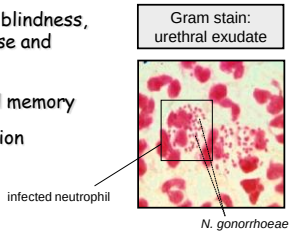
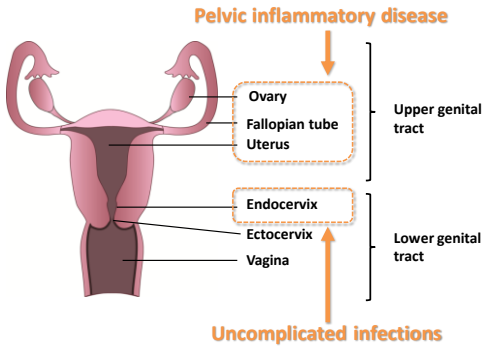
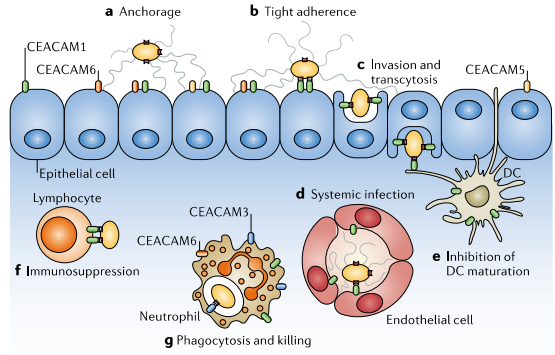
Neisseria gonorrhoeae

- 106 million cases/year (WHO 2012)
- sexually active
- gonorrhea – massive neutrophil response
- sequelae include acquired blindness, pelvic inflammatory disease and female infertility
- elicits little immunological memory
- facilitates HIV transmission



Gonococcal infection of the female genital tract





Gray-Owen and Blumberg *Nature Reviews Immunology* 6, 433–446

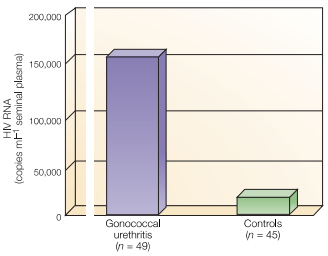
nature REVIEWS IMMUNOLOGY

1. Necessity…

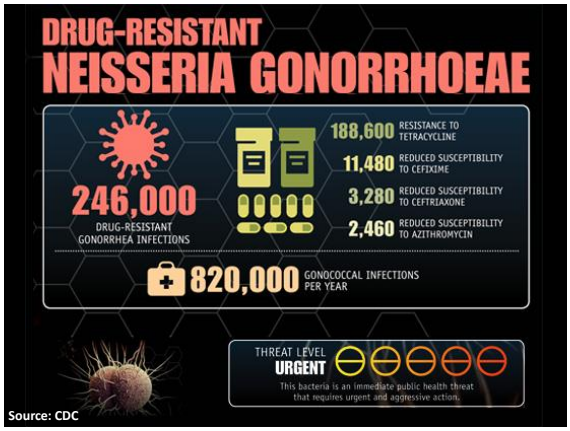
HIV & *Neisseria gonorrhoeae*: Clinical and epidemiological synergy

- Positive correlation has been appreciated for over two decades
- Gonorrhea is associated with a 2-5 fold increased rate of male to female HIV-1 transmission (Fleming and Wasserheit, 1999)
- Women with laboratory-diagnosed *N. gonorrhoeae* infections have a 7-fold increased risk of HIV-1 acquisition (Misana et al., 2012)
- Concurrent infection is associated with:
  - Increased HIV-1 viremia (Anzala *et al.*, 2000, Nkengasong *et al.*,2001)
  - Decreased $CD4^+$ T lymphocyte counts (Anzala *et al.*, 2000)
  - Decreased $CD8^+$ T lymphocyte responses (Kaul *et al.*, 2002)
- The treatment of symptomatic *N. gonorrhoeae* infection leads to decreased HIV-1 DNA detected in urogenital tract swabs in HIV^+ men and women (Ghys *et al.*, 1997; Moss *et al.*, 1995)
- *N. gonorrhoeae* directly stimulates HIV replication by shedding HBP, a novel innate immune agonist (Malott et al., 2013; Gaudet *et al.*, 2015)

Impact of Gonococcal Urethritis on HIV Titers in Seminal Plasma



Modified from Galvin & Cohen (2004)



Source: CDC

"Treatment failure to the last resort of treatment for gonorrhea – third generation cephalosporins – has been confirmed in Austria, Australia, Canada, France, Japan, Norway, Slovenia, South Africa, Sweden and the United Kingdom."

Media centre

WHO's first global report on antibiotic resistance reveals serious, worldwide threat to public health

New WHO report provides the most comprehensive picture of antibiotic resistance to date, with data from 114 countries

News release

30 APRIL 2014 | GENEVA - A new report by WHO–its first to look at antimicrobial resistance, including antibiotic resistance, globally–reveals that this serious threat is no longer a prediction for the future, it is happening right now in every region of the world and has the potential to affect anyone, of any age, in any country. Antibiotic resistance–when bacteria change so antibiotics no longer work in people who need them to treat infections–is now a major threat to public health.

2. Potential…

Epidemiologic Evidence for the Development of Serovar-specific Immunity after Gonococcal Infection

F. A. Plummer, J. N. Simonsen, H. Chubb, L. Slaney, J. Kimata, M. Bosire, J. O. Ndinya-Achola, and E. N. Ngugi
Departments of Medical Microbiology and Medicine, University of Manitoba, Winnipeg, Manitoba, Canada R3E 0W3; Center for Microbiology Research, Kenya Medical Research Institute, Nairobi, Kenya; and Department of Medical Microbiology, University of Nairobi, Nairobi, Kenya

Abstract

We tested the hypothesis that strain-specific immunity occurs after gonococcal infection in a longitudinal study of 227 prostitutes resident in one small community who experienced frequent gonococcal infections. Women were examined and cultured for *Neisseria gonorrhoeae* at 2-wk intervals. Gonococcal isolates were typed according to protein 1 serovar, auxotype, and β-lactamase plasmid type, and classified as to serovar and strain. The hypothesis was tested by comparing the predictions of the hypothesis with the observations of the study. Over the 14-mo period of the study, major changes in the prevalence of specific serovars were observed in the gonococcal population infecting these women. Women with HIV infection experienced a higher rate of gonococcal infection (0.56±0.03 vs. 0.46±0.04, $P < 0.05$, t test) compared with HIV-negative women and were more likely to experience multiple infections with the same strain. The duration of prostitution was inversely related to the frequency of gonococcal infection. Women experiencing an infection with a specific gonococcal serovar were at a 2- to 10-fold reduced risk of reinfection with the same serovar, except for the 1B-1 serovar. The results of the study were consistent with all four predictions of the hypothesis. Infection with a specific gonococcal serovar results in specific but incomplete protection against subsequent infection with the homologous serovar. The mechanism of this protection remains to be determined.

to pilus), there is no clear role for such antibodies in protection against gonococcal infection.

In considering how gonococci interact with human populations (the ecology of *N. gonorrhoeae*), two conclusions seem inescapable. First, humans must have evolved natural defence mechanisms against a pathogen that can so profoundly affect reproduction. Second, that *N. gonorrhoeae* must have evolved mechanisms for evading these defences, to continue to coexist with its obligate host. Over the past decade, our understanding of part of the ecologic relationships between *N. gonorrhoeae* and humans has advanced considerably. We now know that there is great diversity among gonococci and that this diversity is dynamic (6–8). We have also learned that within human populations certain segments (9, 10) (termed high frequency transmitters) are responsible for continued endemicity of *N. gonorrhoeae* in human communities.

We have advanced the hypothesis that the diversity and dynamism of gonococcal populations are ecologic defence mechanisms that allow *N. gonorrhoeae* to continue to exist in human populations that are continually developing immunity to *N. gonorrhoeae* (11). According to the hypothesis, protective strain-specific immunity develops after a natural gonococcal infection, ultimately resulting in immunity of the high frequency transmitter population to the specific gonococcal strains. In the face of this population immunity, a given gonococcal strain dies out. New strains must be continually evolving for *N. gonorrhoeae* to persist in the population. This hypothesis has been expressed by others as well (12). In this

JCI 1989 83:1472-6

THE JOURNAL OF INFECTIOUS DISEASES • VOL. 135, NO. 2 • FEBRUARY 1977

Bactericidal Antibody in Genital Infection Due to *Neisseria gonorrhoeae*

Dennis L. Kasper, Peter A. Rice, and William M. McCormack

From the Channing Laboratory, Department of Medicine, Harvard Medical School, and the Departments of Medicine and Medical Microbiology, Boston City Hospital, Boston, Massachusetts

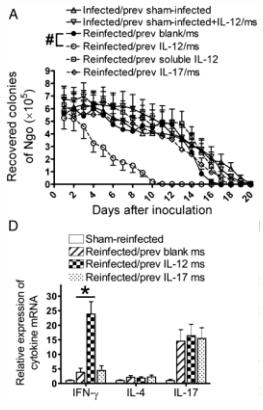
An assay of bactericidal antibody has been developed to study the host response to infection with *Neisseria gonorrhoeae*. This test for antibody was performed on the sera of women who were exposed to *N. gonorrhoeae* but who did not become infected, of patients with various types of genital infection with *N. gonorrhoeae*, and of a small number of individuals with no history of gonorrhea. Antibody was found in the sera of <31% of men and women with uncomplicated gonococcal infection. Prolonged mucosal infection with the gonococcus (>33 days) correlated with the presence of bactericidal antibody. Bactericidal antibody was not detected in 95% of the specimens of acute-phase serum obtained from women with gonococcal pelvic inflammatory disease. The convalescent-phase sera of 70% of women with clinically severe pelvic inflammatory disease showed a rise in titer of bactericidal antibody to the infecting strain of *N. gonorrhoeae*, whereas only 11% of the convalescent-phase sera of women with mild or moderately severe disease showed a similar rise.

Enhancement of Adaptive Immunity to *Neisseria gonorrhoeae* by Local Intravaginal Administration of Microencapsulated Interleukin 12

Yingru Lin, Nejat K. Egilmez, and Michael W. Russell

JID 2013 208:1821-9

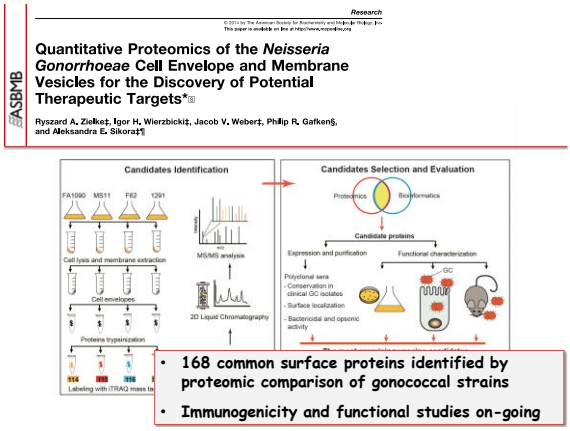
- Vaginal administration of microencapsulated IL-12 administered during primary infection leads to more rapid immune-mediated clearance to secondary infection
- Correlates with heightened Th1 response, and generation of gonococcal-specific serum IgG and mucosal IgA and IgG
- Microencapsulated anti-IL-10 or anti-TGFβ had a similar effect



3. Antigens…

Gonococcal Antigens under Investigation

Antigen	Function	Evidence for protective potential
2C7 mimetic	Bactericidal LOS epitope	Protective by active and passive immunization
TbpB, TbpA	Transferrin receptor	Abs block uptake of iron from Tf
MtrE	OM channel of MtrCDE active efflux pump system	Protective by active immunization
PorB	Nutrient acquisition, serum resistance, invasion	Protective with VRP; loop-specific peptides induce cross-reactive, bactericidal Abs
AniA	Anaerobic growth, biofilm formation	Abs to nonglycosylated AniA block nitrite reductase function
Lst	LOS sialylation; protects against innate effectors	Abs reduce surface sialylation
OmpA	Adhesin, invasin	Bactericidal Abs
OpcA	Adhesin, invasin	Bactericidal Abs

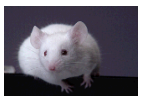


4. Preclinical…

Female Mouse Model: A Tool for Gonorrhea Research

Characteristics of Infection:

- Vaginal colonization for 10-12 days
- Gc in cervicovaginal lumen and tissue and within the lamina propria



BALB/c mouse

- Influx of PMNs in vaginal smears, tissue
- Proinflammatory response due to TLR4-dependent induction of Th17 responses (Feinen, 2010)
- Poor antibody response; susceptible to reinfection

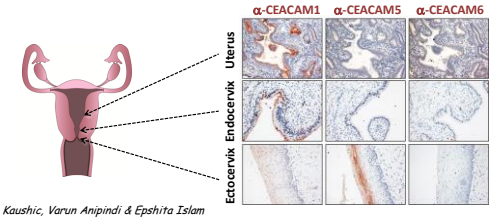
Proven useful for:

- Studying gonococcal evasion of innate effectors
- Identifying immunological pathways
- Product testing (antibiotics, vaginal microbicides, vaccines

Jerse 2011. Front Microbiol.

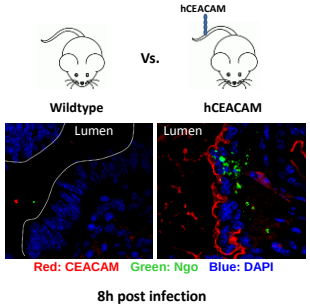
Moving Ahead: 'Humanizing' the Mouse

- Hysterectomy samples from 23 patients
- Stained with monoclonal antibodies specific to CEACAM1, CEACAM5 or CEACAM6



Charu Kaushic, Varun Anipindi & Epshita Islam

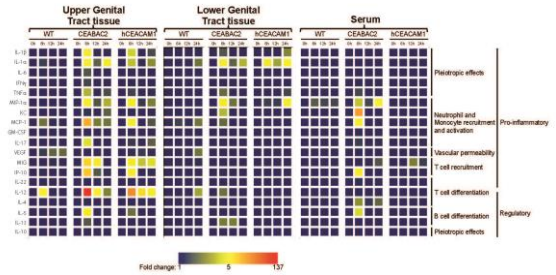
Human CEACAMs facilitate *N. gonorrhoeae* mucosal adherence and penetration



Transcervical infection, β-estradiol, uterine tissue

Epshita Islam

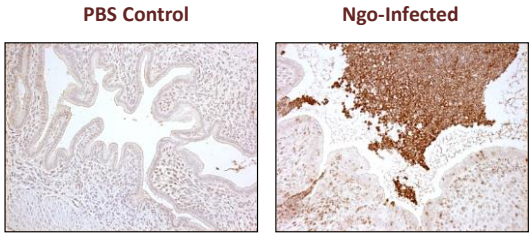
Local and systemic cytokine induction during uterine infection of CEACAM-humanized mice



Transcervical infection, β-estradiol, uterine tissue

Epshita Islam

Neutrophil recruitment into Ngo-infected uterine tissues



Transcervical, Depoprovera, 10^8 Ngo/mouse. 1 day post infection

5. Clinical…

Experimental Human Gonorrhea

- Since the late 1980's, controlled human infection studies conducted in the US under appropriate ethical review with full written informed consent
- Existing program at the University of North Carolina provides a unique opportunity to study pathogen factors and host responses in human infection under controlled conditions.
- Experimental urethral infection of male volunteers is safe (>200 subjects inoculated without serious complications)
- Wild-type GC elicit signs and symptoms of natural infection.

Marcia Hobbs

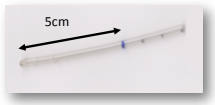
Current eligibility criteria

- Inclusion
  - Healthy male, 18-35 years old
  - Normal genital exam
  - Willing to abstain from sexual activity during study
- Exclusion
  - History of sexually transmitted infection
  - Positive serology for HIV, syphilis, HBV, HCV
  - Abnormal complement activity
  - Allergy to penicillin, ceftriaxone, ciprofloxacin or lidocaine

Marcia Hobbs

Current experimental protocol

- Written informed consent obtained at screening followed by a T/F test of understanding.
- On day of inoculation, subjects admitted to inpatient unit of clinical research center at UNC Hospitals for 6 day trial; written informed consent obtained again.
- ~240 µL of PBS containing 10^4-10^6 organisms instilled into anterior urethra through sterile #8 French pediatric catheter.



- Subjects examined daily for signs & symptoms of urethritis up to 5 days after inoculation. May leave the unit during the day if asymptomatic.

Marcia Hobbs

Treatment and follow-up

- All subjects receive ceftriaxone (250mg IM), either on request due to symptoms, or prior to end of trial, whether or not cultures are positive.
- Follow-up visit within 1 week for targeted clinical exam and test of cure.
- Final 2-week follow-up phone call to assess potential AEs.

Marcia Hobbs

3 Phases of experimental human gonorrhea studies

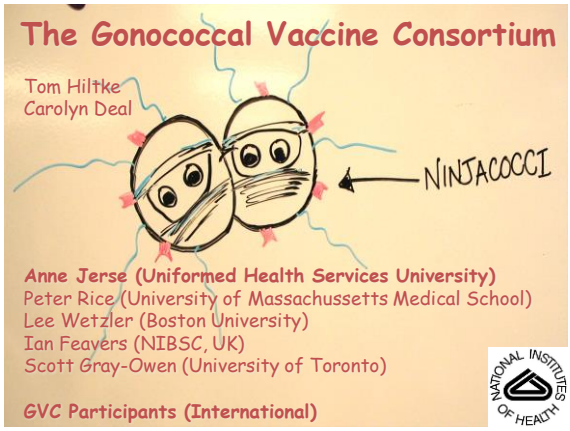
- Past **observational studies** of the natural history of experimental gonococcal infection with "wild-type" strains (Hobbs *et al.* 2011 Frontiers in Microbiology)
- Ongoing **pathogenesis and host response** studies with isogenic mutants
- Future **vaccine & treatment** studies

Marcia Hobbs

6. Looking ahead…

Future Priorities

1. **Greater focus on vaccine development**
   - Antigens
   - Surrogate measures for assessing immunity
   - Continued improvement of preclinical models
2. **Ongoing research on basic aspects of pathogenesis and host response**
   - Genome-based analyses
   - Gonococcal lifestyle within mucosal tissues
   - Human experimental and natural history studies
3. **Concerted effort toward the goal of vaccine development and implementation**
   - Leadership to coordinate interactions between disciplines
   - Sustained funding by funding agencies and nonprofit organizations


The Gonococcal Vaccine Consortium
Tom Hiltke
Carolyn Deal
NINJACOCCI
Anne Jerse (Uniformed Health Services University)
Peter Rice (University of Massachussetts Medical School)
Lee Wetzler (Boston University)
Ian Feavers (NIBSC, UK)
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GVC Participants (International)
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