

COMMENTS TO RESEARCH ARTICLES

Gender bias and limitation of therapeutic effort[☆]

Sesgos de género y limitación del esfuerzo terapéutico

Commentary

Sunden et al. conducted a retrospective analysis comparing a group of women with a group of men admitted to ICU with a diagnosis of severe sepsis or septic shock. The results led them to conclude that care differs by sex in the emergency department, as women have lower completion of the sepsis bundle; however, this is not sufficient to explain the higher likelihood of death in the group of women. Despite possible biases in sample selection, given that in Europe only one in 3 patients diagnosed with sepsis is admitted to ICU, and the lack of information on comorbidities and sources of infection, they found that the association between sex and mortality could be mediated by other unmeasured factors, given the lack of statistical significance in the association.¹ Review studies on sepsis and gender^{2,3} (although, in reality, the variable considered in these studies is sex), are inconclusive and show disparate results on differential care and the higher mortality in women.

Is disaggregation by sex sufficient to explain health inequalities between women and men? To answer this, we need to define 2 fundamental concepts:^{4,5}

- *sex*, understood as the biological expression of the sexed human species, manifested at the anatomical, chromosomal, physiological level, and understood at the epidemiological/statistical level as a dichotomous variable (female/male); and
- *gender*, gender, defined as a socio-cultural construction that differentiates the feminine and the masculine based on the manifestation of socially attributed roles, expression of identities, behaviours and values that determine the way people relate to each other.

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Sunden-Cullberg J, Nilsson A, Inghammar M. Sex-based differences in ED management of critically ill patients with sepsis: a nationwide cohort study. *Int Care Med*. 2020;46:727–736. <https://doi.org/10.1007/s00134-019-05910-9>

Abstract

Purpose: To compare management and outcomes for critically ill women and men with sepsis in the emergency medical services (EMS), the emergency department (ED) and the ICU.

Methods: We used two prospectively compiled Swedish national quality registers, the National Quality Sepsis Registry and the Swedish Intensive Care Registry to identify a nationwide cohort of 2720 adults admitted to an ICU within 24 h of arrival to any of 32 EDs, with a diagnosis of severe sepsis or septic shock between 2008 and 2015.

Results: Patients were 44.5% female. In the EMS, a higher fraction of men had all vital signs recorded–54.4 vs 49.9% ($p=0.02$) and received IV fluids and oxygen–40.0 vs 34.8% ($p=0.02$). In the ED, men had completed 1-h sepsis bundles in 41.5% of cases compared to 30.0% in women ($p<0.001$), and shorter time to antibiotics–65 (IQR 30–136) vs 87 min (IQR 39–172) ($p=0.0001$). There was no significant difference between men and women regarding ICU nursing workload, mechanical ventilation or ICU length of stay. In severity-adjusted multivariable analysis, OR for women achieving a completed sepsis bundle, compared to men was 0.64 (CI 0.51–0.81). Thirty-day mortality was 25.0% for women and 23.1% for men ($p=0.24$). Adjusted OR for female death was 1.28 (CI 1.00–1.64), but the increased mortality was not mediated by differential bundle completion.

Conclusions: Women and men with severe sepsis or septic shock received differential care in the ED, but this did not explain higher odds of death in women.

The biomedical model, traditionally used in research and the care of disease, is based on an androcentric vision. It takes the male pattern as the human pattern, making differences that may exist with women, the other half of human beings, invisible. It is true that there are biological similarities between women and men, given that they are individuals of the same species, but there are also

differences in how diseases present, their prevalence and response to treatment.⁵

Strictly biological differences, linked to sex, are not the only reasons for these differential manifestations. The different life conditions, linked in this case to gender, are a main factor, although less studied. Differences in the time dedicated to care burdens, domestic chores, or leisure, among other elements, determine people's health and generate health inequalities for both sexes.⁴⁻⁶

It is in this scenario where the so-called gender biases come into play, understood as "the difference in the management of men and women with the same clinical diagnosis, which may have positive, negative or neutral health consequences".^{5,7} This erroneous and unequal care is determined by:

- not considering the biological differences that exist between the sexes and
- the influence on the ways disease is experienced due to gender conditioning factors.^{1,5-7}

In the first approach, it is important to investigate and determine whether there are specific differences related to physiological processes that may be mediated by gender. The knowledge gained from research on white men has been extrapolated to the rest of humanity. Little progress has been made since the ban on women's participation in clinical trials imposed in 1977 by the Food and Drug Administration, as women are still under-represented in current research, which still cannot determine the effects of drugs in relation to treatment during women's life cycle stages (menarche, active menstrual cycle and its phases, post menopause), the effects on fertility and the effects in women on hormone replacement therapy.⁵⁻⁸ According to review studies^{2,3} women are represented in sepsis studies at around 30%.

Furthermore, clinical presentation may be different in women and men, but possible differences between the sexes are ignored, termed atypical presentations, for example, the symptoms of acute myocardial infarction in women (only 30% of women present with the traditionally referenced symptoms of infarction: chest pain radiating to the left arm, rather than other more non-specific symptoms such as shoulder pain, abdominal pain, nausea). Because practitioners have not been trained in these differences, they seek an androcentric clinical pattern, and diagnosis and treatment are delayed. The bias towards less diagnostic and therapeutic effort is because possible differences between the sexes and the different ways of experiencing the disease are not considered.^{5,7}

In the present case, the variability of inflammatory markers (tumour necrosis factor alpha, interleukin-6, and interleukin-10) in both groups, and levels of sex hormones, also in both groups and disaggregated by age, considering the fertile cycle in women, could provide important data to consider sex-related difference a determining factor in sepsis mortality.²

In the second approach, there may be differential behaviour by sex in relation to socialisation processes. Gender roles are socially established patterns of behaviour that shape the way people seek help or express their symptoms in the disease process (health-illness) they are going

through. They also determine the way people access health resources, both the level of care (primary care, emergency care, specialist care) and their interaction and communication with health professionals.⁴⁻⁸

Gender roles determine a different presentation of disease between women and men. For example, according to the traditional role of femininity, women have greater self-perception of disorders that they translate into moods and feelings of illness. By contrast, from the traditional role of masculinity, there is a feeling of invulnerability and the self-perception of illness is delayed in time. This behavioural model means that women seek help more frequently and from primary care services than men, who seek help in emergency and specialist care services when their symptoms are more evident. Thus, these ways of experiencing disease or seeking help feed gender stereotypes: women complain more and for more non-specific causes than men, men consult when causes are more severe. These stereotypes form one of the bases of gender bias in care: health professionals give greater credibility to men's disease severity, and here is where the lesser diagnostic and therapeutic effort with women starts.^{7,9}

In the study by Sunden et al. vital signs were recorded less in women, and they also received less treatment (intravenous fluids and oxygen therapy) during outpatient emergency care. Also care in the emergency department was different: the sepsis bundle for men was completed within one hour in 41.5% of cases compared to 30% in women, who were also later to receive antibiotics. This was corroborated by stratifying by age groups for women and men.

To avoid overlooking these sex and gender differences, which influence the health and wellbeing of both women and men, we propose incorporating a gender approach into research and care. This would require the cross-cutting implementation of gender content in the training of health professionals, as well as initiatives to actively include the gender perspective in research, the basis of knowledge.^{3,5-9}

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