



HAls and Gender: Differences in physiology and endocrinology



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Medical Microbiology & Infection Control

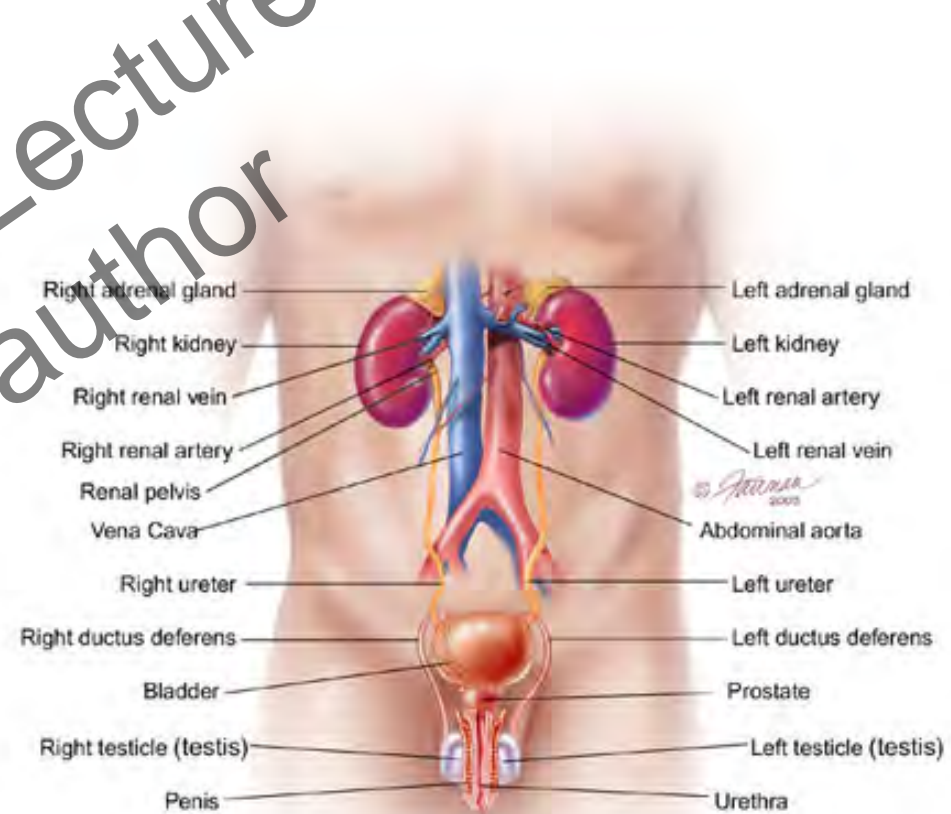
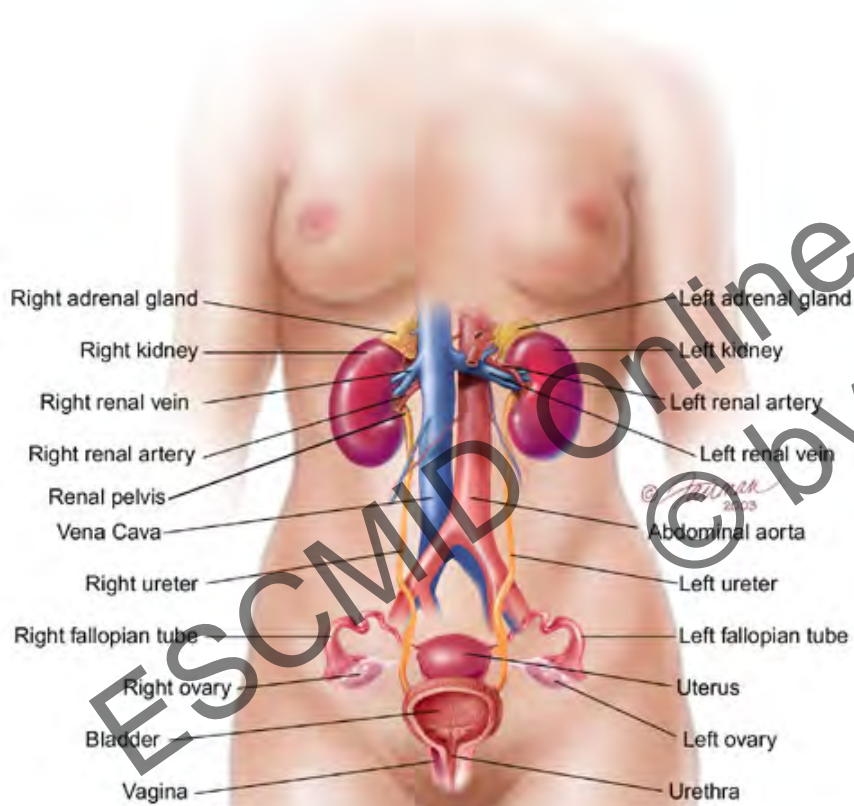


Gender differences in physiology and endocrinology that impact on the predisposition to HAIs

- ❑ Obvious differences
- ❑ Not so obvious differences
- ❑ A difficult-to-classify difference



The Obvious

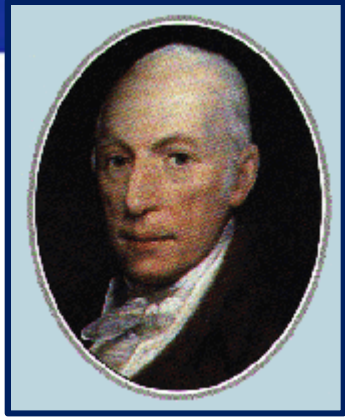


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The Obvious

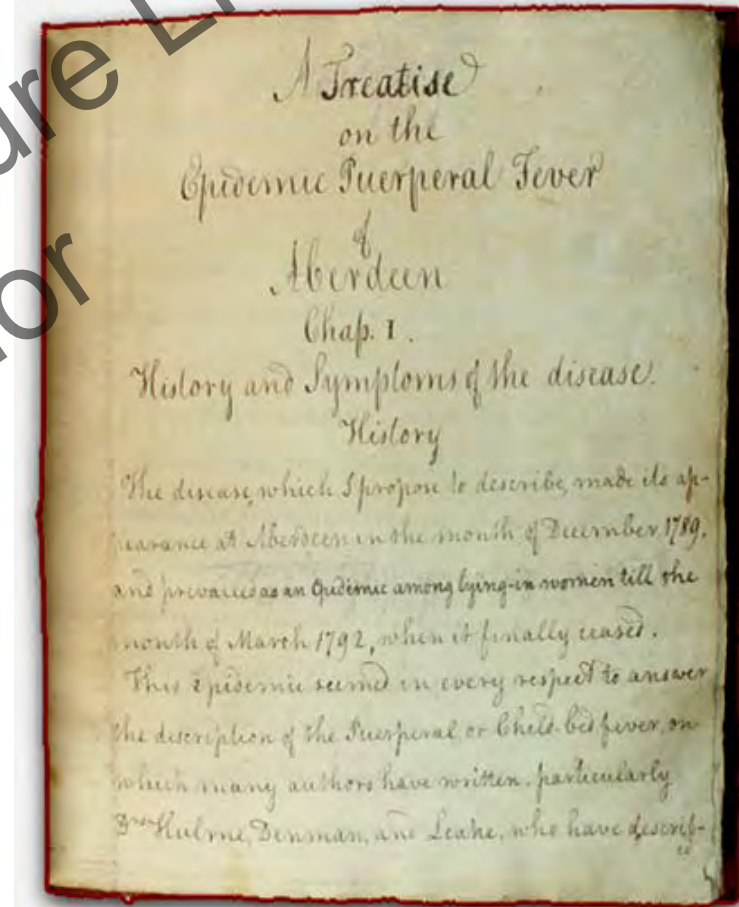
- Female urogenital tract
 - most important impact on HAIs
 - historical impact
 - characteristic organ-related infections



Alexander Gordon
1795 – Aberdeen

“A Treatise on the Epidemic Puerperal Fever of Aberdeen”

- ◆ contagious nature of the disease
- ◆ transmission by doctors, nurses, and instruments
- ◆ possible relation with erysipelas





Sir James Young Simpson

(1811 - 1870)

- Childbed fever
- Surgical wound fever
 - ✓ similar
 - ✓ cross infection
 - ✓ transmitted by doctors, and nurses



1850: *“On the Analogy between Puerperal and Surgical Fever”*



Ignaz Phillip Semmelweis

(1818 - 1865)





The Obvious

Obvious differences with impact on HAIs

- Organs with their own infections:
urinary tract, uterus, ovaria, prostate,
epididymis...



Factors associated with health care-acquired urinary tract infection

Nicholas Graves, PhD,^{a,b} Edward Tong, BS (Hons),^a Anthony P. Morton, MScAppI,^a Kate Halton, MSc,^{a,b} Merrilyn Curtis, MPH,^a David Lairson, PhD,^c and Michael Whitby, MPH^a
Brisbane, Australia, and Houston, Texas

(Am J Infect Control 2007;35:387-92.)

Table 2. Summary ORs of marginal and conditional effects logistic regression models

	Marginal effects						Conditional effects		
	Ordinary logistic			GEE logistic*			Random intercept logistic [†]		
	OR	(95% CI)	P value	OR	(95% CI) [†]	P value	OR	(95% CI)	P value
Fixed part									
Length of stay > national average for ICD-10 code	5.28	(2.46-11.34)	<.001	5.34	(2.37-12.01)	<.001	5.28	(2.46-11.34)	<.001
Male	0.44	(0.26-0.77)	.004	0.44	(0.26-0.76)	.003	0.44	(0.26-0.77)	.004
Transferred from/to another hospital	2.90	(1.39-6.04)	.004	2.88	(1.35-6.13)	.006	2.90	(1.39-6.04)	.004
Some assistance [§]	2.58	(1.51-4.41)	.001	2.60	(1.48-4.57)	.001	2.58	(1.51-4.41)	.001
Underlying neurologic disease	2.59	(1.49-4.49)	.001	2.57	(1.49-4.44)	.001	2.59	(1.49-4.49)	.001
Ever had a stroke	1.94	(1.03-3.67)	.041	1.95	(1.04-3.62)	.036	1.94	(1.03-3.67)	.041
Urinary catheter in situ during admission	5.16	(2.84-9.36)	<.001	5.21	(2.85-9.53)	<.001	5.16	(2.84-9.36)	<.001
Unresolved spinal injury	4.07	(1.04-15.92)	.044	4.04	(1.15-14.24)	.030	4.07	(1.04-15.92)	.044
Admitted with fracture or dislocation	3.34	(1.75-6.38)	<.001	3.43	(1.84-6.41)	<.001	3.34	(1.75-6.38)	<.001
Random part									
σ_U							<.0001		
ρ							<.0001		
Log likelihood	-255.77						-255.77		



- Urinary tract
 - Catheterisation → eliminates gender differences?

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Scandinavian Journal of Infectious Diseases, 2012; 44: 344–349

ORIGINAL ARTICLE

Factors associated with catheter-associated urinary tract infections and the effects of other concomitant nosocomial infections in intensive care units

EKREM TEMİZ¹, NIHAL PISKIN², HANDE AYDEMİR², NEFİSE ÖZTOPRAK², DENİZ AKDUMAN², GUVEN CELEBI² & FURUZAN KOKTURK³

From the ¹Departments of Infectious Diseases and Clinical Microbiology, Bitlis Government Hospital, Bitlis, ²Departments of Infectious Diseases and Clinical Microbiology, and ³Department of Biostatistics, School of Medicine, Zonguldak Karaelmas University, Zonguldak, Turkey

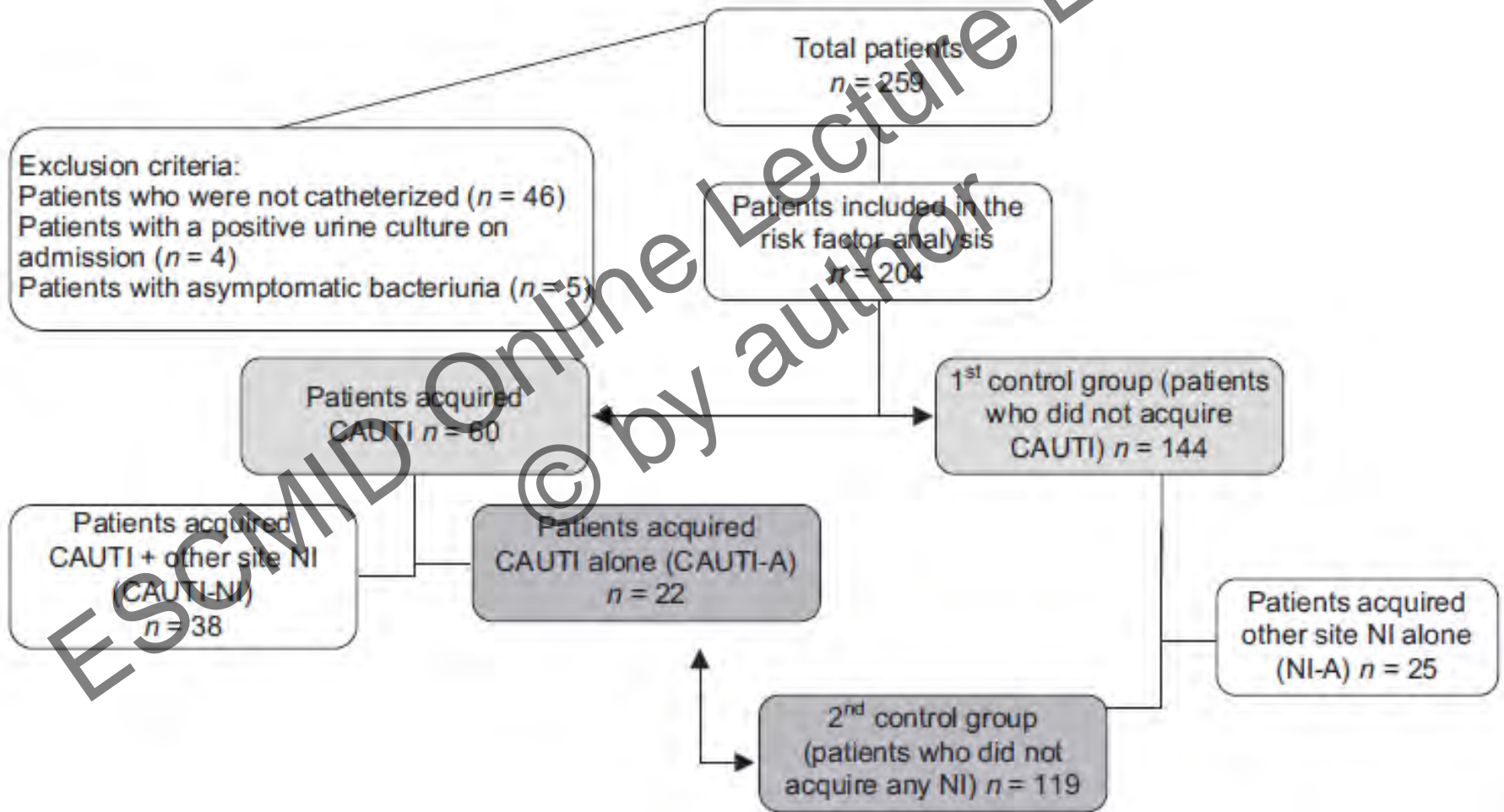




Table II. Results of Cox proportional hazards model.

Variable	Variable	HR	95% CI
In the presence of other site NI ^a	Presence of immune suppression	3.73	1.47–9.46
	Previous antibiotic usage	2.06	1.11–3.83
	Presence of other site NI	1.82	1.04–3.20
In the absence of other site NI ^b	Female sex	2.67	1.03–6.9
	Duration of urinary catheterization (per day)	1.07	1.01–1.13

Temiz *et al*, Scand J Inf Dis, 2012; **44**:344

-Bagshaw *et al*, Curr Opin Infect Dis 2006;**19**:67

-Leone *et al*, Int Care Med 2003;**29**:1077



The Not So Obvious

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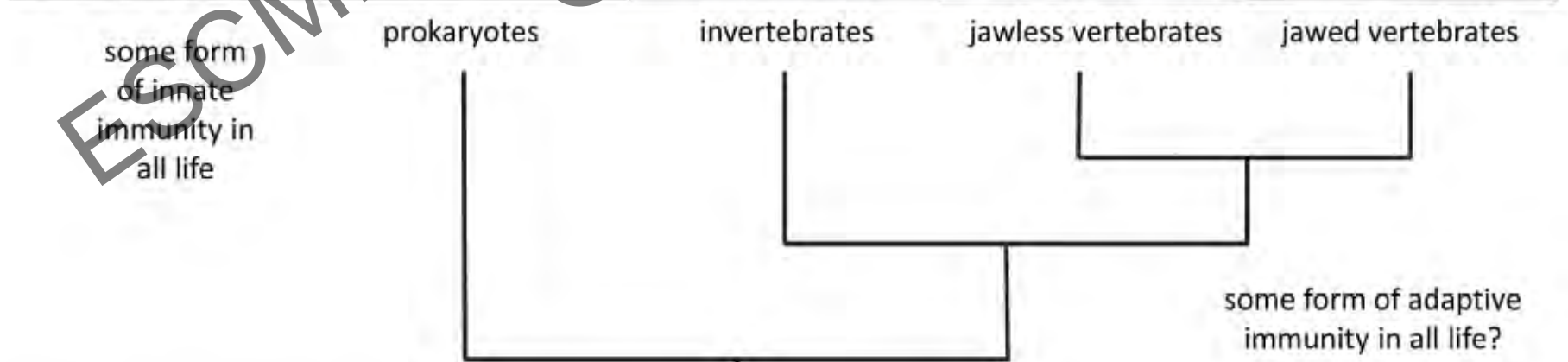
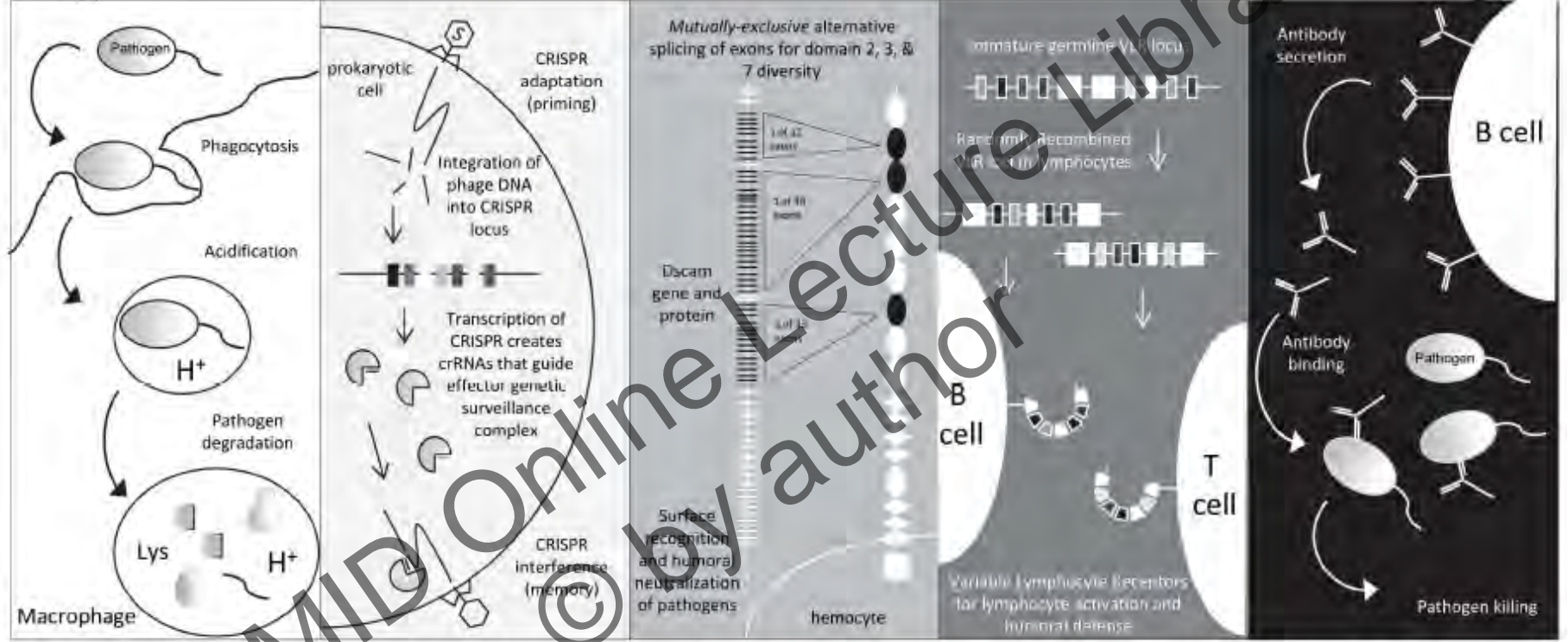


Pearls

Fifty Shades of Immune Defense

Michael F. Criscitiello^{1,2*}, Paul de Figueiredo^{2,3,4,5}

1 Comparative Immunogenetics Laboratory, Texas A&M University, College Station, Texas, United States of America, **2** Department of Veterinary Pathobiology, Texas A&M University, College Station, Texas, United States of America, **3** Borlaug Center, Texas A&M University, College Station, Texas, United States of America, **4** Department of Microbial and Molecular Pathogenesis, Texas A&M Health Science Center, College Station, Texas, United States of America, **5** Department of Plant Pathology & Microbiology, College Station, Texas, United States of America





The Not So Obvious

- Impact of gender and endocrinology on the immune system

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Immune Cells Have Sex and So Should Journal Articles

Sabra L. Klein

The W. Harry Feinstone Department of Molecular Microbiology and Immunology, Department of Biochemistry and Molecular Biology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland 21205

Facts:

- autoimmune diseases: 80% are women
- asthma: > 60% are women
- mortality of H5N1: 2-6 higher in women
- mortality from all malignant cancers: 1.6 higher in women



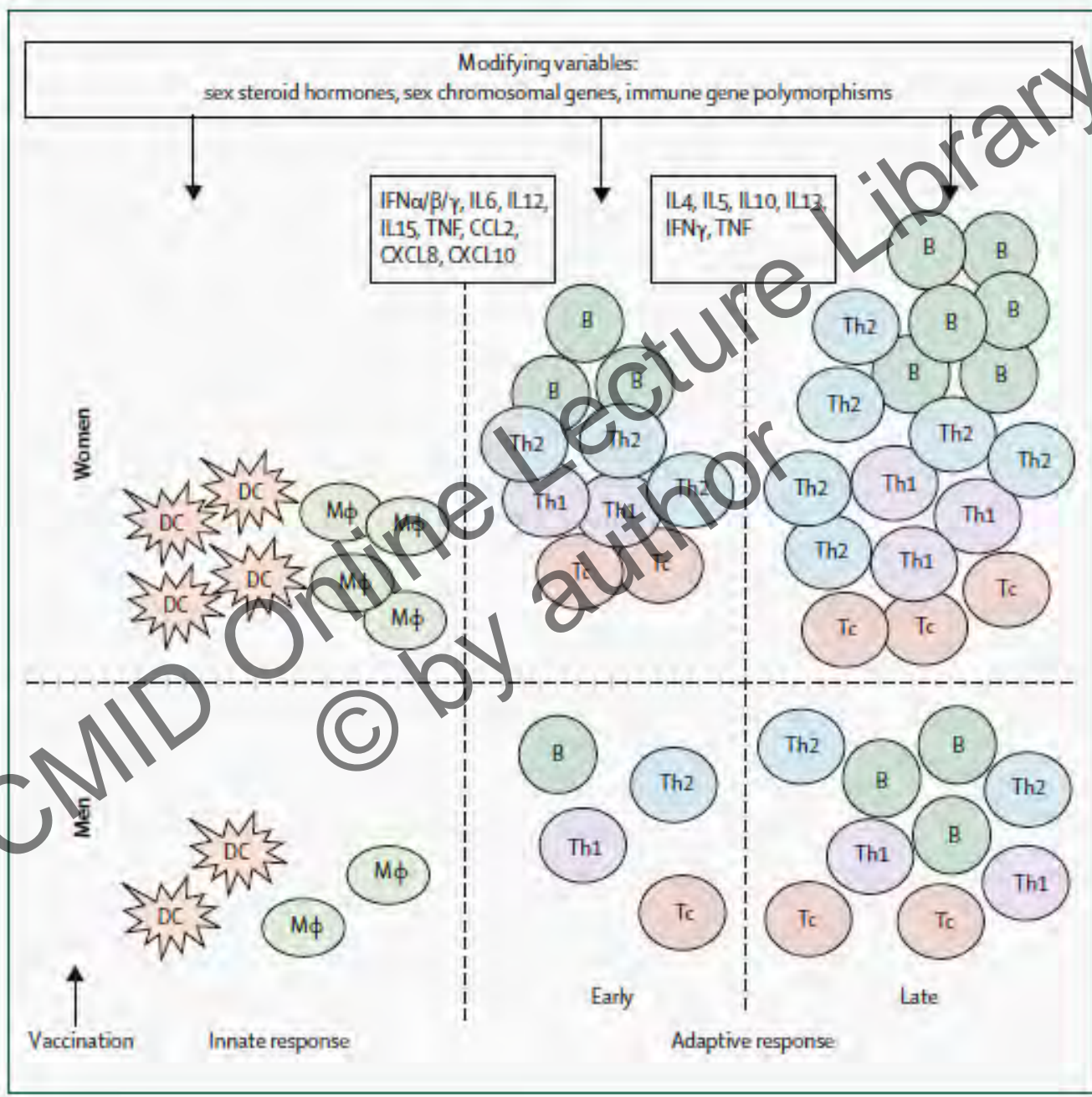
Immune response in females compared to males

- Innate immunity
 - differences in induction of genes associated with toll-like receptor pathways and interferon responses: 10-fold greater expression
 - number and activity of innate immune cells (monocytes, macrophages, dendritic cells): higher
 - inflammatory immune responses: higher
 - antigen-presenting cells: more efficient
 - natural killer cell activity: lower



Immune response in females compared to males

- Adaptive immunity
 - antigenic stimulation, vaccination, infection: greater humoral and cell-mediated immune responses
 - basal levels of Ig and antibody responses to viruses and vaccines: higher
 - CD3⁺, CD4⁺ counts, CD4⁺ to CD8⁺ ratios, Th1 responses: higher
 - IFN- γ , IL-4: higher
 - proportions of regulatory T-cells in response to certain viruses: higher



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Klein SI *et al* Lancet Infect Dis 2010,10:338



Mechanisms of sex differences in immune function

- Sex steroids
 - Testosterone, estradiol, progesterone influence functioning of immune cells
 - Hormones bind to specific receptors on lymphoid tissue cells, circulating lymphocytes, macrophages, dendritic cells → influence cell signaling pathways
 - Androgens and progesterone are suppressive and antiinflammatory, estrogens are proinflammatory

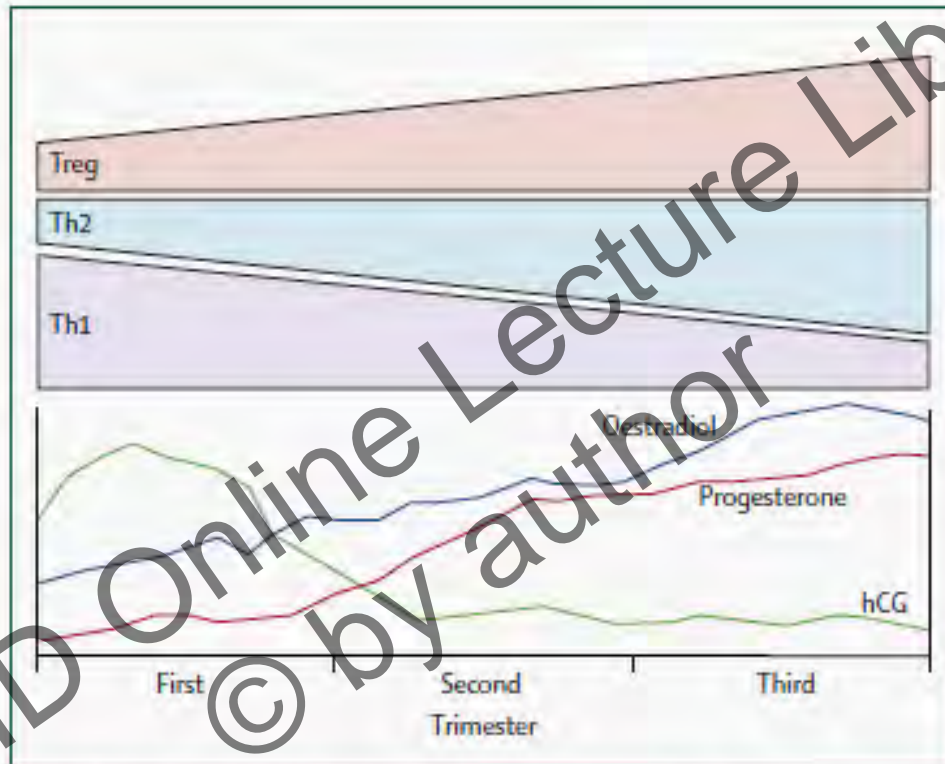


Figure 2: Hormonal changes during pregnancy affect T-cell responses
 The upper panel illustrates the shift in the T helper 1 (Th1) versus T helper 2 (Th2) balance toward a Th2 bias by the third trimester of pregnancy and the corresponding changes in regulatory-T-cell (Treg) activity. The bottom panel illustrates the variations in oestradiol, progesterone, and human chorionic gonadotropin (hCG) during the trimesters of pregnancy. Variations in sex hormone levels can lead to substantial alterations in T-cell activity during pregnancy.



Mechanisms of sex differences in immune function

- X-linked genes and genetic polymorphisms
 - Due to inherent imbalance in expression of genes encoded on X and Y chromosomes
 - Many genes on the X chromosome regulate immune function
 - Y chromosome genes affect sex-dependent susceptibility to autoimmune diseases



Infectious disease pathogenesis differs between sexes

- Different susceptibility to variety of pathogens
- Example:
 - females 40% less HIV RNA in circulation than males
 - females matched to same HIV load have 1.6-fold higher risk of developing AIDS (due to host inflammatory responses)



Infectious disease pathogenesis differs between sexes

Differences in immune response also depend on the microbe:

→ interaction between gender-specific immune responses and immune response to specific microbe

Example: estrogen induces TH1 inflammatory response to Lyme disease, but a TH2 protective response to *Taenia crassiceps*



Infectious disease pathogenesis differs between sexes

Microbe	Susceptibility in males	Susceptibility in females
<i>Treponema pallidum</i>	Yes	
<i>Borrelia burgdorferi</i>		Yes
<i>Listeria monocytogenes</i>		Yes
<i>Vibrio vulnificus</i>	Yes	
<i>Cryptococcus neoformans</i>	Yes	
<i>Candida albicans</i>		Yes
<i>Shistosoma mansoni</i>	Yes	
<i>Leishmania tropica</i>		Yes
<i>Taenia solium</i>		Yes
<i>Herpes simplex</i>		Yes
<i>Respiratory syncytial virus</i>	Yes	

Adapted from: McClelland & Smith, Arch Immunol Ther Exp 2011;59:203



The Xs and Y of immune responses to viral vaccines

Sabra L Klein, Anne Jedlicka, Andrew Pekosz

Sex differences in response to vaccination

- Yellow fever: difference in early innate immune response and in side-effects (>60% in women)
- Influenza: humoral immune responses higher in women
- MMR: age at time of vaccination and being female most important predictors of antibody persistence
- Hepatitis A: greater antibody response in females

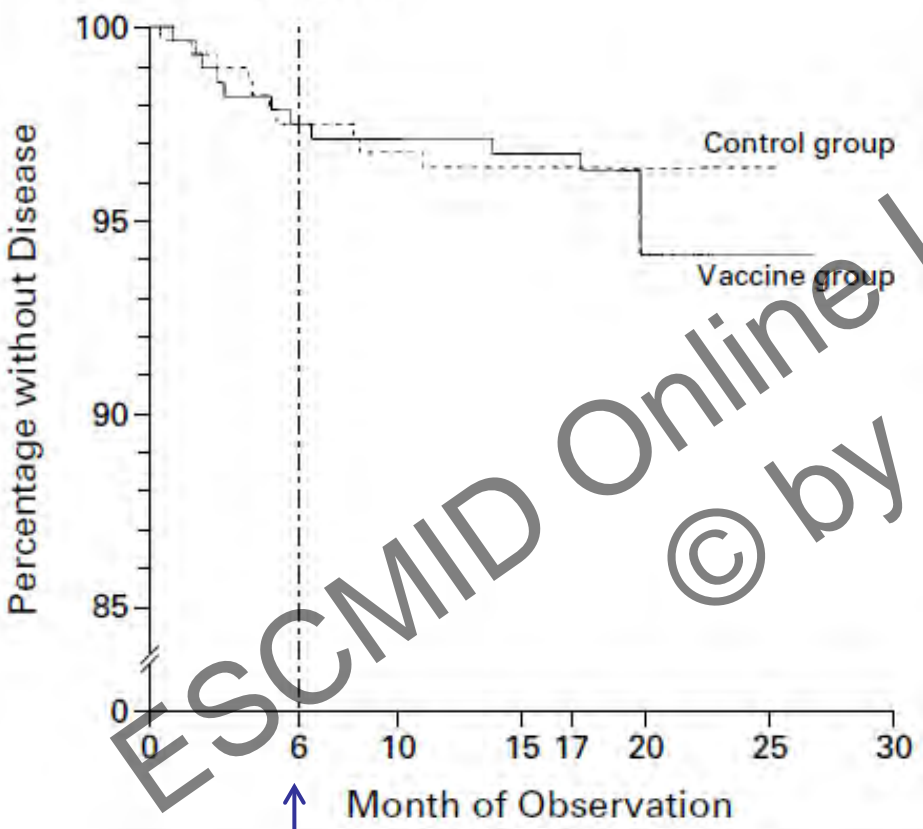
GLYCOPROTEIN-D-ADJUVANT VACCINE TO PREVENT GENITAL HERPES

LAWRENCE R. STANBERRY, M.D., PH.D., SPOTSWOOD L. SPRUANCE, M.D., ANTHONY L. CUNNINGHAM, M.D.,
DAVID I. BERNSTEIN, M.D., ADRIAN MINDEL, M.D., STEPHEN SACKS, M.D., STEPHEN TYRING, M.D., PH.D.,
FRED. Y. AOKI, M.D., MONCEF SLAQUI, PH.D., MARTINE DENIS, PH.D., PIERRE VANDEPAPELIERE, M.D.,
AND GARY DUBIN, M.D., FOR THE GLAXOSMITHKLINE HERPES VACCINE EFFICACY STUDY GROUP*

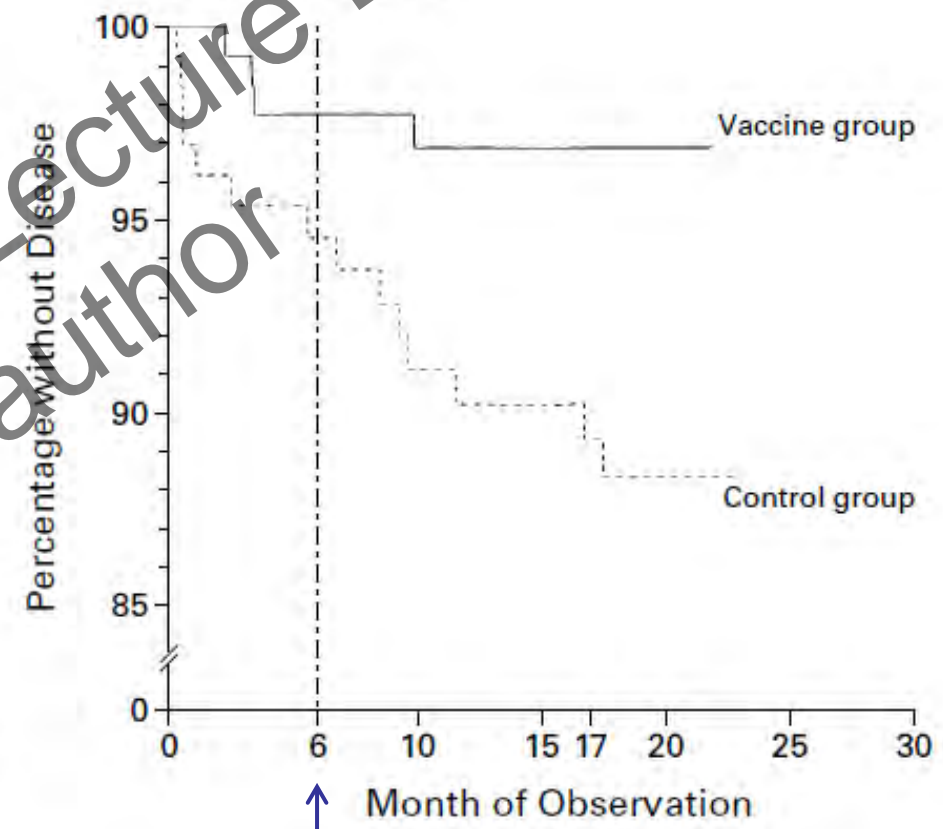
- Vaccine efficacious in women seronegative for HSV-1 and HSV-2
- Efficacy was 73 to 74% in women
- Not efficacious in women seropositive for HSV-1 and seronegative for HSV-2 at base line
- Not efficacious in men



C Male Subjects



B Female Subjects



3rd and final vaccine or control injection



Fifty Shades of Immune Defense

Title borrowed from M.F. Criscitiello, P. de Figueiredo

- Many differences in immune reactions between females and males
- Influence of sex hormones and specific genes on X and Y chromosomes on immune defenses
- Complicated interplay between gender-specific immune responses and immune response to specific microbes



A difficult-to-classify difference

- Compliance with hand hygiene:
 - All studies show higher compliance of nurses compared to physicians
 - Better compliance of female sex?
Or confounding by profession?



A difficult-to-classify difference

INFECTION CONTROL AND HOSPITAL EPIDEMIOLOGY NOVEMBER 2007, VOL. 28, NO. 11

ORIGINAL ARTICLE

Determinants of Good Adherence to Hand Hygiene Among Healthcare Workers Who Have Extensive Exposure to Hand Hygiene Campaigns

Hugo Sax, MD; Ilker Uçkay, MD; Herve Richet, MD; Benedetta Allegranzi, MD; Didier Pittet, MD, MS

Female sex, training, and campaign exposure increased the likelihood of compliance with hand hygiene



Conclusion

- Physiology, endocrinology and not yet explained gender differences seem to impact susceptibility to infections in general, and thereby potentially also susceptibility to health care-associated infections
- Gender is a little evaluated aspect of susceptibility to health care-acquired infections and deserves more attention