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Commentary

Does gender affect the outcome of community-acquired *Staphylococcus aureus* bacteraemia?

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Sex and gender play an active role in the incidence and outcomes of major infectious diseases, including malaria, tuberculosis, human immunodeficiency virus infection, hepatitis, and influenza [1]. Both biological differences (e.g. hormonal cycles and cellular immune-mediated responses) and cultural, behavioural and socio-economic differences are important determinants of course and outcome of infectious diseases [1]. Given this background, we read with great interest the study by Smit *et al.* exploring gender differences in outcomes of *Staphylococcus aureus* bacteraemia in northern Denmark [2]. The authors used population-based medical registers to analyse the outcome of community-acquired *S. aureus* bacteraemia in 2638 adult patients between 2000 and 2011 [2]. The results, which had been adjusted for co-morbidities and age, suggest that gender has a significant impact on all-cause 30-day mortality with women having a 30% higher risk than men [2].

The association between gender and mortality risk has been investigated for hospital-acquired infections, bacterial pneumonia, endocarditis and sepsis with inconsistent results [3–11]. Some authors reported that female gender independently predicts mortality [4–7,11]; others found no association [8,9,12] or an increased risk for men [10]. Specifically for sepsis, women appear to be at lower risk of developing the condition than men [13]. Angele *et al.* reported evidence that dihydrotestosterone and high oestradiol may be protective after adverse circulatory conditions such as septic shock [14]. Studies in healthy volunteers challenged with *Escherichia coli* lipopolysaccharide showed a gender difference in immunological and cardiovascular response to the exogenous agent [15].

Although women may be less likely to develop sepsis, if they do, their risk of death may be distinctly greater. In an American cohort of 18 757 intensive care unit (ICU) patients, women with severe sepsis had a higher risk of death than men [5]. A German cohort study of 3902 patients from 24 medical or surgical ICUs, found a two-fold higher risk of death in female patients [16]. Two studies of *S. aureus* bacteraemia reported a significantly higher risk of 30-day and long-term mortality in female patients [6,7]. Conversely, two studies did not find any association [12,16]. Adrie *et al.* in a cohort of 1692 patients showed that women older than 50 years had a 31% lower mortality risk than men in the same age group [17]. The VIRSTA study was conducted in eight tertiary-care centres in France and analysed survival in 1972 patients. Week 12 case-fatality rate was not different according to patient gender [12]. Major limitations of these studies include retrospective design, selection bias, heterogeneous case mix, small sample size and lack of clinical and therapeutic data (timing and appropriateness of therapy), follow up and differentiation between hospital- and healthcare-associated infections. Most important is the lack of information on the attributable mortality of sepsis because all published studies analysed only overall short-term or long-term mortality. The Smit *et al.* study provides new evidence-based data confirming the negative association between female gender and sepsis survival [2]. The strength of their results lies in adequate sample size, access to individual level and population-based clinical data, and complete follow-up. The association remains after adjusting for co-morbidities. After stratification, female patients with cancer and diabetes are more likely to not survive sepsis compared with men [2]. Sepsis might therefore accentuate the impact of underlying diseases on the overall mortality.

Interestingly, explanations of this increased mortality risk seem to not be associated with biological diversity between the sexes. An

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advantage in younger women in response to infection has been proved [18]. Sex hormone levels effect bacterial infection outcomes with oestrogens promoting and androgens suppressing immune responses [19]. In rodents, survival of polymicrobial sepsis is highly hormone-dependent with enhanced pro-inflammatory cytokine production favouring females [18]. Female mice also tolerate sepsis better than males, and androgen receptor blockade reverses this effect [19]. Women should therefore lose their survival advantages after menopause. However, clinical data from a retrospective cohort of 5081 patients found higher ICU death rates in women younger than 50 who developed pneumonia with respect to men [11]. In the Smit *et al.* study, it is unlikely that sex hormones had a significant impact because the mean age of women was 71 years [2]. Although the difference in mortality between genders is consistent in all age groups, in the younger group (15–39 years), it should be interpreted with caution because of the low number of deaths in this group [2].

One possible explanation for the increased mortality observed in women of all ages is the gender difference in healthcare-seeking behaviour resulting in women delaying hospital presentation and so reaching the emergency room in a more advanced stage than men. In a recent meta-analysis including more than 40 million individuals visiting general practitioners, we found that women are 27% more likely to receive a prescription for antibiotics than men [20]. It is therefore possible to speculate that greater access to antibiotic therapy by general practitioners may delay attending the hospital and receiving subsequent care.

Differences in sepsis management of male and female patients may account for the difference in mortality risk. Inequity in quality of care among sexes at ICU admission has been reported [3,21]. Vertical inequity has been described in patients with myocardial infarction or neurological bleeding. Men had lower APACHE II scores than women, suggesting that disease severity admission criteria for women were more stringent than for men and horizontal inequity can occur [22]. Pietropaoli *et al.* reported that women with sepsis were less likely than men to receive prophylaxis for deep vein thrombosis, invasive mechanical ventilation and haemodialysis catheterization at ICU admission [5]. Gender-related bias in the provision of care and use of hospital resources for women has been also reported in patients with bacterial pneumonia [21]. Women older than 50 years were less likely than men to receive life-supporting treatments [21]. Time intervals from admission to initiation of treatment or from fever to initiation of treatment may also differ between men and women. In a retrospective observational study in 771 patients with sepsis in an urban academic emergency department, the mean time to first antibiotics for women (184 minutes) was significantly longer than for men (153 minutes; adjusted odds ratio 1.18, 95% CI 1.07–1.30), even after adjusting for age, race, ethnicity, presumed source of infection, sequential organ failure assessment (SOFA) score and lactate.[23]

Results from the Smit *et al.* study require careful interpretation [2]. Generalizability of the results may be limited by the specific epidemiological setting with very low rate (0.5%) of methicillin-resistant *S. aureus* (MRSA) and lack of information about infection foci. Outcome of sepsis due to MRSA could be subject to different confounding factors, e.g. previous antibiotic therapy [24]. The Smit study evaluated register data on community-acquired bloodstream infections in northern Denmark, and it cannot be assumed that the results can be generalized to other aetiologies, sources of sepsis, ethnic groups, or socio-economic statuses, or to healthcare-associated infections. Most importantly, existence of differences in choice of empiric antibiotic therapy and appropriateness of therapeutic regimens remain unexplored.

In this era of individualized medicine, outcome differences between genders must be studied closely. A 30% difference in mortality cannot be left unexplained and strongly suggests that implementation of protocols for individualized antibiotic therapy should start to include not only patients' clinical information but also gender-related data such as differences in hormonal effects and disease pathophysiology. It is, however, the non-biological factors that cause more concern and warrant thorough exploration. Crucially, potential gender inequality in patient management and distribution of resources at both institutional and national levels must be evaluated and, if present, investigated and reduced as a matter of urgency. Until more data are available, consideration of patient gender should be part of the routine triage and management of sepsis. Further studies of pathophysiology and clinical characteristics of sepsis in women are needed to eliminate the current inequity between women and men in sepsis survival. A prospective, cohort study including centres with different MRSA rates and collecting epidemiological (i.e. origin of sepsis) and clinical (i.e. timing of first symptoms and of empiric and targeted therapy) data as well as sepsis-attributable short-term and long-term mortality would provide the missing evidence to support the implementation of measures to reduce difference in mortality among sexes.

Transparency declaration

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