

Estrogen and Recurrent UTI Shape Urinary Microbiome Structure and Function

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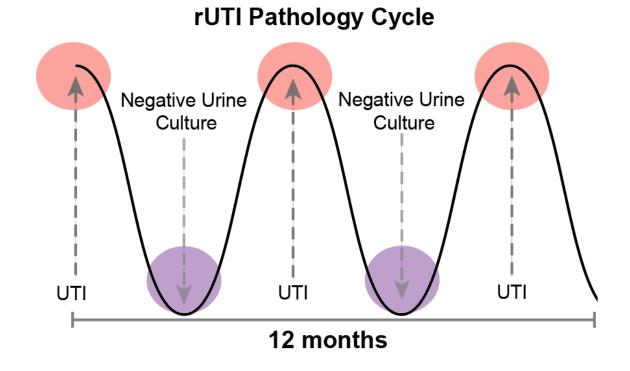
The University of Texas at Dallas

8th ICCMg Conference

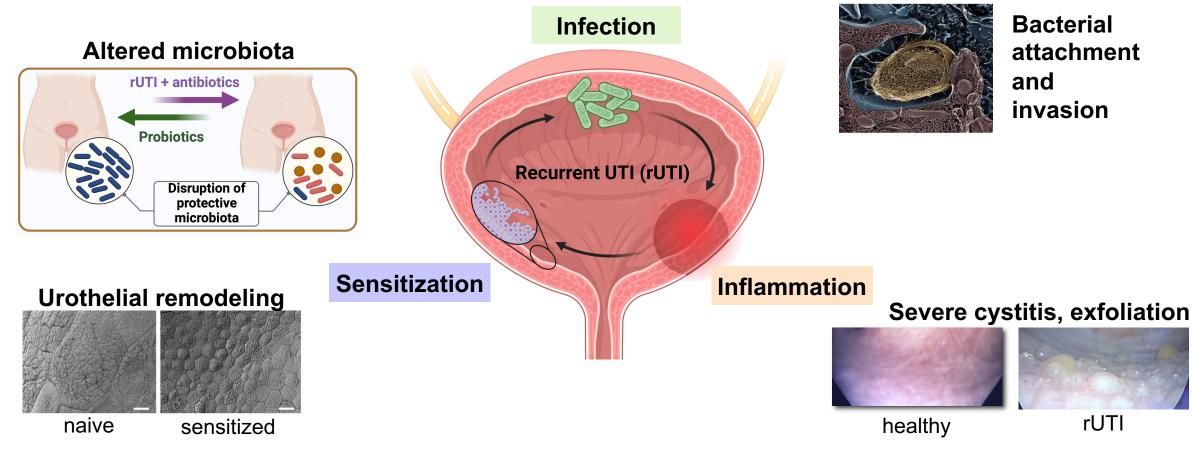
November 16th, 2023

Recurrent UTI significantly reduces quality of life

- Recurrent UTI (rUTI): cycles of infection w/ intervening negative urine culture
- Premenopausal: ~25% UTI → rUTI
- Postmenopausal: >50% UTI → rUTI
- Cycles can go on for years severely diminishes quality of life



The Vicious Cycle of Recurrent UTI

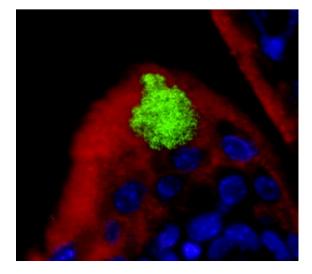


O'Brien et al. Nature Microbiol 2016, Mulvey et al. PNAS 2000

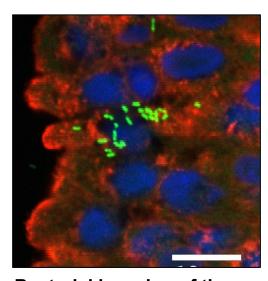
Who are the culprits?

In order of prevalence:

- Escherichia coli (UPEC)
- Enterococcus faecalis
- Klebsiella pneumoniae



UPEC invasion of the mouse bladder Rosen et al. Infect. Immun. 2008



Bacterial invasion of the human bladder De Nisco et al. JMB 2019

• Other: (Staphylococcus spp., Proteus mirabilis, Pseudomonas aeruginosa, Streptococcus spp., Enterobacter spp.)

Uropathogenic bacteria can invade deep into the

bladder wall

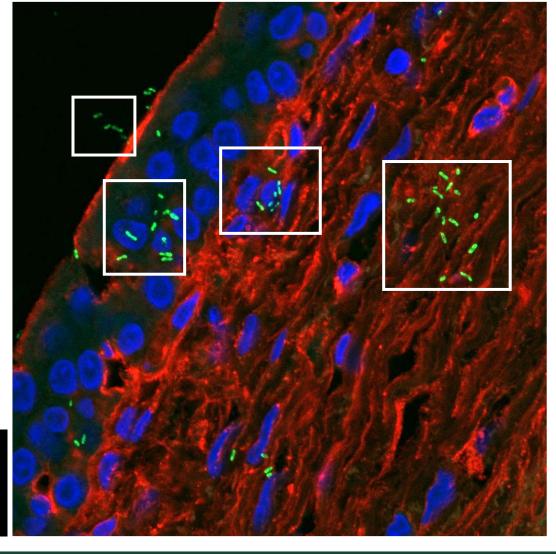
- Mucosa
- Superficial/Transitional Epithelium
- Basal Epithelium
- Sub-epitheulium

Where antibiotics can't reach them

New therapies needed!

De Nisco et al. JMB 2019

Bacteria Mucin/Actin



The New York Times

DEADLY GERMS, LOST CURES

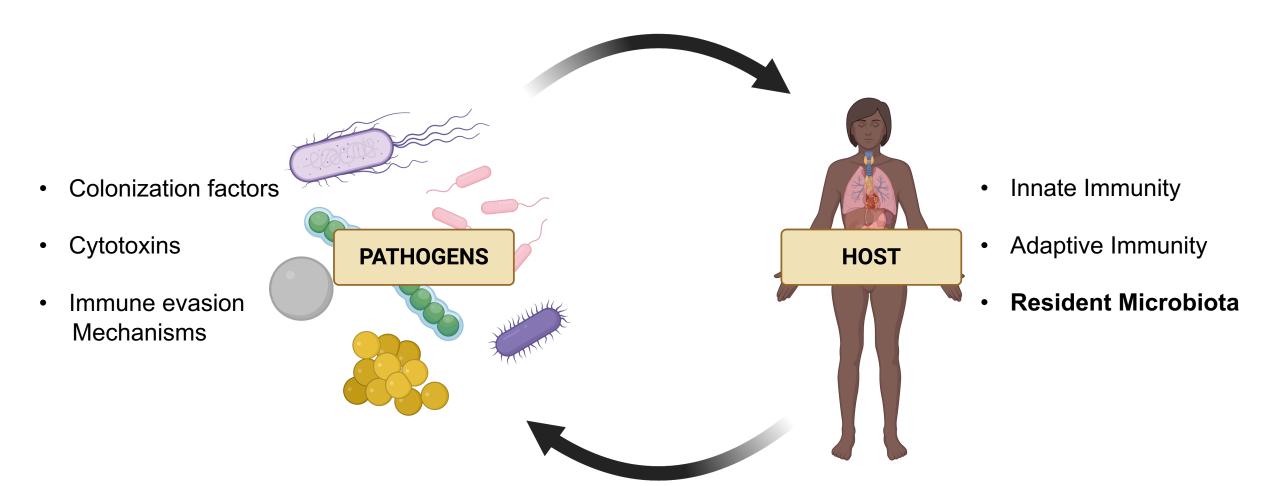
Urinary Tract Infections Affect Millions. The Cures Are Faltering.

As the infections become increasingly resistant to antibiotics, some standard treatments no longer work for an ailment that was once easily cured.

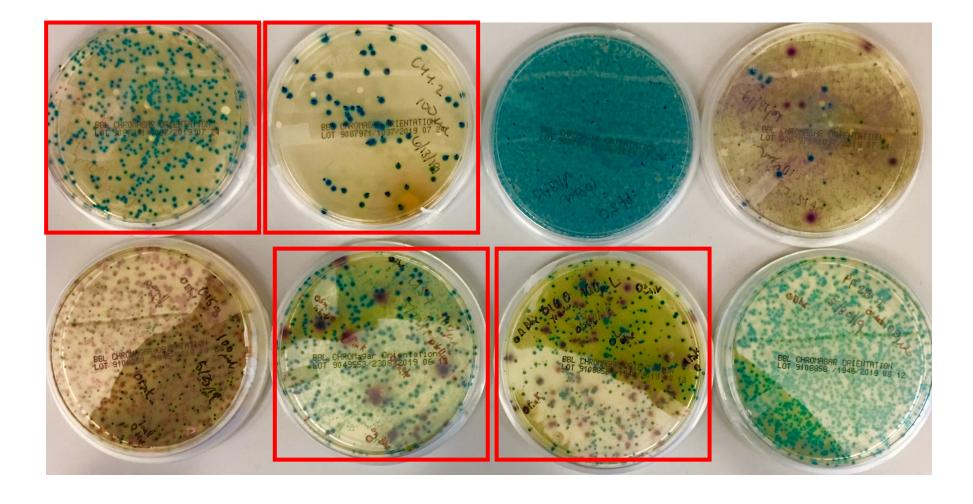
Matt Richtel, *The New York Times*, July 2019



Infection is *not* a one-sided conversation

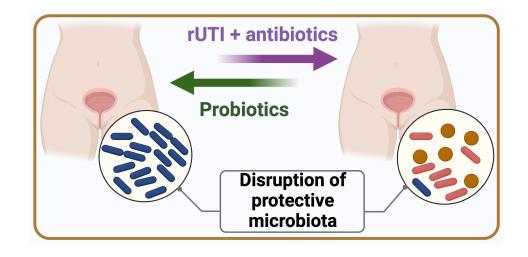


Urine is NOT sterile – a urinary microbiome exists!





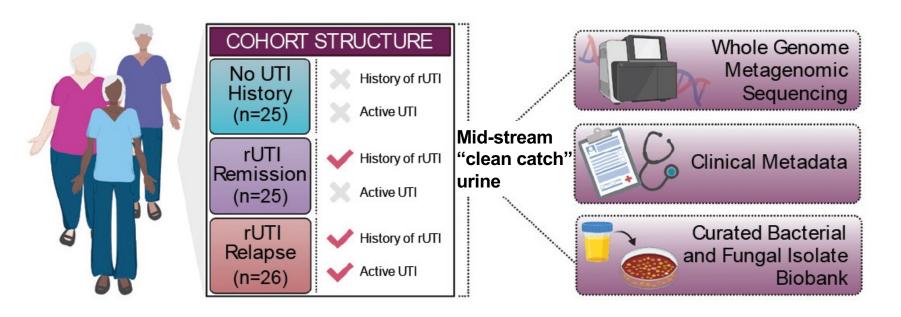
Does urobiome structure and function contribute to rUTI susceptibility in women?

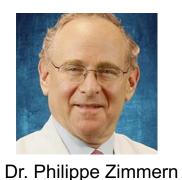


Can probiotic approaches be used to restore a beneficial urinary microbiota in women with rUTI?



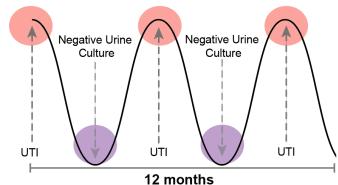
Urine WGMS human cross-sectional cohort design





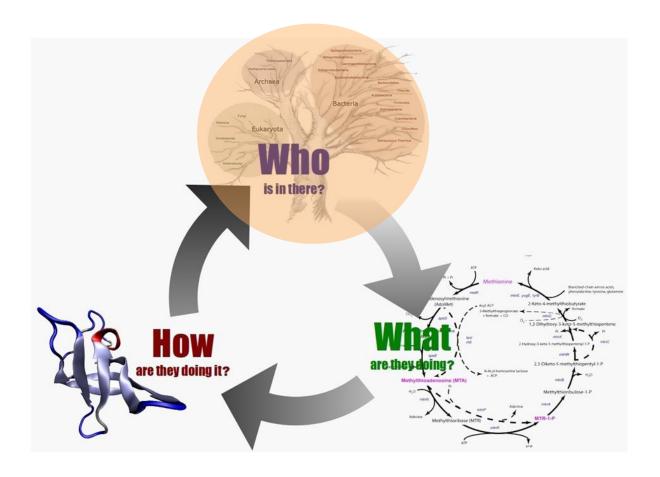
Dr. Kelli Palmer **UTSW Medical Center UT-Dallas**







Are there microbial biomarkers of rUTI susceptibility in the urinary microbiome?

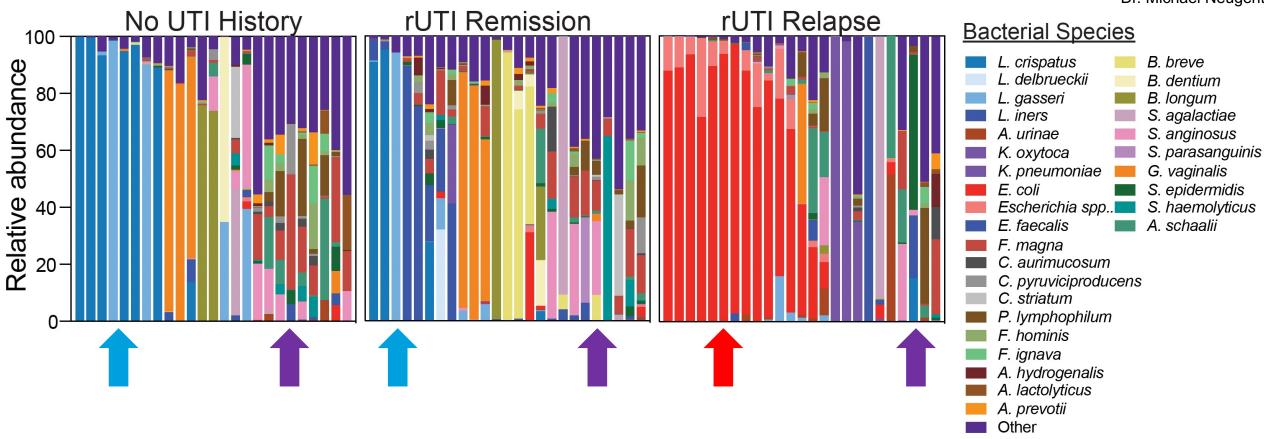




Taxonomy of the postmenopausal microbiome



Dr. Michael Neugent



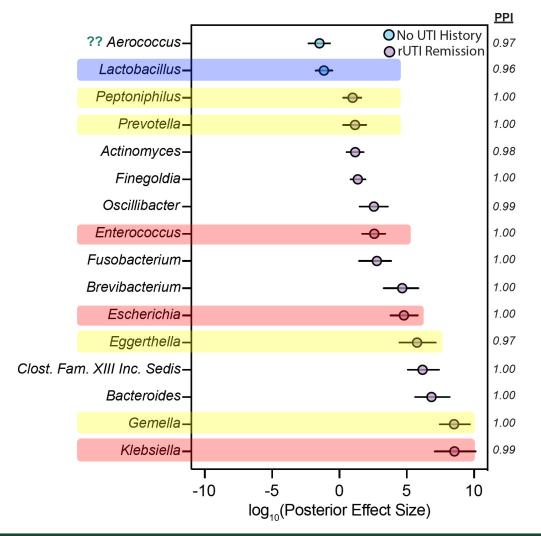
Neugent et al. Cell Reports Medicine 2022



Bayesian modeling reveals potential microbial biomarkers of rUTI susceptibility



Dr. Qiwei Li





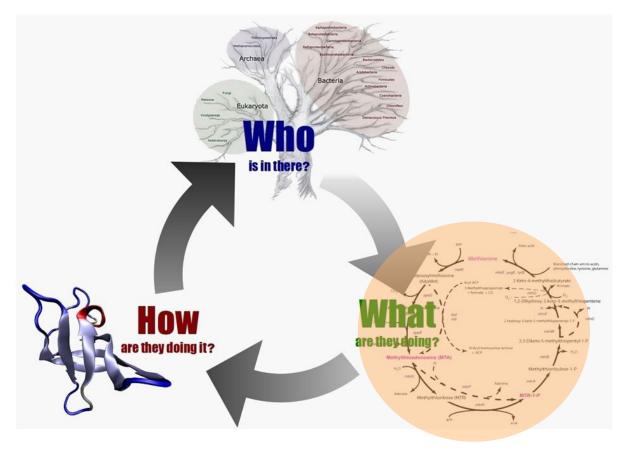


Are these remnants of past infection??

Neugent et al. Cell Reports Medicine 2022



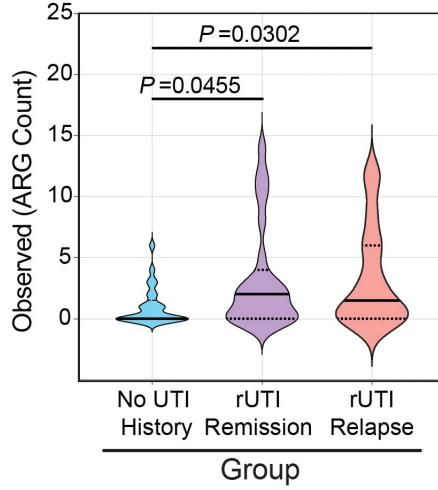
Does rUTI history alter urinary microbiome function?



Does a history of rUTI and antibiotic therapy alter the number of Antibiotic Resistance Genes (ARGs) encoded by the urinary microbiome?

Urobiomes of women with no UTI history harbor significantly less ARGs

- Used GROOT to quantify ARGs encoded in each metagenome
- ARGs were enriched in women in the rUTI Remission and Relapse Groups
- Even in the absence of active UTI, the urobiome of women with rUTI history is enriched in **ARGs** compared to women with no UTI history

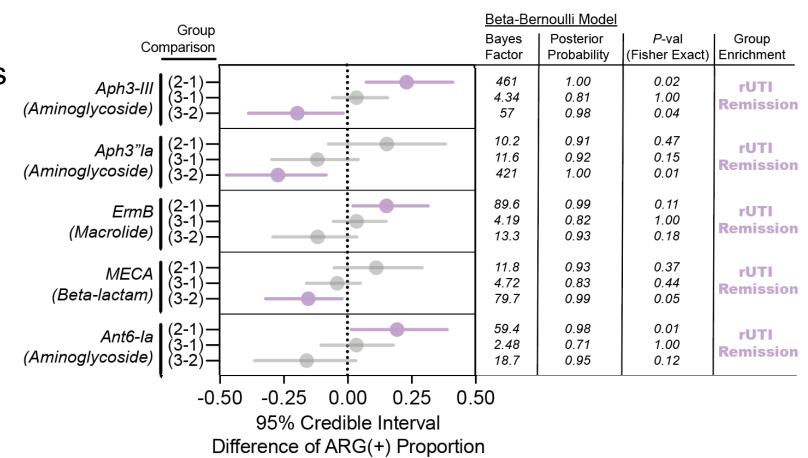


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ARGs enriched in the urobiomes of women with rUTI history

- Significantly enriched ARGs in **rUTI Remission** Group:
 - **Aminoglycoside** 3'phosphotransferases
 - **Aminoglycoside** Onucleotidyltransferase
 - **Macrolide** resistance
 - **β-lactam** resistance



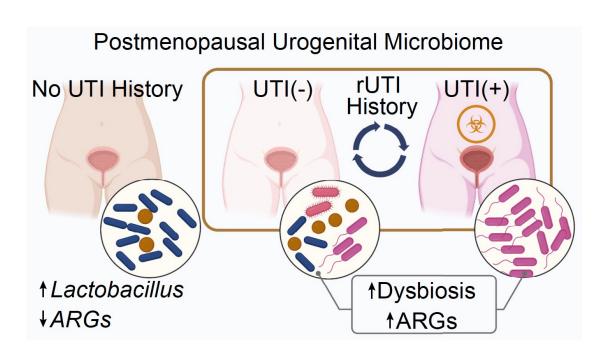
Neugent et al. Cell Reports Medicine 2022



Conclusions and Future Questions – Part 1

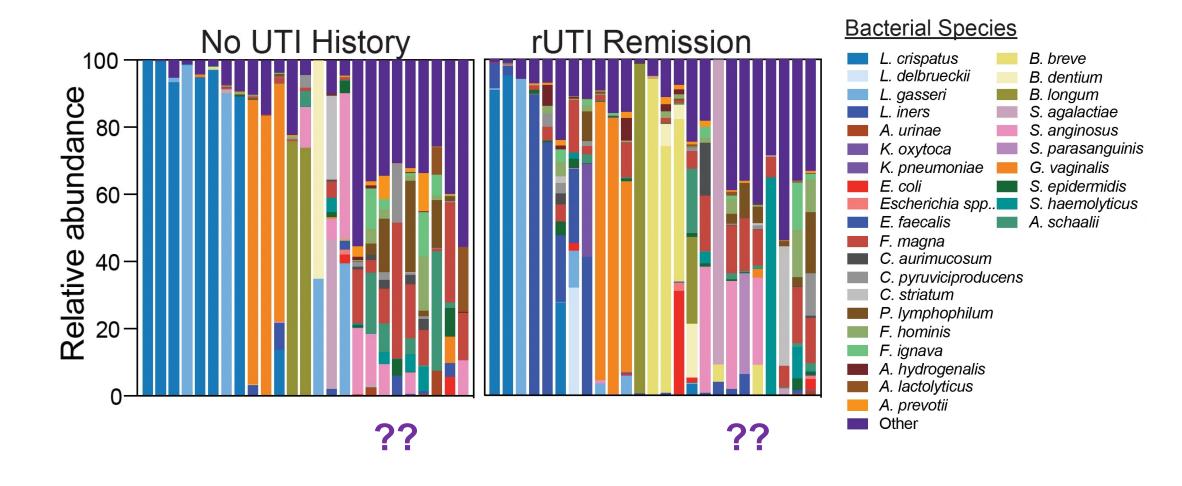
- Species involved in vaginal dysbiosis may be biomarkers of rUTI susceptibility
 - Peptoniphilus lacrimalis
 - Prevotella timonensis
 - Gemella spp.
 - Eggerthella spp.

- Enrichment of ARGs in rUTI remission suggests **residual ARGs** after infection
 - Aminoglycoside, macrolide, and β-lactam ARGs enriched in **remission** urobiomes



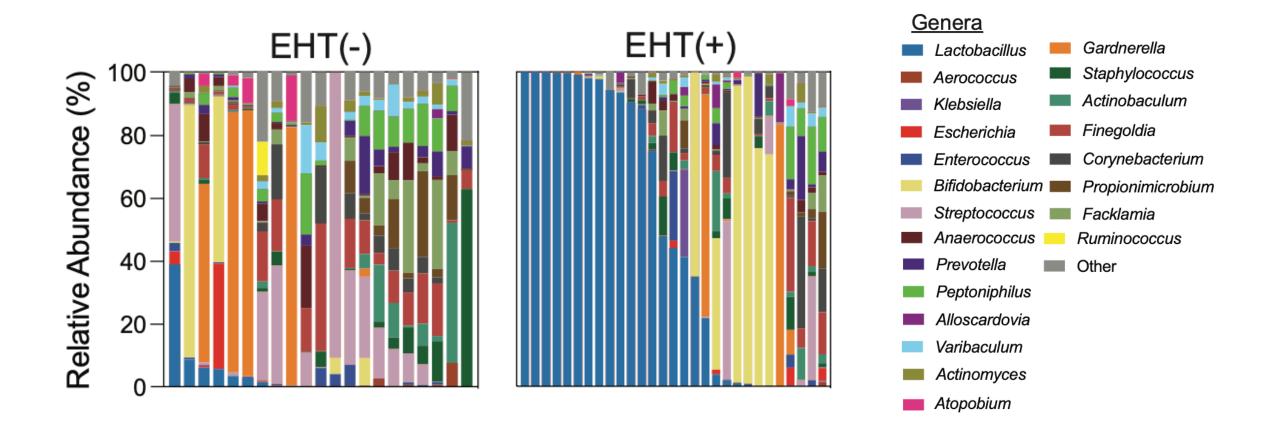


Clinical factors impacting urinary microbiome composition in postmenopausal women



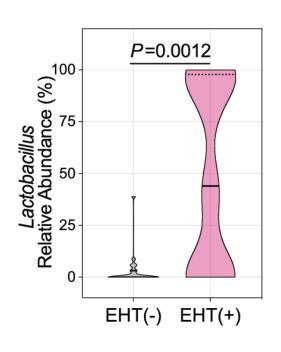


Urinary Lactobacillus almost exclusively associated with estrogen hormone therapy in PM women

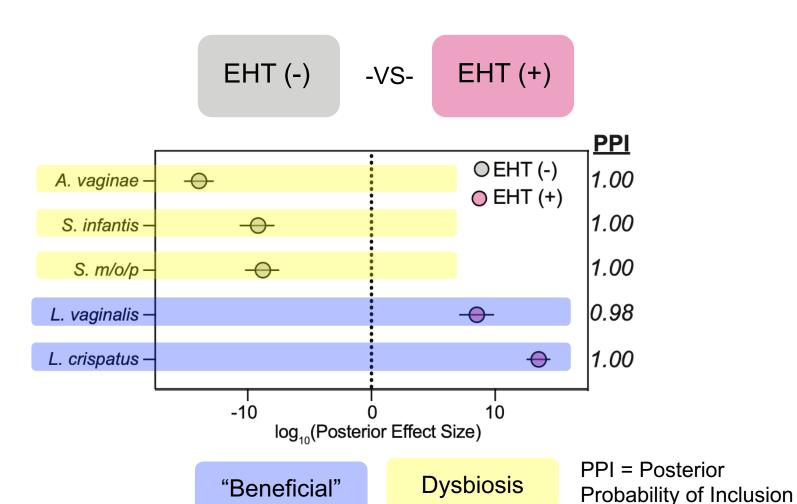


EHT as a major driver of urinary microbiome composition in postmenopausal women

Lactobacillus Abundance

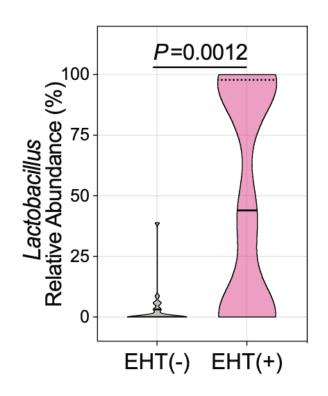


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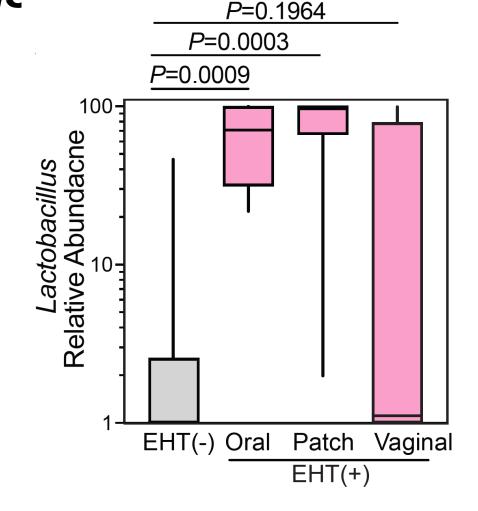


Modality dependent differences in association between EHT and Lactobacillus

Lactobacillus Abundance

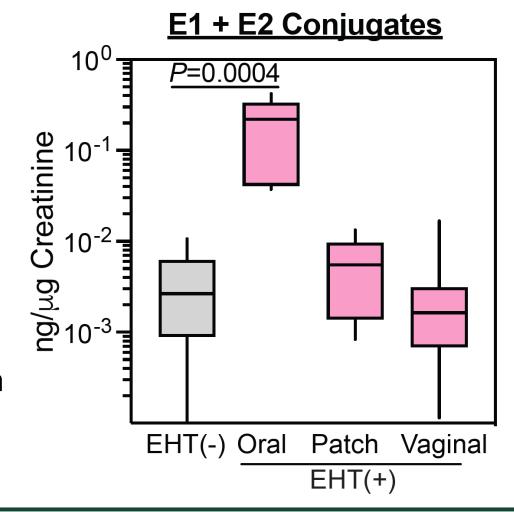


Stratify by EHT Modality

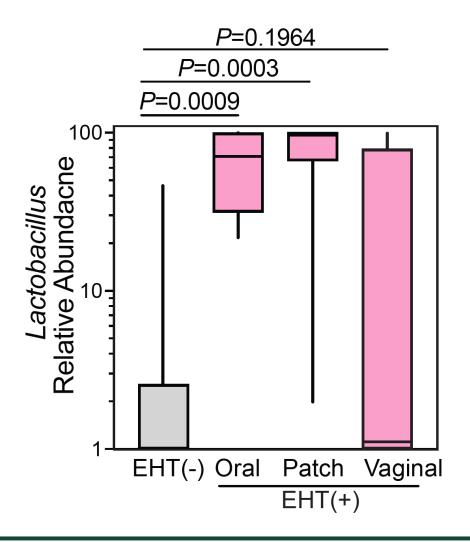


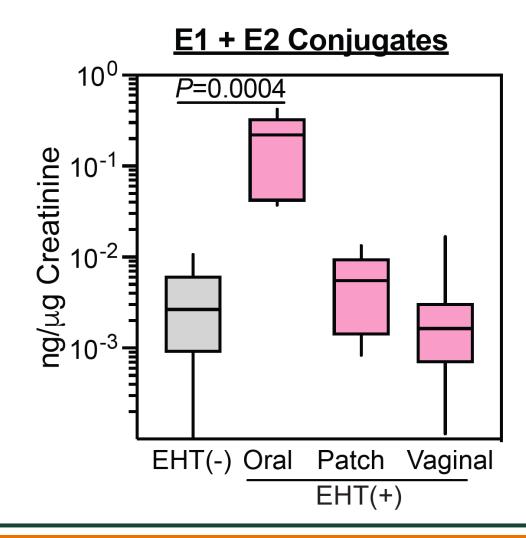
Quantitation of excreted EHT metabolites by LC-MS/MS

- Differences between modalities could be due to:
 - compliance
 - formulation
 - dosage
- Quantified urinary estrogens by LC-MS/MS
- Urinary estrogen concentration highest in women taking oral EHT



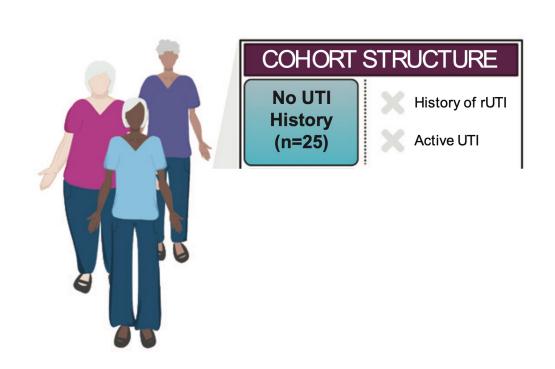
Association between urinary estrogen concentration and Lactobacillus abundance

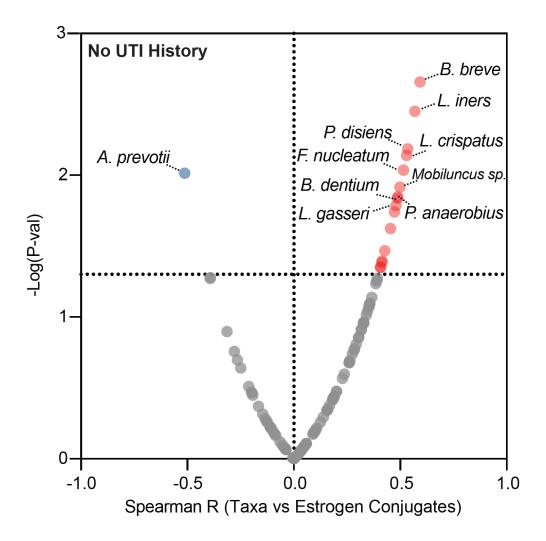






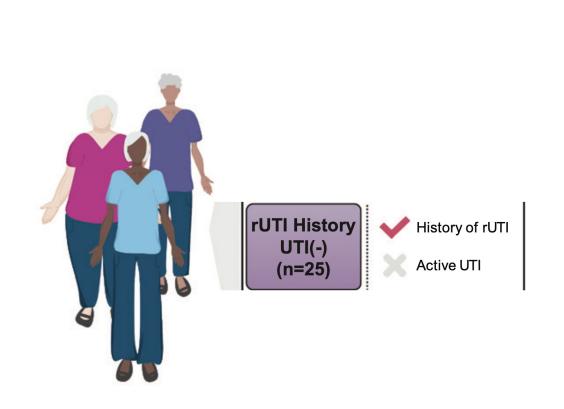
Which urinary taxa correlate with high urinary estrogen?

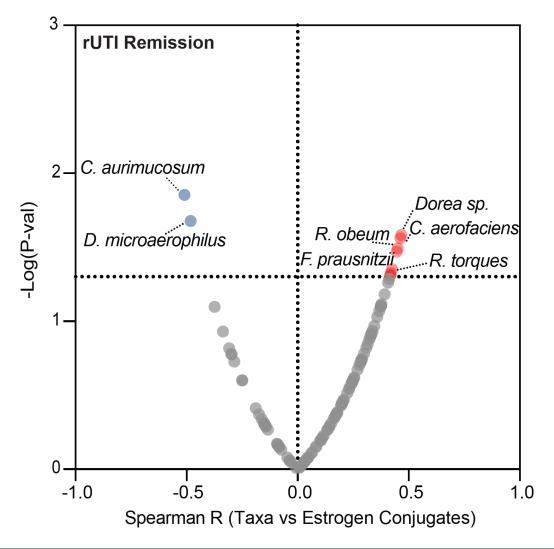






Which urinary taxa correlate with high urinary estrogen?

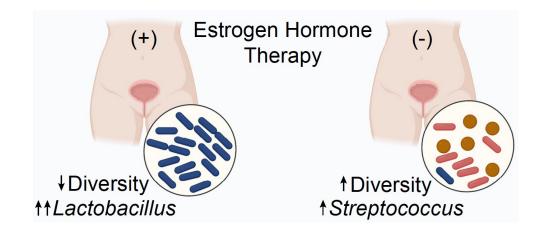






Conclusions and Future Questions – Part 2

- EHT associated with enrichment of L. crispatus in the urobiome
- The modality of EHT may be important!
 - oral EHT most robust urinary *Lactobacillus* enrichment
 - vEHT more variable seen with the vaginal microbiome in multiple studies
- Correlation between urinary estrogens and urinary microbiota influenced by rUTI history
 - L. iners, L. crispatus and L. gasseri correlate with estrogens in No UTI history group





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