Sex Differences in COVID-19 Immunity

Sabra L. Klein, Ph.D.
Professor
Molecular Microbiology and Immunology
Co-Director
Center for Women’s Health, Sex, and Gender Research
Sex is a biological variable that affects immune responses

Libert et al. 2010 *Nat Rev Immunol* 10:594
Sex differences in immunity over the life course

**In utero**

- Increased inflammatory responses in males

**Childhood/ pre-puberty**

- ↑ Inflammation in males
- ↑ NK cells in males

**Post-puberty/ adulthood**

- ↑ Inflammation in females
- ↑ NK cells in males

**Old age**

- ↑ Inflammation in males
- ↑ IL-10 in females
- ↑ NK cells in females

**Innate immunity**

- Increased IgE levels in males
- CD4/CD8 ratios and CD4+ T cell numbers equal
- CD8+ T cell numbers equal
- IgA levels in males ≥ females
- IgM levels in males ≥ females
- IgG and IgM levels equal
- B cell numbers equal
- Treg cell numbers in males ≥ females

**Adaptive immunity**

- CD4/CD8 ratios and CD4+ T cells ↑ in females
- CD8+ T cells ↑ in males
- T cell activation/proliferation ↑ in females
- Treg cells ↑ in males
- B cells ↑ in females
- Immunoglobulins ↑ in females

---

Klein and Flanagan 2016 Nat Rev Immunol, 16:626-38
Sex and gender intersect to alter the outcome of infectious diseases
Females are more likely than males to survive SARS-CoV-2 infection

Sex-disaggregated worldwide COVID-19 data

Countries w/ male bias
45%

Countries w/ female bias
34%

Countries w/o sex bias
21%

COVID-19 Cases

COVID-19 Deaths

Bischof, Wolfe, & Klein. 2020 J Clin Invest 10.1172/JCI13930610.1172/JCI139306; https://globalhealth5050.org/covid19/
The burden of SARS-CoV-2 is worse for men (data from France)

Salje et al. 2020 Science 10.1126/science.abc3517
Male-biased fatality rates across countries and ages

Scully et al. 2020 Nat Rev Immunol 10.1038/s41577-020-0348-8
How sex could impact COVID-19

Scully et al. 2020 Nat Rev Immunol 10.1038/s41577-020-0348-8

A protective treatment?
In one Italian study, men with prostate cancer who received drugs that suppress androgens were much less likely to be infected with SARS-CoV-2.

<table>
<thead>
<tr>
<th></th>
<th>MEN ON ANDROGEN-DEPRIVATION THERAPY (ADT)</th>
<th>MEN NOT ON ADT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total men with prostate cancer</td>
<td>5273</td>
<td>37,161</td>
</tr>
<tr>
<td>Number infected with SARS-CoV-2</td>
<td>4</td>
<td>114</td>
</tr>
<tr>
<td>Estimated cases per 10,000</td>
<td>8</td>
<td>31</td>
</tr>
</tbody>
</table>

†Risk of lower respiratory tract infections among males
†Secretion of inflammatory cytokines in severe cases, data not disaggregated by sex

Johns Hopkins Bloomberg School of Public Health
Males, older adults, and patients with severe COVID-19 have greater cytokine responses.
Women have greater CD8+ T cell activity than men during COVID-19

Takahashi et al. 2020 Nature
doi.org/10.1038/s41586-020-2700-3
Which factors contribute to greater antibody responses?

- **Anti-S1 IgG**
- **anti-S IgG**
- **anti-S-RBD IgG**
- **NT**

**Sex**
- Female vs. Male

**Age**
- Age/10

**Hospital**
- Not hospitalized vs. Hospitalized

**Time since PCR+**
- Days since swab/10

Klein et al. 2020 JCI doi: 10.1172/JCI142004
Males, older adults, and hospitalized patients have greater antibody responses

Klein et al. 2020 JCI doi: 10.1172/JCI142004
Being male and hospitalized are predictors of greater antibody responses
Males shed more virus and for a longer duration of time than females.
Acknowledgements

Financial support provided by:
NIH/NIA SCORE U54 AG062333
NIH/NCI SERONET U54 CA260492
NIH/NIAID HHS N272201400007C
NIH/NICHD R01HD097608
DoD W911QY-20-9-0012

- Sabra Klein, PhD and lab
  - Santosh Dhakal, PhD
  - Morgan Sherer, PhD
  - Patrick Creisher, PharmD
  - Abhinaya Ganesan
  - Harish Narasimhan, MHS
  - Han-Sol Park, PhD
  - Janna Shapiro, MS
  - Rebecca Ursin, MS
  - Yishak Woldetsadik
  - Aihui Wang

- Andy Pekosz, PhD and lab
- Sean Leng, MD
- Eileen Scully, MD
- David Sullivan, MD
- Aaron Tobian, MD
- Arturo Casadevall, MD, PhD
- Kim Davis, PhD and lab
- Anne Jedlicka, MS
- Amanda Dziedzic, MS
- Michael Betenbaugh, PhD
- The Gender and COVID-19 Working Group, including Rosemary Morgan, Eveylyn Bischof and Jeannette Wolfe