Società Medico Chirurgica di Ferrara

Medicina, Cura e Genere

Museo MAGI' 900, Pieve di Cento – 6 maggio 2016

SEPSI E DIFFERENZE DI GENERE

Massimo Gallerani
U.O. di Medicina Interna Ospedaliera
Azienda Ospedaliero Universitaria di Ferrara

Sex Differences in Infectious Diseases–Common but Neglected

Jan van Lunzen[1,2] and Marcus Altfeld[2,3]

[1]Infectious Diseases Unit, University Medical Center Hamburg-Eppendorf, [2]Heinrich-Pette-Institute, Leibniz Institute for Experimental Virology, Hamburg, Germany; and [3]Massachusetts Institute of Technology and Harvard, Ragon Institute of Massachusetts General Hospital, Boston

Women and men are different—and this fundamental observation extends to their susceptibility and response to different diseases, including autoimmune and infectious diseases. Apart from cultural and behavioral differences between the sexes that play a prominent role in the exposure to pathogens, increasing data show that women and men also differ in their immune responses to infections. This applies to infections with viruses, bacteria, and parasites, including the pathogens most relevant for human health, causing malaria, tuberculosis, AIDS, hepatitis, and influenza. Only recently, the biological pathways responsible for these sex-based differences in the manifestations of infectious diseases have been started to be unveiled. These include immunological pathways affected by sex hormones, as well as consequences of differential expression of X-chromosome–encoded genes on immune responses to pathogens. Further research is required to gain a better understanding of the differences in immunity to infections between women and men in order to develop individualized treatment concepts in infectious diseases that take sex-specific host factors into account.

Differenze tra maschi e femmine

- **nella suscettibilità alle malattie infettive**
- **di esposizione a malattie infettive**
- **di assistenza sanitaria e di trattamento**
- **nelle conseguenze di malattie infettive**

Cause di tale differenza

Implicazioni di differenze di sesso e di genere tra per sorveglianza e risposta all'infezione

Epidemiology and recent trends of severe sepsis in Spain: a nationwide population-based analysis (2006-2011)

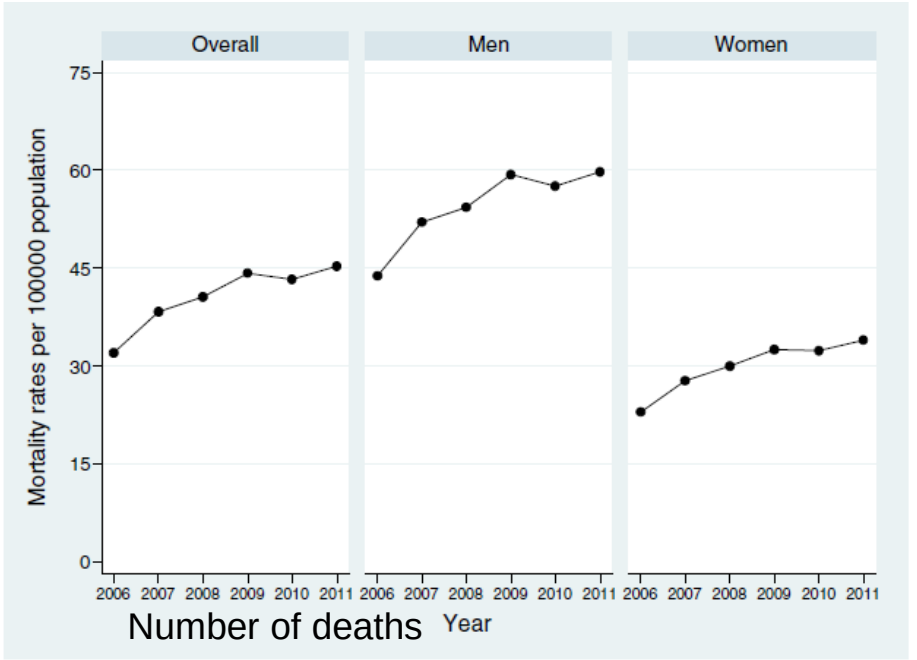
Bouza *et al. BMC Infectious Diseases* 2015, **14**:717
http://www.biomedcentral.com/1471-2334/14/717

Carmen Bouza*, Teresa López-Cuadrado, Zuleika Saz-Parkinson and José María Amate-Blanco

Over the 6-year period we identified 240939 cases of severe sepsis nationwide representing 1.1% of all hospitalisations. Overall 58% of cases were men, 66% were over the age of 65 and about 67% had associated comorbidities.

This study shows that hospitalizations with severe sepsis are frequent and associated with substantial in-hospital mortality

Number of cases

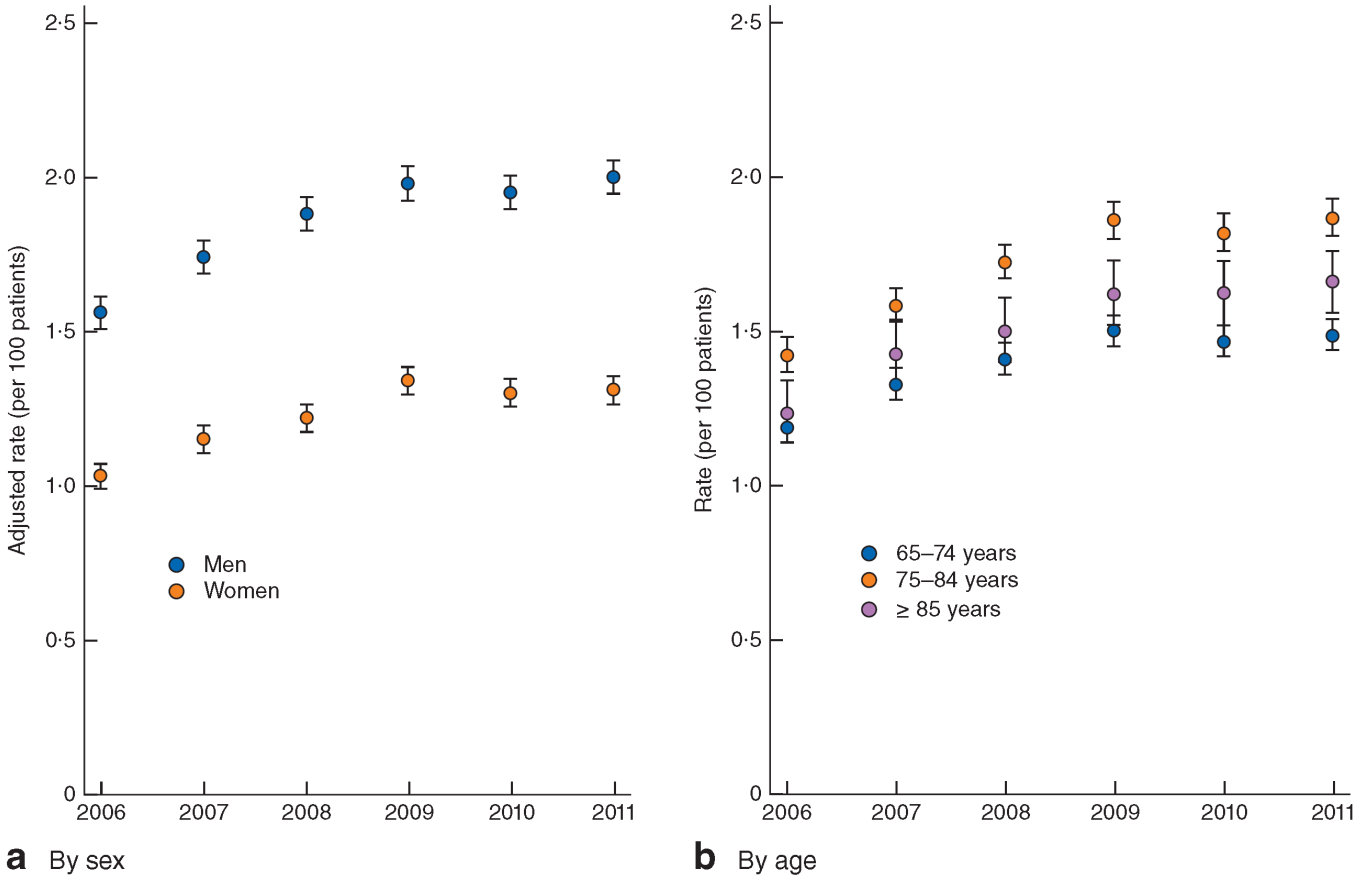


Number of deaths

Characteristics, incidence and temporal trends of sepsis in elderly patients undergoing surgery

C. Bouza, T. López-Cuadrado and J. M. Amate-Blanco

Critical Care 2012, 16:R92



A total of 44.342 episodes of sepsis were identified, representing 1,5 per cent of all 2871199 surgical hospital admissions of patients aged 65 years or older. The rates varied with age and sex. The in-hospital case-fatality rate was 43,9 per cent (19.482 patients), and associated with age, co-morbidity and organ dysfunction.

Gender Differences in Human Sepsis

Jörg Schröder, MD; Volker Kahlke, MD; Karl-Hermann Staubach, MD; Peter Zabel, MD; Frank Stüber, MD

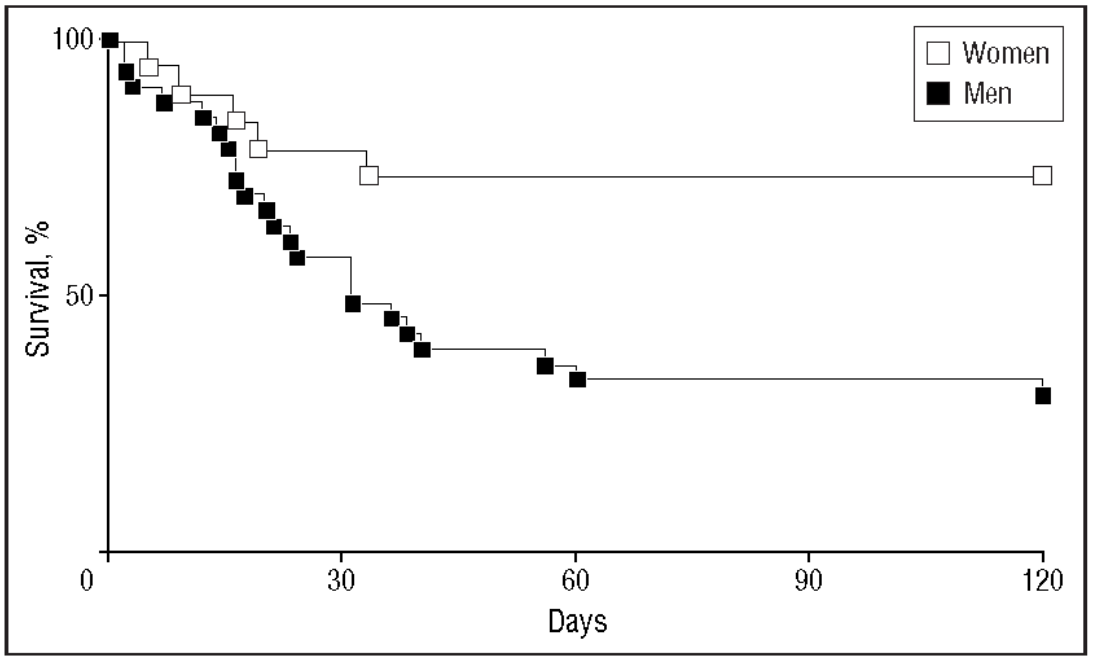


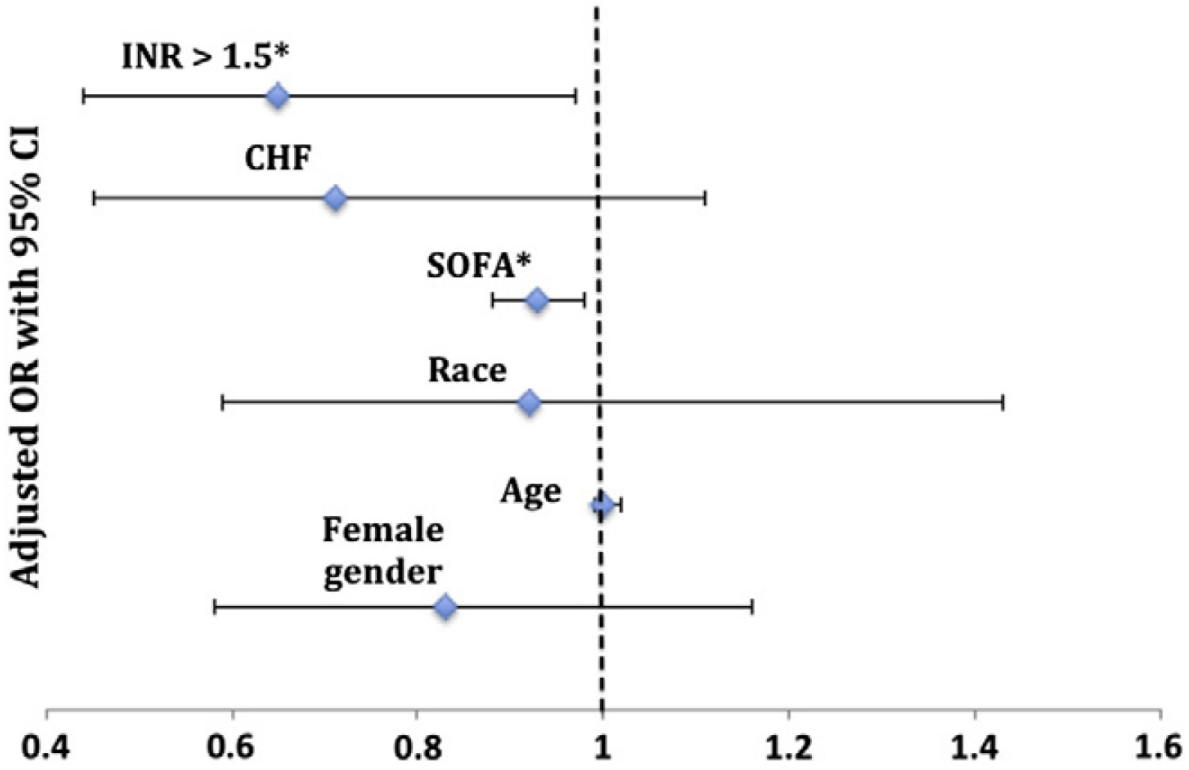
Figure 2. *Kaplan-Meier hospital survival analysis for female and male patients. Survival was significantly different between men and women with severe sepsis (P<.008 for hospital survival, log-rank test).*

Arch Surg. 1998;133:1200-1205

The DISPARITY Study: do gender differences exist in Surviving Sepsis Campaign resuscitation bundle completion, completion of individual bundle elements, or sepsis mortality?☆,☆☆

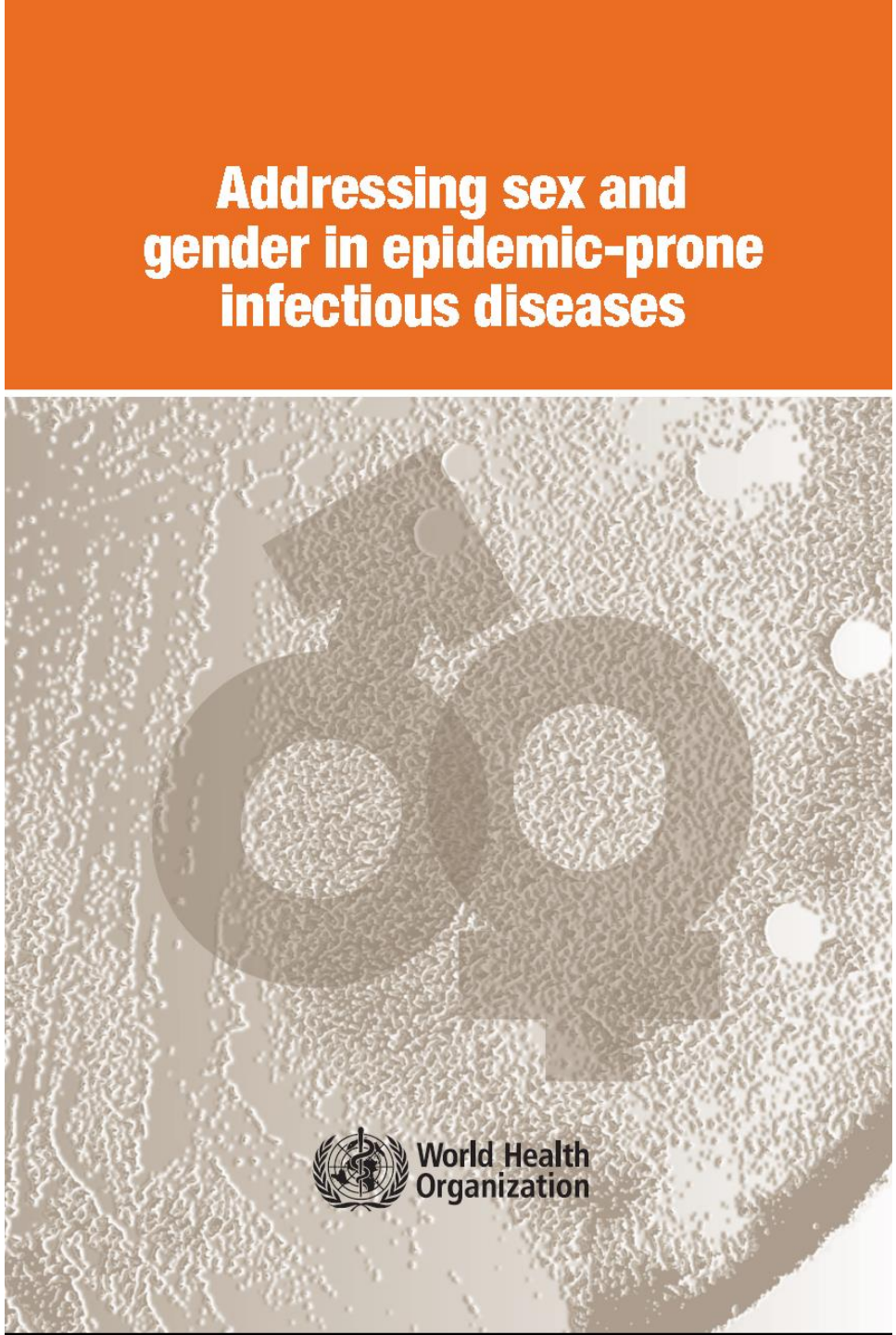
Tracy E. Madsen, MD [a,b,*], James Simmons, MD [c], Esther K. Choo, MD, MPH [a,b], David Portelli, MD [b], Alyson J. McGregor, MD [a,b], Anthony M. Napoli, MD [a,b]

[a] *Division of Women's Health in Emergency Care, The Alpert Medical School of Brown University, Department of Emergency Medicine, Rhode Island Hospital, Providence, RI*
[b] *The Alpert Medical School of Brown University, Department of Emergency Medicine, Rhode Island Hospital, Providence, RI*
[c] *Boston University School of Medicine, Department of Medicine, Boston Medical Center, Boston, MA*



- 840 patients were enrolled. The mean age was 66 years; 44.8% were women.
- There was no association between gender and bundle completion (OR = 0.83, 95% CI 0.58-1.16), controlling for age, race, Sequential Organ Failure Assessment, congestive heart failure, and coagulopathy.
- In-hospital mortality did not differ by gender.

Journal of Critical Care 29 (2014) 473.e7–473.e11



BIOLOGICAL SEX DIFFERENCES

Fundamental differences between males and females exist at every biological level, from that at the organism as a whole, to organs and organs systems, to individual cells. These biological differences are complex, and may conferm advantages either to males or females depending on the infectious agent.

Gender-related differences

Gender influences both patterns of exposure to infectious agents and the treatment of infectious disease.

- Time spent at home and away from home
- Responsibility for caring for livestock
- Health care received
- Responsibility for caring for the sick
- Scientific knowledge about treatment

DISEASE	INFANTS	YOUNG CHILDREN (AGE 1–5 YEARS)	POSSIBLE REASONS FOR MALE FEMALE DIFFERENCES SUGGESTED BY INVESTIGATORS
Diarrhoeal disease	Incidence higher for males	Mortality rates often higher for females despite similar or slightly higher incidence rates for males.	Higher incidence rates for male children may be caused by greater male mobility. Higher female case-fatality rates found in some countries may be due to poorer health care.
Acute lower respiratory infections and pneumonia	Mortality rates higher for males	Sex differences in mortality for young children vary. Generally only small differences in incidence rates.	Mortality rates higher for males in infancy probably due to less mature lungs in boys during infancy. This disadvantage abates in early childhood.
Neonatal tetanus	Mortality rates higher for males		It is not known why mortality rates are higher for males.
Measles		Similar infection rates, but higher female mortality rates observed.	Possibly less adequate medical care is provided to girls. Possibly girls are exposed to a larger dose in the home.
Dengue		Some evidence to suggest that girls are more likely to have dengue shock syndrome than boys.	Biological reasons, related to a more aggressive immune system response have been cited as possible causes of more severe illness in girls.

Sex differences in morbidity and mortality for selected epidemic-prone infectious diseases amog infants and young children

Impact of Gender on Sepsis Mortality and Severity of Illness for Prepubertal and Postpubertal Children

Ghuman AK, Newth CJL, Lhemani RG - J Pediatr 2013; 163: 835-40.

- Prepubertal females (n = 272; 9.9% mortality) and prepubertal males (n = 303; 10.9% mortality) had similar mortality and severity of illness .
- Postpubertal females (n = 233; mortality, 5.6%) had lower mortality than postpubertal males (n = 212; mortality, 11.8%; P = .03).
- Postpubertal children, female gender was independently associated with a lower initial severity of illness (Pediatric Index of Mortality PIM 2 ROM: OR, 0.77; 95% CI, 0.62-0.96; P = .02).

	Females (n = 233)	Males (n = 212)	*P* value
Age, months, median (IQR)	211.3 (201.8-230.2)	210.4 (201.7-230.3)	.77*
Mechanical ventilation, n (%)†	35 (24.3)	45 (32.8)	.15‡
Dialysis, n (%)§	14 (11.8)	10 (8.8)	.59‡
PICU LOS, days, median (IQR)	2.50 (1.37-5.67)	2.90 (1.30-6.35)	.66*
PIM 2 ROM, median (IQR)	0.013 (0.009-0.041)	0.013 (0.010-0.050)	.02*
Mortality, n (%)	13 (5.6)	25 (11.8)	.03‡

These outcome differences in postpubertal children may reflect a hormonal influence on the response to infection or differences in underlying comorbidities, source of infection, or behavior.

Gender Affects Cardiovascular Performance and Cellular Immunity After Injury

With highest estrogen levels

- Estrogen, DHEA, ER agonists
- Flutamide

With high DHT and low estrogen levels

Estradiol

5α-dihydrotestosterone

Preserve or Enhance Functions

Depression of Function

- Improves cardiovascular functions
- Rapid blood volume restitution

Mϕ Lymphocyte

- Cytokine release maintained (e.g., IL-3)
- Preserved splenocyte proliferation
- Maintained MHC Class II expression
- Oophorectomy or menopause reduces function

- Reduces cardiovascular functions

Mϕ Lymphocyte

- Cytokine release altered
- Reduced splenocyte proliferation
- Decreased MHC Class II expression
- Castration improves function

Virulence 2014; 5:1, 12-19.

Influence of Gender on the Outcome of Severe Sepsis*

A Reappraisal

Christophe Adrie, MD, PhD; Elie Azoulay, MD, PhD; Adrien Francais, PhD; Christophe Clec'h, MD; Loic Darques, MD; Carole Schwebel, MD; Didier Nakache, PhD; Samir Jamali, MD; Dany Goldgran-Toledano, MD; Maïté Garrouste-Orgeas, MD; and Jean François Timsit, MD, PhD; for the OutcomeRea Study Group†

Background: **The influence of gender on survival of patients with severe sepsis is unclear. Earlier studies suggested better survival in women, possibly related to the sex-steroid profile.**
Methods: **To investigate whether mortality from severe sepsis was higher in men than in women and whether the difference varied with menopausal status, we studied 1,692 patients with severe sepsis included in the OutcomeRea database over an 8-year period. We conducted a nested case-control study, accurately matching men and women on three criteria: a death propensity score, age, and center. Subgroup analyses were performed on individuals ≤ 50 years old (men vs premenopausal women) and > 50 years old (men vs postmenopausal women).**
Results: **We matched 1,000 men to 608 women with severe sepsis before and after adjustment for confounding factors (*ie*, chronic respiratory failure; metastatic cancer; immunocompromised status; emergency surgery, acute respiratory failure, and shock at admission; urinary tract infection; and type of microorganism). Overall hospital mortality was significantly lower in women (adjusted odds ratio [OR], 0.75; 95% confidence interval [CI], 0.57 to 0.97; p = 0.02). In the group > 50 years old (481 women, 778 men), hospital mortality was significantly lower in women (OR, 0.69; 95% CI, 0.52 to 0.93; p = 0.014). Hospital mortality was not significantly different between men and women in the younger group (127 women, 222 men) [OR, 1.01; 95% CI, 0.52 to 1.97; p = 0.98]. Level of care, as assessed using the nine equivalents of nursing manpower use score, was identical in men and women.**
Conclusions: **Among individuals > 50 years old with severe sepsis, women have a lower risk of hospital mortality than men.** ***(CHEST 2007; 132:1786–1793)***

Variables	OR‡	95% CI	p Value
Overall matched cohort (608 women, 1,000 men)			
After matching on risk factors for death			
ICU mortality	0.80	0.62–1.03	0.09
Hospital mortality	0.78	0.61–1.01	0.06
After adjusting for confounding variables†			
ICU mortality	0.75	0.58–0.98	0.03
Hospital mortality	0.75	0.57–0.97	0.02
Patients > 50 yr old (481 women, 778 men)			
After matching on risk factors for death			
ICU mortality	0.73	0.55–0.97	0.03
Hospital mortality	0.71	0.54–0.94	0.02
After adjusting for confounding variables†			
ICU mortality	0.70	0.52–0.94	0.018
Hospital mortality	0.69	0.52–0.93	0.014
Patient < 50 yr old (127 women, 222 men)			
After matching on risk factors for death			
ICU mortality	1.33	0.72–2.46	0.36
Hospital mortality	1.34	0.73–2.44	0.35
After adjusting for confounding variables†			
ICU mortality	1.01	0.51–1.99	0.98
Hospital mortality	1.01	0.52–1.97	0.98

Influence of gender mortality in patients with severe sepsis

- **Overall hospital mortality was significantly lower in women (OR, 0.75; p 0.02).**
- **Hospital mortality was not significantly different between men and women in the younger group [OR, 1.01; p 0.98].**
- **In the group > 50 years old, hospital mortality was significantly lower in women (OR, 0.69; p 0.014).**
- **Level of care, as assessed using the nine equivalents of nursing manpower use score, was identical in men and women.**

- A large regional Italian cohort included 3,902 patients (63.5% male). Female were significantly older than male patients (66 ± 16 years vs. 63 ± 16 years, P < 0.001).
- Intensive Care Unit (ICU) mortality was similar in men and women in the whole cohort (20.1% vs. 19.8%, P = 0.834), but in patients with severe sepsis was significantly greater in women than in men (63.5% vs. 46.4%, P = 0.007).

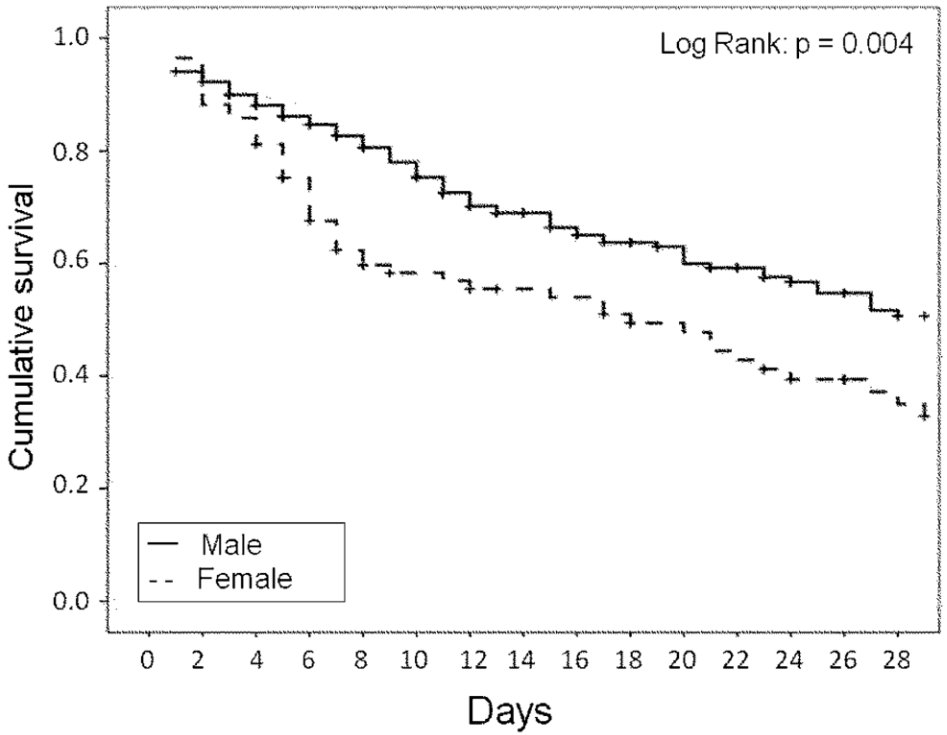


Figure 2 Kaplan-Meier survival curves representing 28-day survival according to gender in patients with severe sepsis.

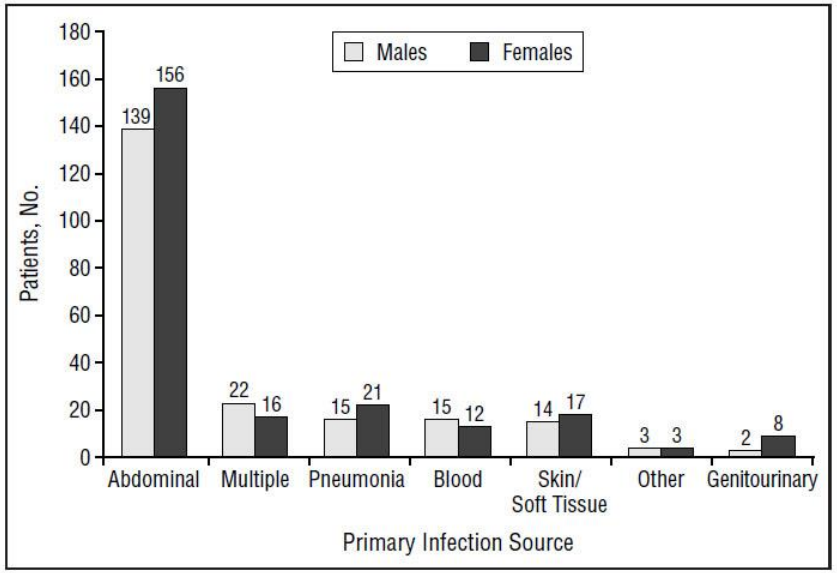
Female gender was independently associated with a higher risk of ICU death in patients with severe sepsis (odds ratio = 2.33, P = 0.009) but not in the whole cohort (odds ratio = 1.07, 95% CI = 0.87 to 1.34).

The influence of gender on the epidemiology of and outcome from severe sepsis

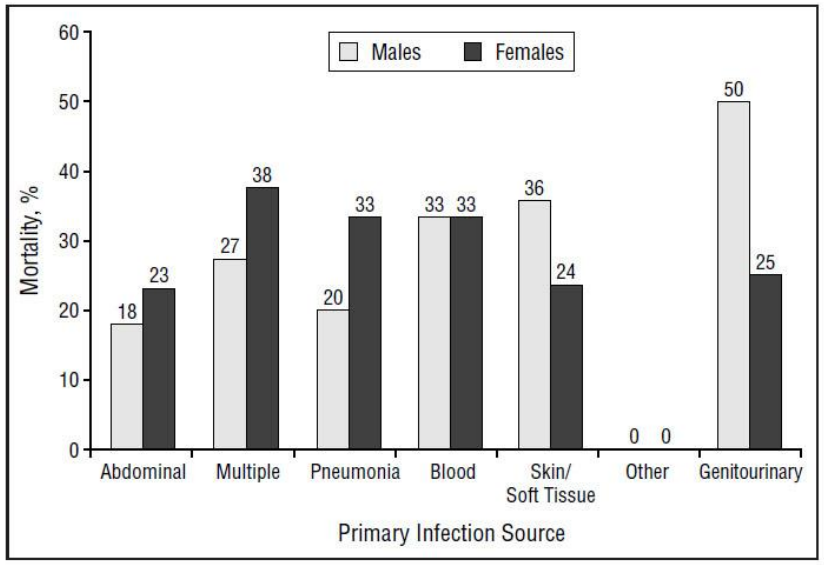
Sakr *et al. Critical Care* 2013, **17**:R50

Gender-Based Differences in Outcome in Patients With Sepsis

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



Preponderance of intra-abdominal infections among patients with sepsis admitted to the surgical intensive care unit. However, there was no difference in case mix between males and females.



Mortality rates as a function of primary source of infection. No differences between females and males.

- 1348 patients admitted in surgical intensive centers.
- There were no demographic differences between genders.
- The difference in mortality rates between female and male patients was not significant, except in octogenarians.
- In multivariate analysis APACHE III (p< 001), maximal multiple dysfunction score (P < 001) and female gender (p < 0,02) predicted mortality.

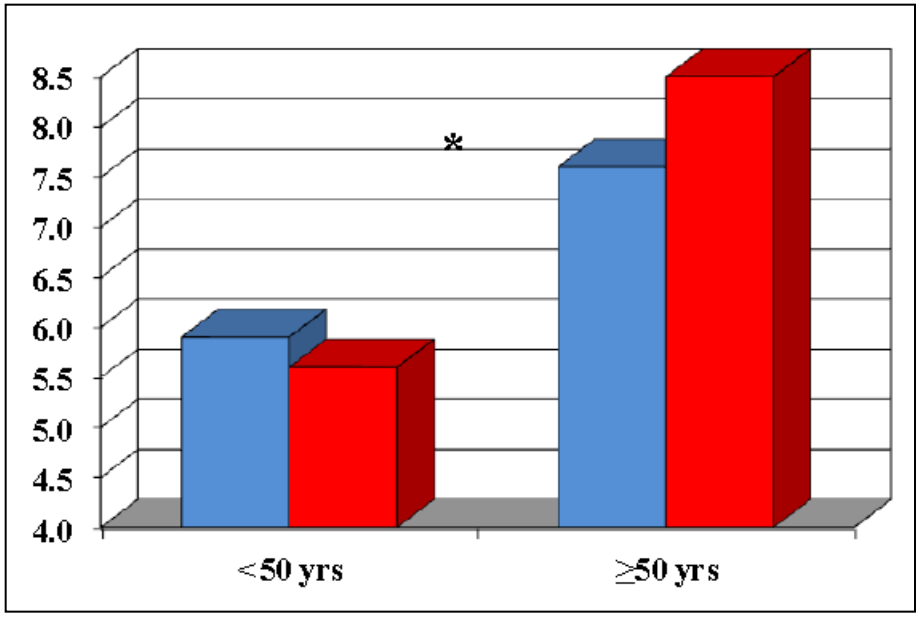
Arch Surg. 1999;134:1342-1347

Association of gender with outcomes in critically ill patients

Kamran Mahmood[1*], Kamal Eldeirawi[2] and Momen M Wahidi[1]

261,255 consecutive patients admitted to adult ICUs in United States from January 2004 to December 2008 were included.

Crude ICU mortality of gender goups based on age



* p-value for interaction is <0.0001

- Among the critically ill patients, women less than 50 years of age had a lower ICU mortality compared to men,
- 50 years of age or older women did not have a significant difference compared to men.
- **Women had a higher mortality compared to men after coronary artery bypass graft surgery and lower mortality with COPD exacerbation.**
- **There was no difference in mortality in acute coronary syndrome, sepsis or trauma.**

Crit Care 2012 May 22;16(3):R92. doi: 10.1186/cc11355.

Mortality in sepsis and its relationship with gender

Nasir N,Jamil B, Siddiqui S, Talat N, Khan F, HussainR

Pak J Med Sci 2015;
31(5):1201-1206.

ABSTRACT

Background and Objective: Sepsis remains a leading cause of death across the world, carrying a mortality rate of 20-50%. Women have been reported to be less likely to suffer from sepsis and to have a lower risk of mortality from sepsis compared to men. The objective of this study was to determine the relationship between gender and mortality in sepsis, and compare cytokine profiles of male and female patients.

Methods: This was a prospective case series on 97 patients admitted with sepsis. Clinical and microbiological data was gathered, blood samples were collected for cytokine (IL-10, IL-6 and TNFa) levels and patients were followed up for clinical outcome.

Results: There were 54% males and 46% females, with no significant difference of age or comorbids between genders. Respiratory tract infection was the commonest source of sepsis, and was more common in females (60%) compared to males (39%) (p=0.034). Males had a higher mortality (p=0.048, RR 1.73) and plasma IL-6 level(p=0.040) compared to females. Mean IL-6 plasma level was significantly (p<0.01) higher in patients who died vs. who recovered.

Conclusion: Our study shows that males with sepsis have a 70% greater mortality rate, and mortality is associated with a higher IL-6 plasma level.

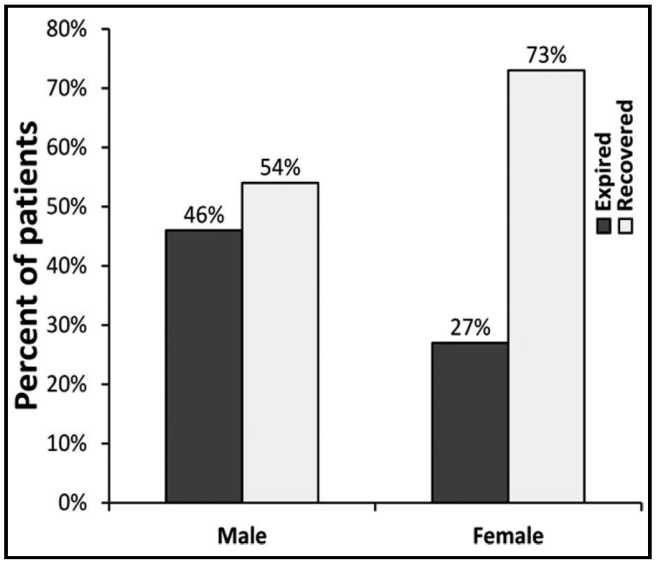


Fig.1: Bar chart comparing proportion of male and female patients expired and recovered. Difference was significant (p=0.048, Chi square test).

Predictors of *Clostridium difficile* infection severity in patients hospitalised in medical intensive care

Nagham Khanafer, Abdoulaye Touré, Cécile Chambrier, Martin Cour, Marie-Elisabeth Reverdy, Laurent Argaud, Philippe Vanhems

World J Gastroenterol 2013 November 28; 19(44): 8034-8041

Factors independently associated with severe *Clostridium difficile* infection among patients in medical intensive care unit

Variables	Unadjusted OR (95%CI)	*P* value	Adjusted OR (95%CI)	*P* value
Glasgow coma score	1.16 (0.99-1.36)	0.15	-	
Diabetes mellitus	4.89 (1.00-23.93)	0.04	-	
Previous PPI exposure	2.55 (0.67-9.66)	0.17	-	
Coamoxiclav (in the previous 8 wk)	2.43 (0.65-9.07)	0.18	-	
Fluoroquinolones (in the previous 8 wk)	6.0 (1.12-32.28)	0.026	9.29 (1.16-74.28)	0.036
C-reactive protein (mg/L; 10 mg/L increments)	1.10 (1.02-1.18)	0.014	1.11 (1.02-1.21)	0.021
Male gender	5.11 (0.95-27.55)	0.045	8.45 (1.06-67.16)	0.044

Gender differences in outcome and use of resources do exist in Swedish intensive care, but to no advantage for women of premenopausal age

Carolina Samuelsson[1,2*], Folke Sjöberg[3,4], Göran Karlström[5], Thomas Nolin[6] and Sten M Walther[7]

127,254 consecutive Intensive Care Registry ICU admissions from 2008 through 2012

- There was no sex difference in risk-adjusted mortality, and there was no sex difference in risk-adjusted mortality in the group 45 years of age and younger.
- For the group of patients older than 45 years of age, we found a reduced risk-adjusted mortality in men admitted for cardiac arrest.
- For the cohort as a whole, and for those admitted with multiple trauma, male sex was associated with a higher nurse workload score and a longer ICU stay.
- **The premenopausal female sex was not associated with a survival advantage following intensive care in Sweden.**
- **Men used more ICU resources per admission than women did.**

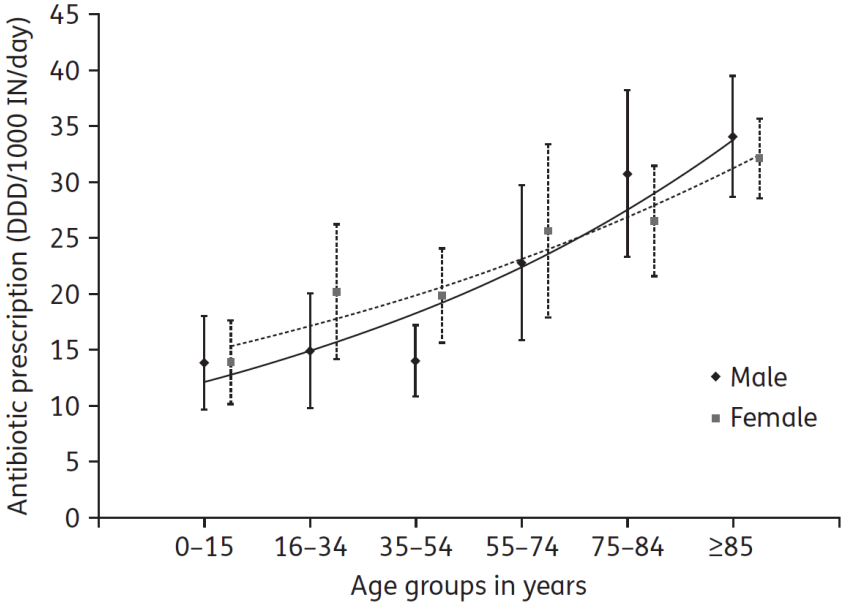
Gender differences in antibiotic prescribing in the community: a systematic review and meta-analysis

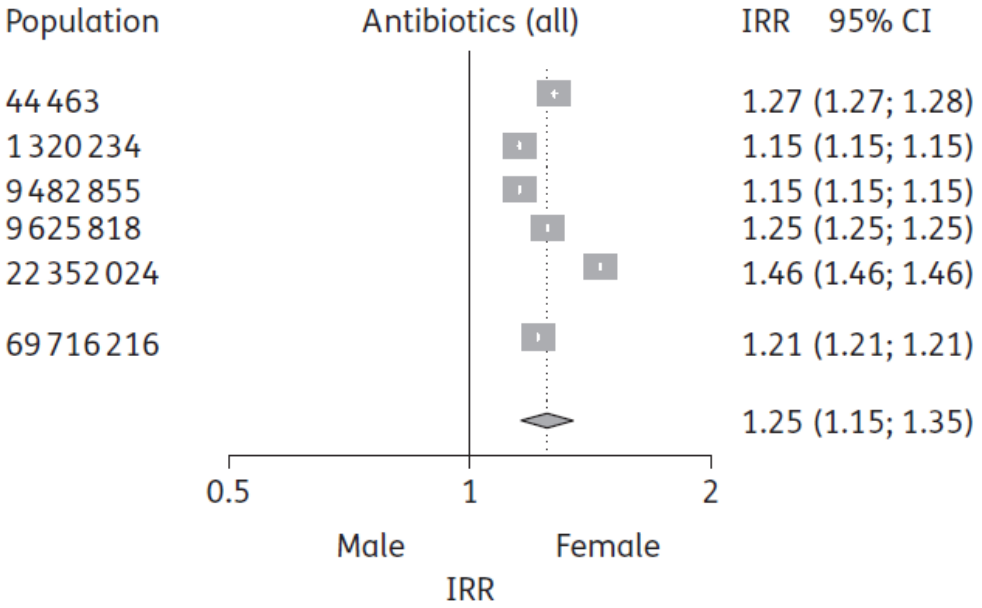
Schroder W. Et al. J Antimicrob Chemother 2016

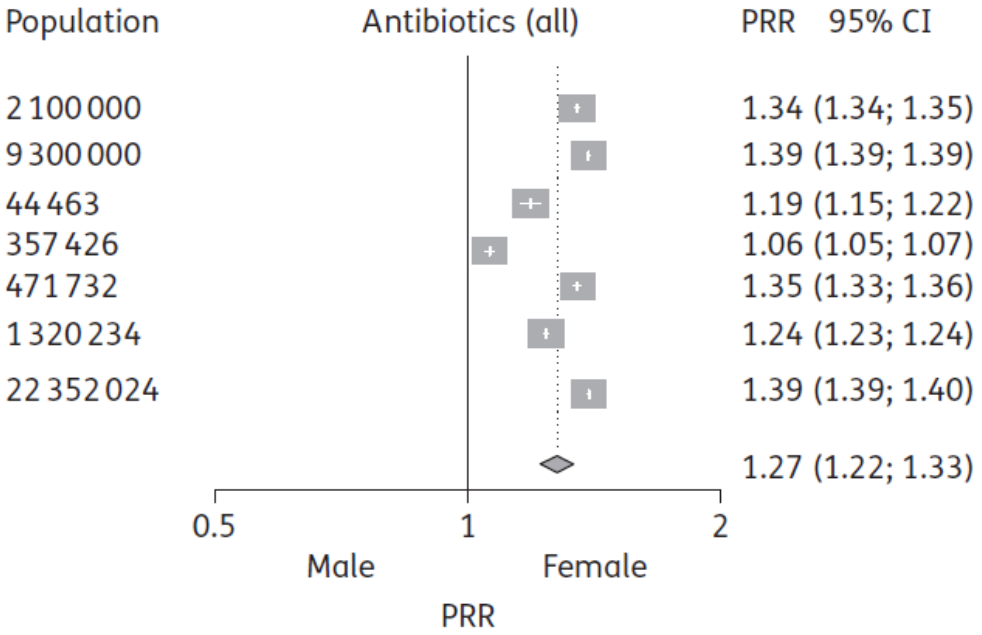
Ricerca su tutti gli studi - pubblicati dal 1976 al 2013 - che hanno analizzato la prescrizione di antibiotici nelle cure primarie (5 nazionali e 6 regionali).

Le donne avevano una probabilità superiore del 27% rispetto agli uomini di ricevere una prescrizione di antibiotici nella loro vita.

La quantità di antibiotici prescritti alle donne è risultata superiore del 36% rispetto a quella rilasciata agli uomini nella fascia di età dai 16 ai 34 anni e maggiore del 40% dai 35 ai 54 anni. In particolare, la quantità di cefalosporine e macrolidi prescritti per le donne erano più elevate del 44% e del 32% rispetto a quelli prescritti per gli uomini.







Possibili spiegazioni - quanto meno relative alla realtà italiana - si possono dedurre dalle statistiche che certificano come le donne si rivolgano più spesso al medico curante, forse sentendo più dei maschi la necessità di dover guarire subito e quindi insistendo maggiormente per ottenere una prescrizione.

Inoltre, da fonti dell'Istituto superiore di sanità, risulta che le donne commettano più spesso degli uomini l'errore di trattare con antibiotici una comune patologia virale come l'influenza, favorendo ulteriormente il fenomeno della resistenza batterica agli antibiotici.

Gender Differences in Rates of Carriage and Bloodstream Infection Caused by Methicillin-Resistant *Staphylococcus aureus*: Are They Real, Do They Matter and Why?

Hilary H

[1]Departme

Molecular

- Males are more prone to bacterial sepsis, but some studies suggest females may have a poorer prognosis from BSI.
- Hand-hygiene behavior varies according to gender.
- Males are less compliant, which in turn may predispose them to higher colonization and infection rates.
- Female hormones such as estrogen affect the expression of virulence factors in Pseudomonas aeruginosa, and although not studied, this may also apply to S. aureus.

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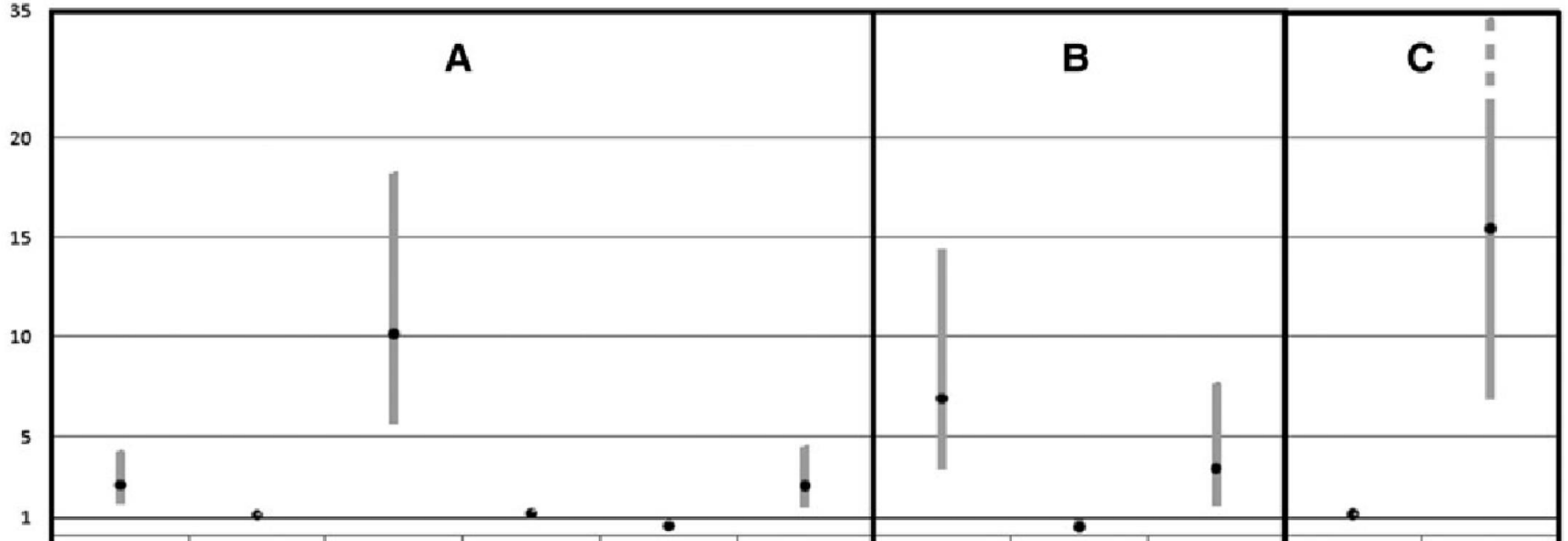
specific infection prevention campaigns, and other factors such as the possible role of contact sports and occupation.

- 2266 patients with Urinary tract infections (UTIs) were considered (73,7% women), 116 developed sepsis and 84 (54,8% female) with a fatal outcome.
- In hospital mortality was associated with P. aeruginosa infection, female gender, Charlson comorbidity index, age and E. coli infection.



	A						B			C	
	Female	Age	Sepsis	CCI	E.Coli	P. Aeruginosa	Sepsis	E. Coli	P. Aeruginosa	Age	Sepsis
● OR	2.570	1.047	10.152	1.148	0.500	2.541	6.918	0.458	3.387	1.086	15.459
95% C.I.	1.543–4.283	1.011–1.084	5.645–18.259	1.038–1.270	0.320–0.780	1.422–4.543	3.324–14.397	0.251–0.837	1.492–7.689	1.031–1.145	6.912–34.574
p	<0.001	0.036	<0.001	0.038	0.002	0.002	<0.001	0.011	<0.001	0.002	<0.001

FIG. 2. Factors independently associated with in-hospital mortalityin the whole population **(A)**, female subgroup **(B)**, and male subgroup **(C)**. Odds ratios (ORs) with their relative 95% confidence intervals (95% CIs) are shown. CCI, Charlson comorbidity index.

JOURNAL OF WOMEN'S HEALTH
Volume 24, Number 7, 2015

Is Female Gender as Harmful as Bacteria? Analysis of Hospital Admissions for Urinary Tract Infections in Elderly Patients

Fabio Fabbian, MD,[1,*] Alfredo De Giorgi, MD,[1,*] Pablo Jesús López-Soto, PhS,[2] Marco Pala, MD,[1] Ruana Tiseo, MD,[1] Rosario Cultrera, MD,[3] Massimo Gallerani, MD,[4] and Roberto Manfredini, MD[1]

JOURNAL OF WOMEN'S HEALTH
Volume 24, Number 7, 2015

CONSIDERAZIONI CONCLUSIVE

- Esiste un rischio diverso di infezione nei due sessi
- Cause di tale differenza
- Esiste un diverso rischio di morte per infezione tra sessi

CONSIDERAZIONI CONCLUSIVE

- I fattori che potrebbero spiegare le differenze tra i sessi nelle malattie infettive sono molteplici e comprendono fattori sociali, comportamentali e biologici.
- L'individuazione dei percorsi biologici sottostanti queste differenze possono consentire non solo una migliore comprensione della patogenesi e patologia, ma anche lo sviluppo di interventi e terapie che prendano in considerazione queste differenze sessuali
- Nuovi approfondimenti sulle differenze di sesso-based possono svolgere un ruolo importante nello sviluppo di trattamenti individualizzati che prendono in considerazione la diversità patogenica, la suscettibilità e le peculiarità legate al sesso.
- E' noto il bias degli uomini inseriti negli studi clinici, pertanto le prove di efficacia nella ricerca di differenze sesso-specifici in particolare per le malattie infettive sono ancora molto critiche.