS was small (305, including only 85 females), the period of inclusion during spring and summer induced a seasonal bias with different sources of SS as compared with winter, the percentage of ICU-acquired SS was high (61% in females), and females with SS were significantly older than males (67.7 versus 63.1 years); only 12 female patients were younger than 50 years of age. The median length of stay was short, precluding an interpretation of the Kaplan-Meier curve. No information on hospital or long-term outcome is

provided. Studies with long-term follow-up have shown that male gender was associated with a worse prognosis. Weycker and colleagues [2] reported 5-year mortality rates of 77.5% in males and 70.2% in females. Also, it should be noted that the global incidences of SS for the whole population (7.8%) and for females (6%) were low and that ICU mortality rates for all patients (51.1%) and for females (63.5%) were very high given the values of simplified acute physiology score (SAPS) and Sequential Organ Failure Assessment (SOFA).

SS has been identified as a major factor in ICU bed occupancy, ICU cost, and ICU mortality [3-6]. The incidence of SS and septic shock is increasing over time [5-8] because of better diagnostic tools or refined definition [9] but more importantly because of change in case mix (older patients and patients with comorbidities and immunosuppression). The ICU population is getting older, and the sex ratio is in favor of females after 80 [10,11]. Moreover, immunosenescence might explain the higher incidence of SS in older patients [12], and atypical clinical presentation might increase the delay of diagnosis and treatment, both contributing to a higher mortality in older patients [11]. Since female patients were older than males in the study by Sakr and colleagues, age might have contributed to the higher mortality in female patients.

The impact of gender on prognosis may be related to sexual steroid hormone, although the contribution of young females (<50 years) to the whole population of SS is small (only 12 out of 85 female patients). In fact, numerous animal experiments suggest that gender may influence outcome and that a better outcome can be observed when hormonal status is orientated toward a female phenotype. During experimental hemorrhagic shock in male rats, outcome is improved by the administration of testosterone blocker or by castration [13]. In the same model, the outcome of female mice is improving when circulating estrogens are at their maximal values (that is, during the premenstrual phase) [14]. When proestrus and ovariectomized rodents are subjected to sepsis by cecal ligation and puncture after trauma-hemorrhage, ovariectomized mice exhibit a significantly higher death rate. Finally, in this animal model, estrogen administration in males and ovariectomized females prevents immune function impairment

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(assessed by interleukin-1 and interleukin-6 macrophage production) and cardiac contractility decreases. Similar results have been observed in experimental endotoxigen challenge in rats [15]. An intravenous endotoxigen bolus decreases blood pressure in male rats, but blood pressure is not modified in female animals. Interestingly, this deleterious effect of endotoxin in male rats is abolished by prior surgical castration [15].

Several clinical studies report increased estradiol levels in male patients with septic shock whereas circulating testosterone levels were dramatically decreased. In a preliminary observational survey performed in our ICU, circulating estradiol levels, measured during the first three days following ICU admission, were dramatically increased (reaching about six times the control levels) in a cohort of 40 male patients with SS or septic shock (unpublished data). Moreover, circulating estradiol values correlated with SAPS II, and the highest levels were observed in the most severe patients (patients with shock or with a fatal outcome). Mean circulating testosterone levels were dramatically decreased (reaching only a third of normal lower value) and never reached the minimal normal value of healthy men. Patients with shock had the lowest testosterone levels, but measured testosterone values did not differ according to outcome.

Given these clinical observations, it seems that sexual hormonal pattern among male patients with SS is adaptative in order to minimize deleterious effects of testosterone. There is little room, if any, for testosterone blockade. A sexual hormonal therapeutic modulation in SS and septic shock aimed at increasing circulating estradiol levels is appealing. This hypothesis needs to be assessed through randomized controlled trials.

Abbreviations

ICU, intensive care unit; SAPS, simplified acute physiology score; SS, severe sepsis.

Competing interests

The authors declare that they have no competing interests.

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