Efflux pumps in *Neisseria gonorrhoeae*: cause of resistance and targets for therapeutics/vaccines?

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No financial disclosures or conflicts

**History of Resistance & Shrinking Pipeline**

Unemo and Shafer, 2014

To Effectively Counteract Resistance With New Drug Development, It Is Important To Understand Mechanisms of Resistance

**N. gonorrhoeae** Efflux Pumps

Unemo and Shafer, 2014
For ceftriaxone resistance: mosaic PBP2 and overproduction of the MtrCDE efflux pump.

**The mtrCDE locus**

![Diagram of mtrCDE locus with annotations]

Mtr Efflux Pump-Deficient Gonococci Have a Survival Defect in a Murine Model of Lower Genital Tract In Females (Jerse et al. 2003)

![Graph showing mean duration of recovery with Log CFU and day post-inoculation]

Promoter mutations: High R
MtrR mutations: Intermediate R

**Cis- and Trans-Acting Mutations That Increase Resistance**

![Diagram showing cis- and trans-acting mutations]

**Loss of the MtrCDE Efflux Pump Increases Gonococcal Susceptibility to Antimicrobials**

**Important β-Lactams Previously or Currently Used to Treat Gonorrhea: Clinically Resistant Strains of Historical Importance**

![Diagram showing β-lactams and isolates]
A Single Nucleotide Change Can Account for the Mtr Phenotype in High Level Resistant Strains

Western Blot Showing Over-Production of MtrCDE

The Emerging Threat of Untreatable Gonococcal Infection

Can We Exploit the MtrCDE Efflux Pump In Efforts to Counteract Antibiotic Resistance Expressed by Gonococci?

Comparison of MtrE3-467 Immunization/Challenge Results Using CT versus CpG as the Adjuvant

Conclusions

• The MtrCDE efflux pump is an important part of how gonococci develop resistance to antibiotics
• This pump is also important for bacterial survival during an experimental infection
• Expression of the mtrCDE operon is regulated by cis- and trans-acting factors
• Propose that the MtrCDE efflux is a target for new drug discovery or an antigen for a future vaccine
Special Thanks To Collaborators

• Ann Jerse Ph.D. and her lab group (Bethesda, USA): all mouse work and antibiotic resistance collaborations for nearly 15 years.
• Magnus Unemo Ph.D. and Daniel Golparian (Orebro, SE): clinical significance of mtr mutations.
• Edward Yu Ph.D. and his lab group (Ames, USA): structural biology of Mtr efflux pump proteins MtrD and MtrE and EPIs.
• Fred Sparling M.D. (Chapel Hill, USA)

Many thanks to the NIH and VA for funding support.