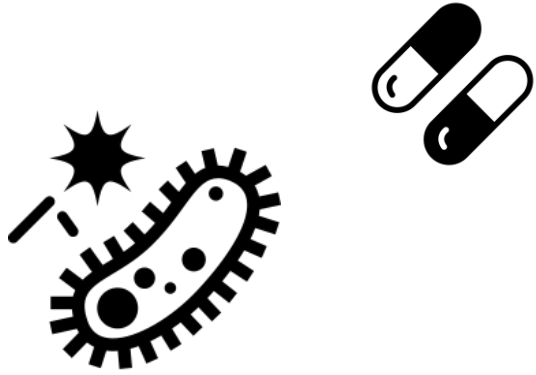




Urobiome and Clinical Applications

Nazema Y. Siddiqui MD MHSc

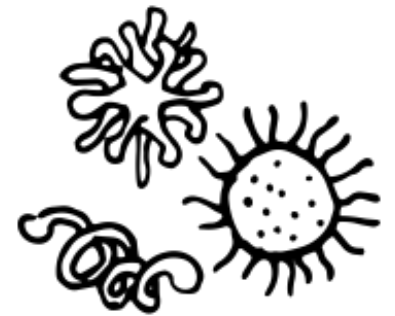
Associate Professor

Department of Obstetrics & Gynecology

Division of Urogynecology & Pelvic Reconstructive Surgery

Division of Reproductive Sciences

Duke University School of Medicine



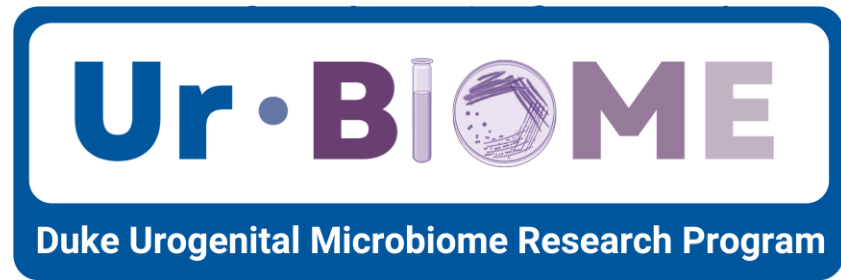
Disclosures

- Research Contracts:
Medtronic, Inc.; Ethicon J&J -> Caldera Inc.; Locus Biosciences
- Royalties: UpToDate[®]
- Funding for research by:
NIH/NICHD Award # U10 HD041267
NIH/NIDDK Award # R01 DK138121

Background

- **Clinician Scientist**
 - 50% Urogynecology & Reconstructive Pelvic Surgery
 - 50% Research effort (clinical + laboratory)

Duke Urinary Microbiome Research Program



Nazema Siddiqui, MD, MHS
Principal Investigator



Silvia Grant, PhD, PMP

- Research Program Leader II
- Senior Microbiome Scientist



Elizabeth Howell, MD

- Fellow, Urogynecology



Christina Bergemann, PhD

- Postdoctoral Associate
- KURe Scholar



Rachel Kim, BS

- Laboratory Research Analyst I



Ama Kwabia, BS

- Graduate Student
- Molecular Genetics & Microbiology



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Lisa Karstens, PhD
Co-Investigator

Bioinformatics and
Computational Biology
Oregon Health & Science
University

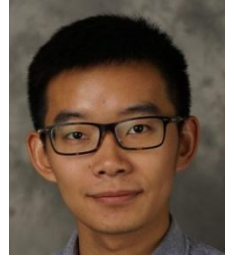


Li Ma, PhD
Co-Investigator

Department of Statistical
Science
Duke University



Zhuoqun (Carol) Wang

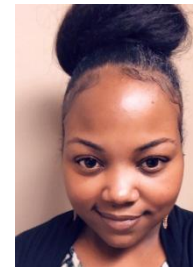


Jialing Mao, PhD



Tanya Sysoeva, PhD
Collaborator

Biological Sciences
University of Alabama -
Huntsville



Yasmeen Bruton, MA



Paige Green, MS



Nortorious Coleman-Taylor, MSCR



Claire McLaughlin, BA

Statistical Science



Carole Grenier, BS
Laboratory Research Analyst

Research Coordinators



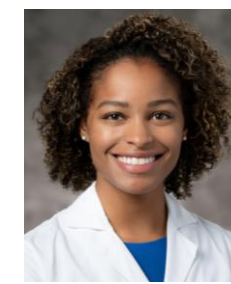
Monique Vaughan, MD
Fellow, FPMRS



Leanne Teh
MD Candidate



Nicole Diaz
MD Candidate



Gabrielle Rohrer, MD
Urology Resident



Emily Romanoff
MD Candidate

Nicole DeNisco, PhD
Collaborator

Biological Sciences
University of Texas –
Dallas



01

Timeline of Microbiome Discovery

EVOLUTION OF HUMAN MICROBIOME SCIENCE

From Discovery to Precision Medicine: The Gut–Vagina–Bladder Axis



PRE-2010
FOUNDATION ERA



GUT
MICROBIOME

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of gut microbiome** ★

Culture-independent methods
reveal vast microbial diversity
and metabolic potential.

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★ Urinary communities described

Characterization of urinary microbial
communities and associations with
lower urinary tract symptoms.

(Hilt et al., JCI, 2014)
(Thomas-White et al., Nat Rev Urol, 2015)
(Komesu et al., 2018)



Objectives

01

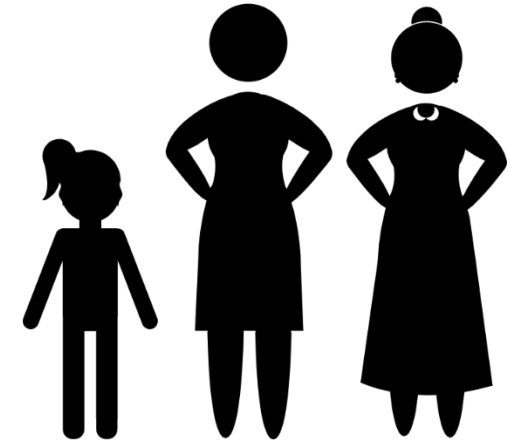
Timeline of Microbiome Discovery

02

Applications for rUTI

Recurrent UTI

- True prevalence estimates are difficult
 - Definitions vary
 - Lack of diagnostic precision
- Up to 30% of menopausal women have recurrent UTI^{1,2}
- Substantially higher with aging



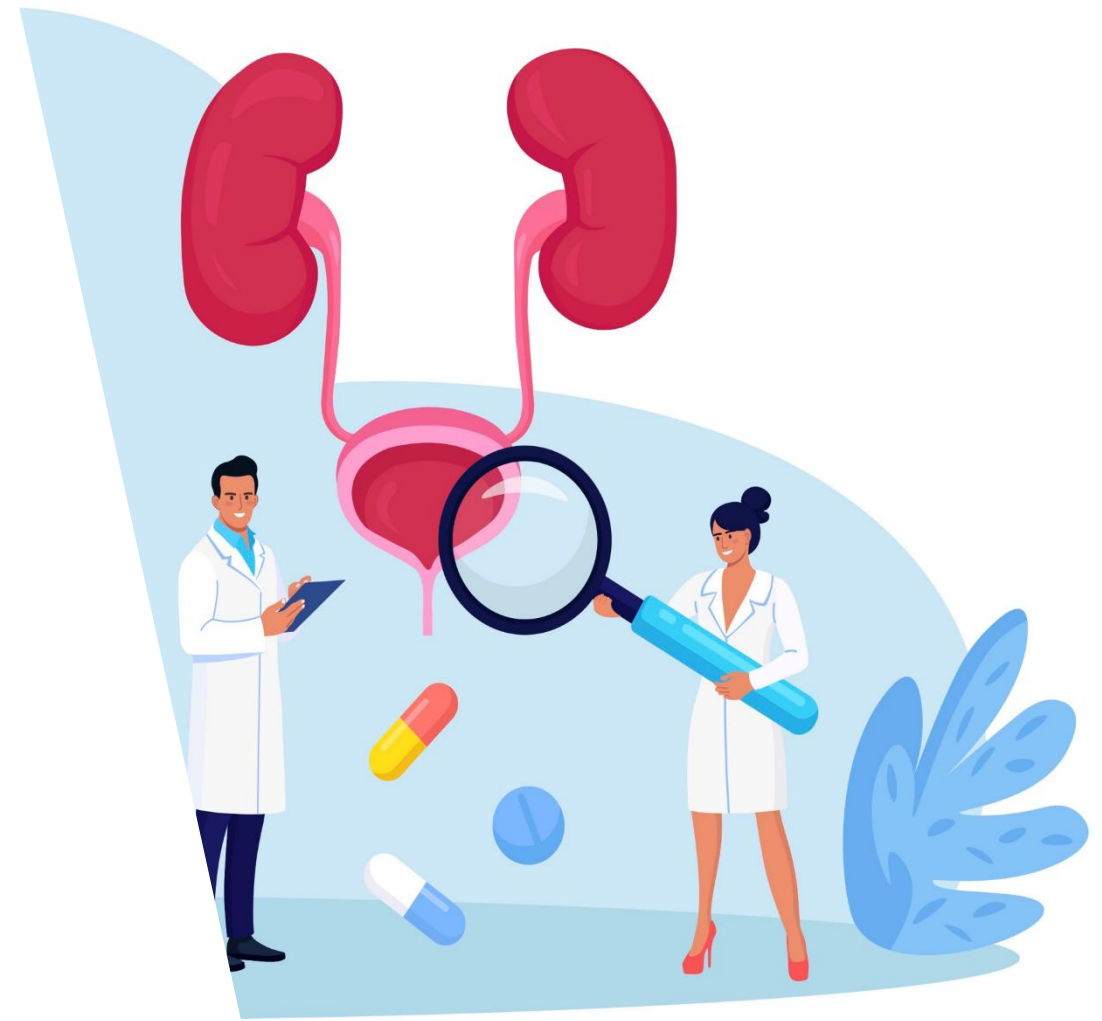
1. Rowe & Juthani-Mehta *Infect Dis Clin North Am* 2014
2. Ikaheimo et al. *Clin Infect Dis* 1996.

Recurrent UTI









IS URINE REALLY STERILE?

Sci Show



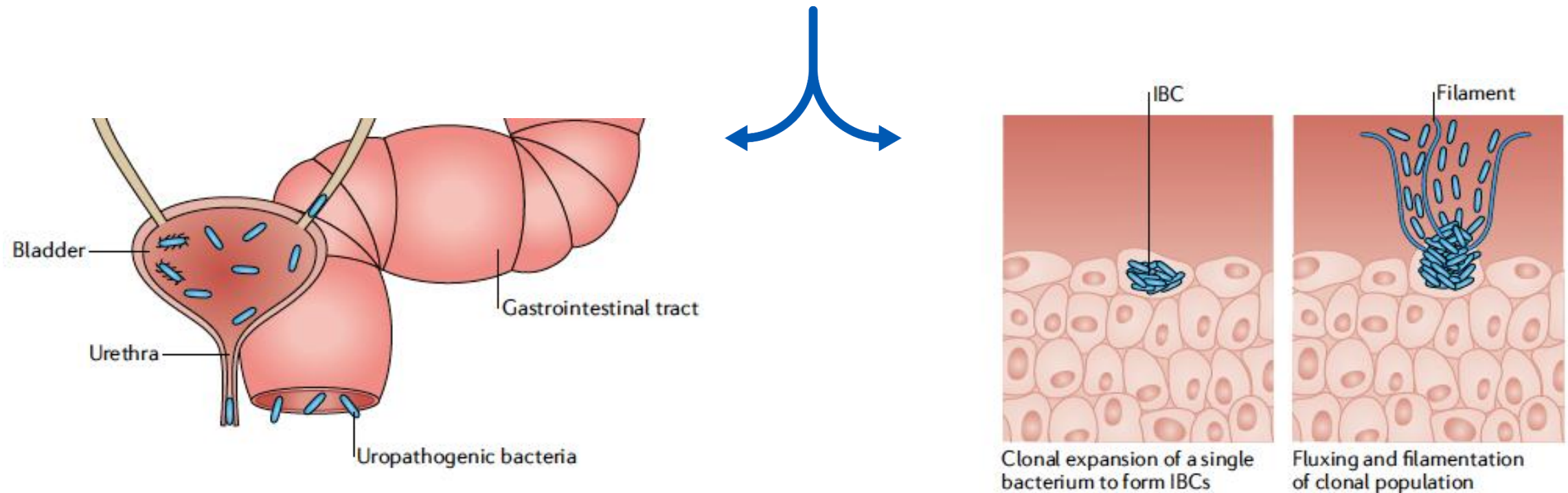
Urinary Microbiome?

Wolfe et al (2012). Evidence of uncultivated bacteria in the adult female bladder. *J Clinical Microbiology*; 50(4): 1376-1383.



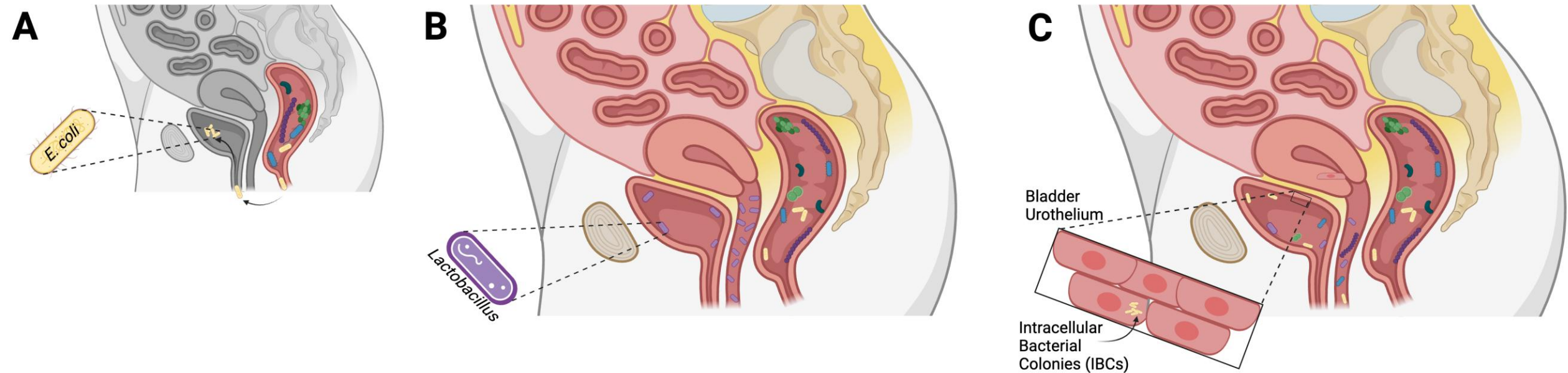
Recurrent UTI

Pathogenesis



Recurrent UTI

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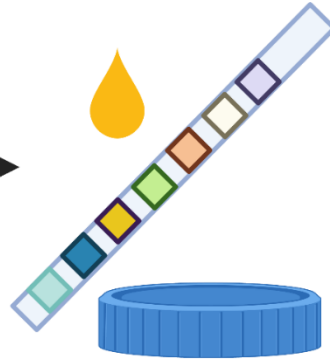
Siddiqui NY, Bradley MS. Updates in Clinical Management of Recurrent Urinary Tract Infections. Obstet Gynecol. 2025 Sep 4. doi: 10.1097/AOG.0000000000006060. Epub ahead of print. PMID: 40907025.

Diagnosis



UTI Diagnostics

Urine sample



>1+ LEUKOCYTES
>1+ BLOOD
+ NITRITE

Standard
Urine Culture



Negative Urinalysis

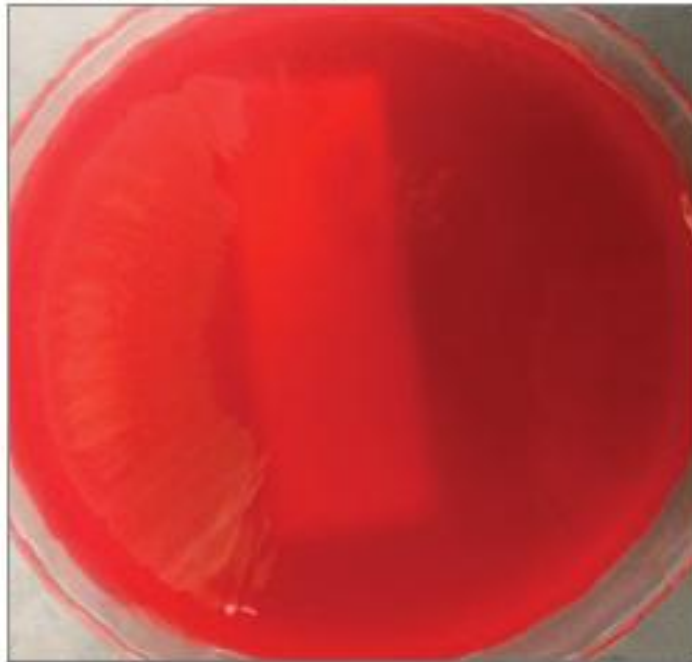
No growth

"Mixed Flora"

Growth of
organism w/ CFU

Standard Urine Culture...

Standard urine culture



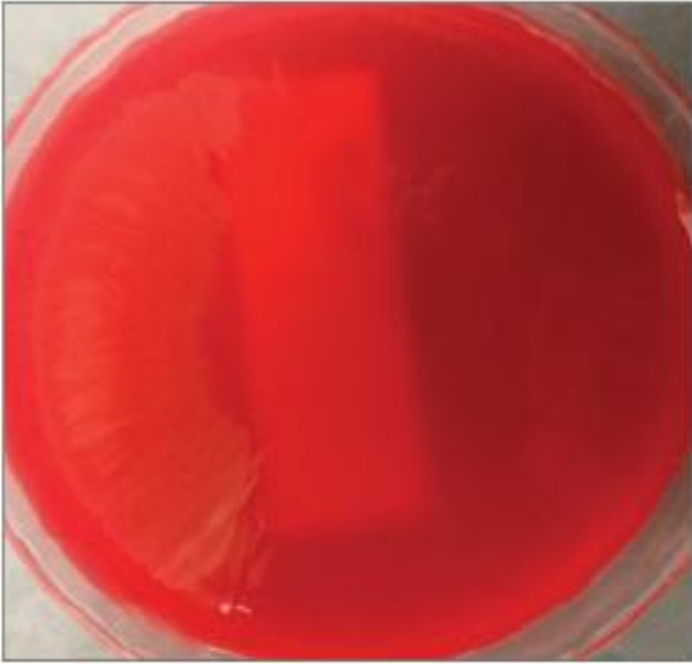
Blood agar, 1 μ L, 24 hours, aerobic

Adapted from June 9, 2016 ASM Microbe presentation by Alan J.1

Standard Urine Culture...

...is an imperfect test for microbes!

————— This urine is not sterile —————

Standard urine culture  Blood agar, 1 μL, 24 hours, aerobic	Enhanced quantitative urine culture  Blood agar, 100 μL, 48 hours, 5% CO₂
---	---

Adapted from June 9, 2016 ASM Microbe presentation by Alan J. Wolfe, PhD: "Urine Is Not Sterile: Why We Should Care."



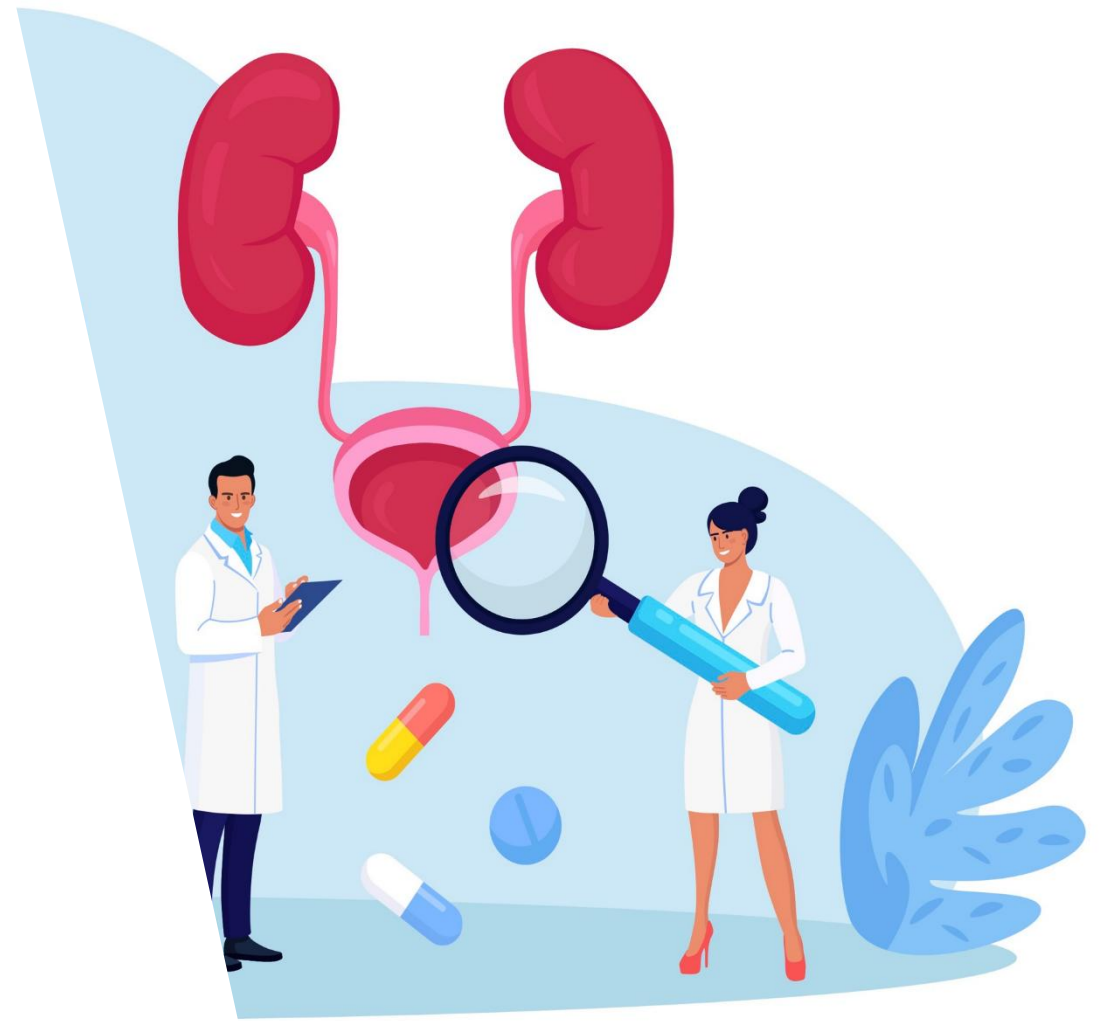
Molecular Diagnostics?

- Understand the test & report
- Consider the microbiome
- Not the holy grail...(may be helpful)

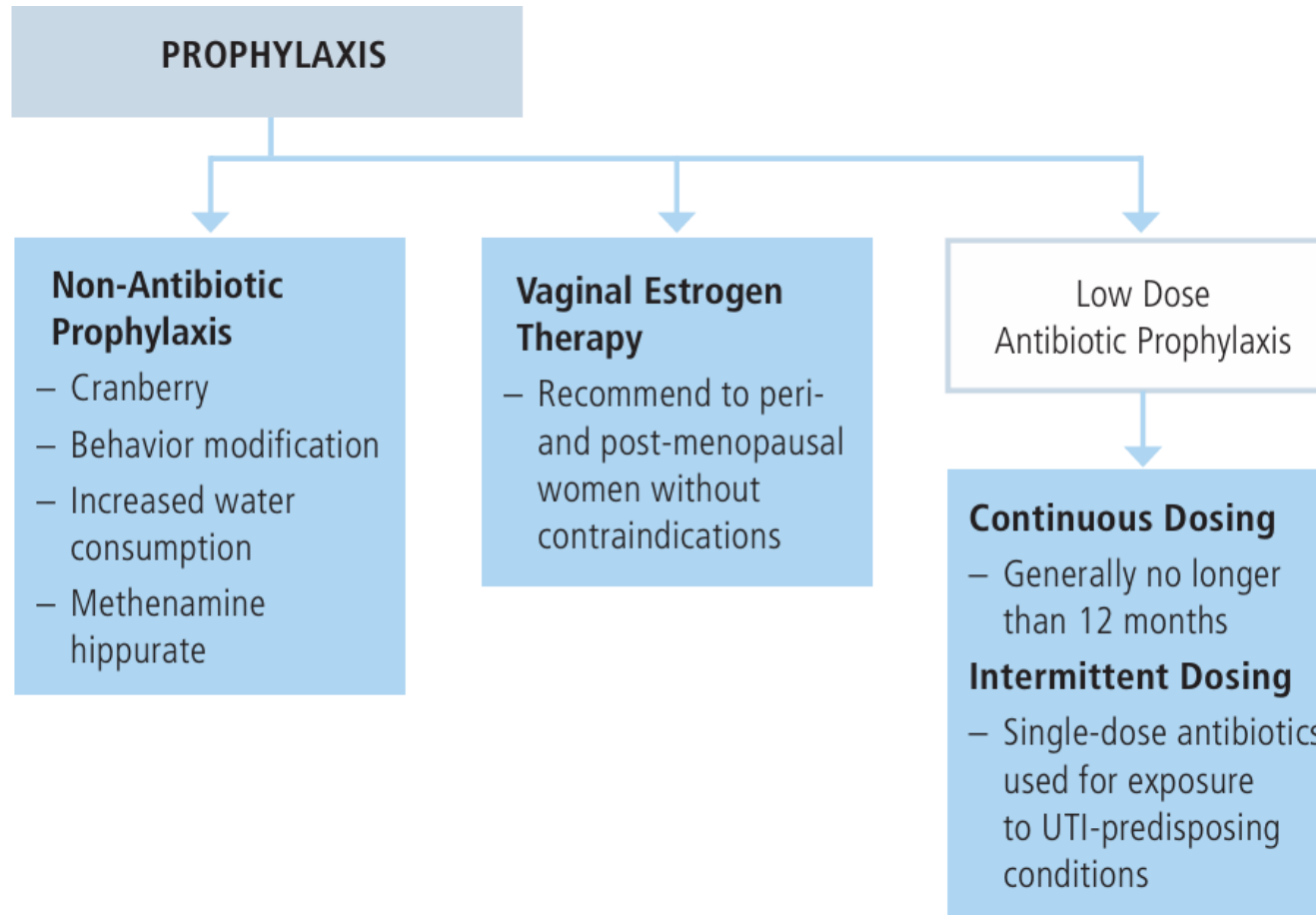
Treatment



Prevention



Prevention



Paradigm shift



Postmenopausal Recurrent UTI

What is happening within the postmenopausal urinary microbiome?

How is this associated with recurrent UTIs?

How might therapies affect the microbiome?

☆ Microbiota metabolites ☆ Host metabolites
● Microbiota protein ● Host protein

Nature Reviews | Urology

Recurrent UTI

THE JOURNAL
of UROLOGY®

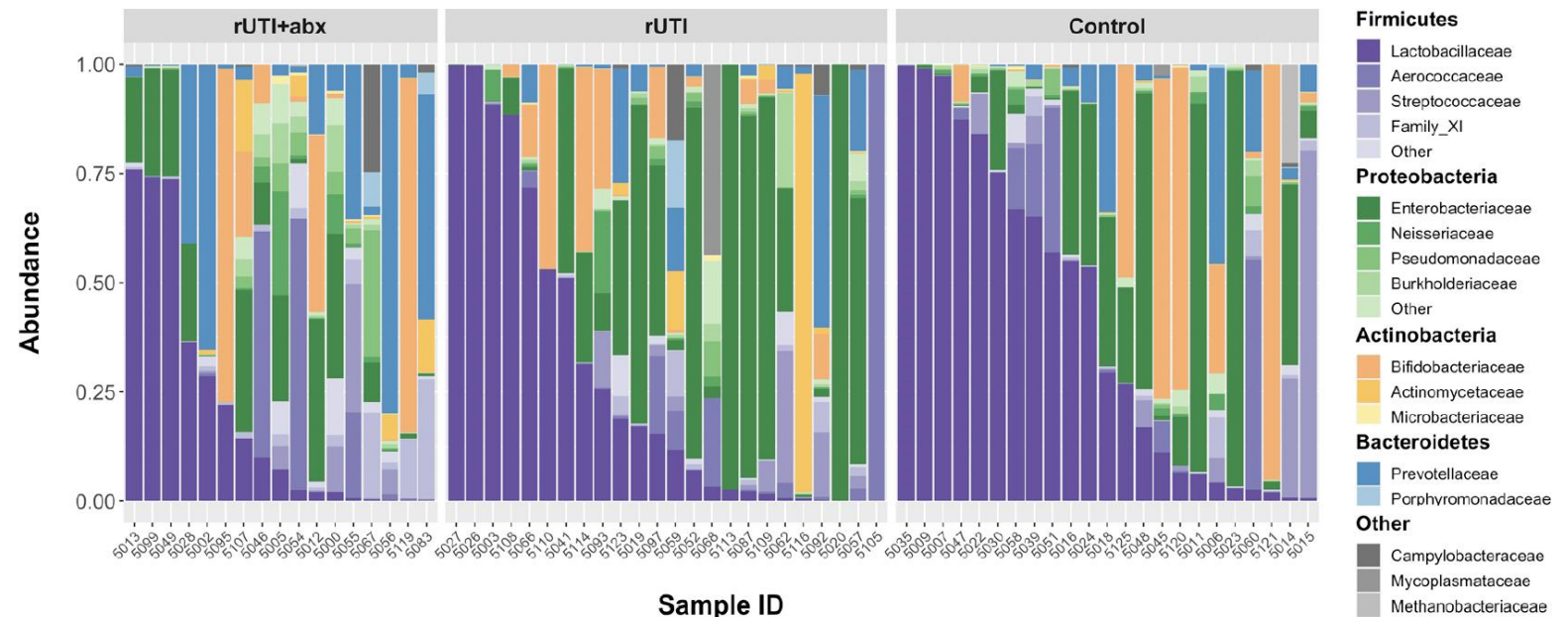
www.auajournals.org/journal/juro

The Urinary Microbiome in Postmenopausal Women with Recurrent Urinary Tract Infections

Monique H. Vaughan, Jialiang Mao, Lisa A. Kai

Correspondence: Nazema Y. Siddiqui (email: nazema.siddiqui@duke.edu).

Full-length article available at <https://www.auajournals.org/10.1097/JU.0000000000001940>.



Interference of *Lactobacillus* with pathogens


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ORIGINAL RESEARCH article

Front. Cell. Infect. Microbiol., 23 June 2022

Sec. Microbiome in Health and Disease

Volume 12 - 2022 |

<https://doi.org/10.3389/fcimb.2022.870603>

This article is part of the Research Topic

The Urogenital Microbiota in Urinary Tract Diseases

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Commensal Urinary Lactobacilli Inhibit Major Uropathogens *In Vitro* With Heterogeneity at Species and Strain Level


James A. Johnson¹,

Lydia F. Delaney¹,

Vaishali Ojha¹,


Medha Rudraraju


¹, Kaylie R. Hintze¹,

Nazema Y. Siddiqui² and

Tatyana A. Sysoeva^{1*}
¹ Department of Biology, University of Alabama in Huntsville, Huntsville, AL, United States

² Division of Urogynecology and Reconstructive Pelvic Surgery, Department of Obstetrics and Gynecology, Duke University, Durham, NC, United States

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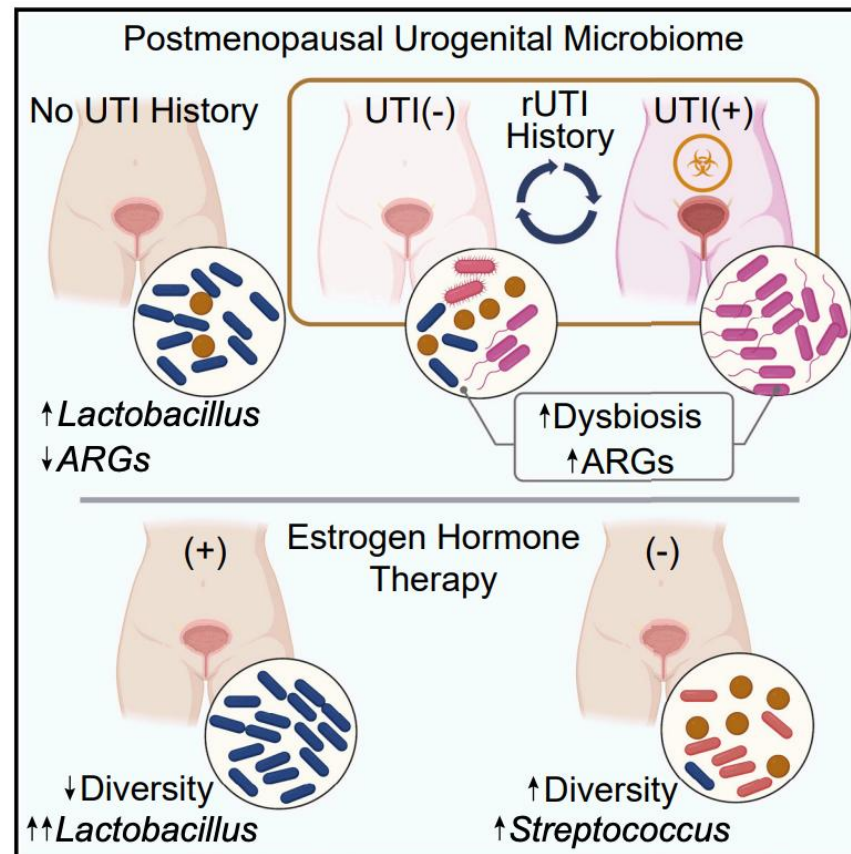
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Recurrent urinary tract infection and estrogen shape the taxonomic ecology and function of the postmenopausal urogenital microbiome

Graphical abstract



Authors

Michael L. Neugent, Ashwani Kumar, Neha V. Hulyalkar, ..., Philippe E. Zimmern, Kelli L. Palmer, Nicole J. De Nisco

Correspondence

nicole.denisco@utdallas.edu

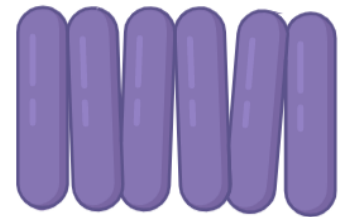
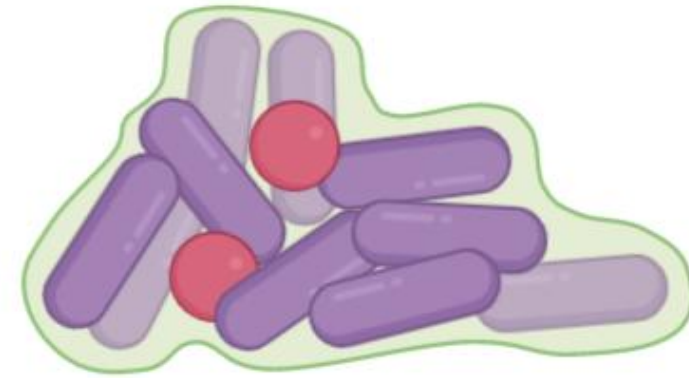
In brief

Neugent et al. use metagenomic sequencing, advanced urine culture, and metabolite profiling to survey the urogenital microbiome of postmenopausal women, finding clinically important associations relevant to recurrent UTI susceptibility. These findings provide a foundation for the future development of novel therapeutic and diagnostic strategies for recurrent UTI in postmenopausal women.

Lactobacilli

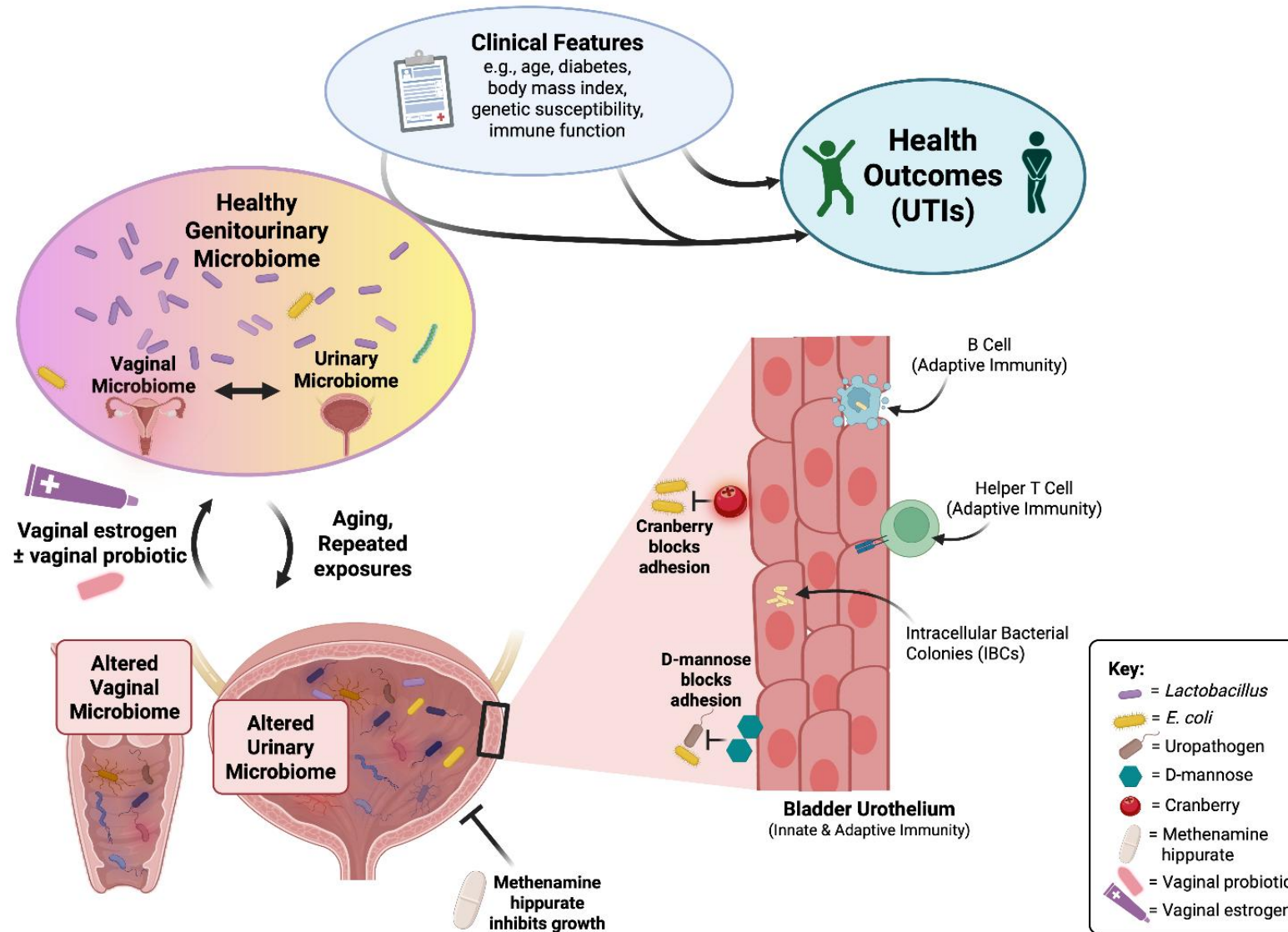
Use multiple mechanisms to counteract other organisms^{1,2}

- Aggregation promoting factors (APF)
- Secretion of organic acids
- Secretion of bacteriocins (bacterial toxins)³



Microbiome & urinary disorders





Objectives

01

Timeline of Microbiome Discovery

02

Applications for rUTI

03

Applications in OAB

What is OAB?

What is OAB?

- “Symptoms of urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence...”

Haylen et al. (2010) IUGA/ICS joint report on the terminology for female pelvic floor dysfunction. NUU. 29:4-20.

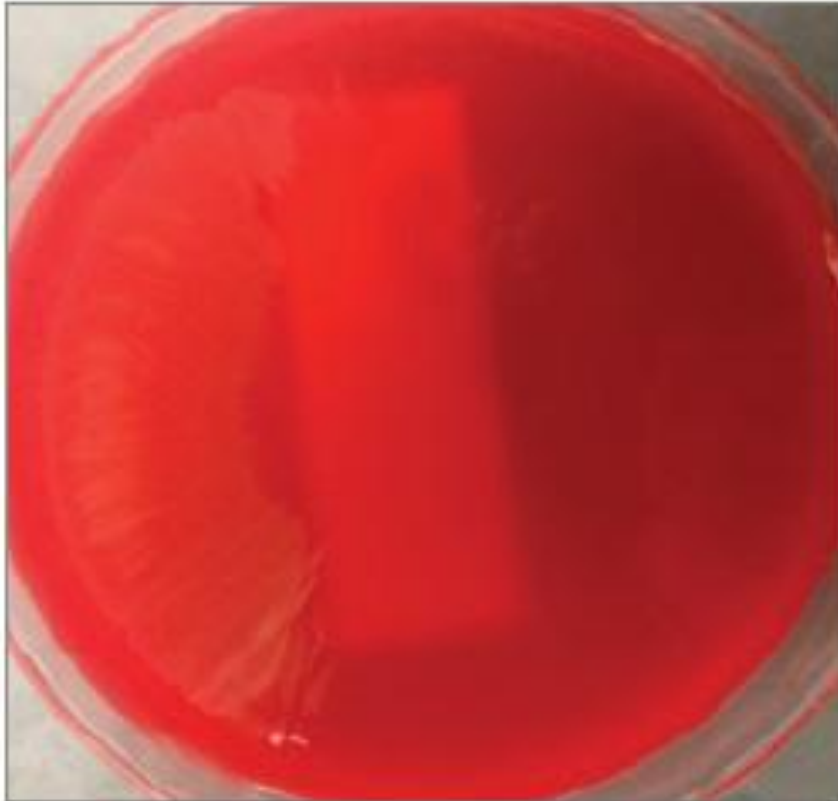
What is OAB?

- “...in the **absence of urinary tract infection (UTI)** or other obvious pathology” ^{1,2}

1. Haylen et al. (2010) IUGA/ICS joint report on the terminology for female pelvic floor dysfunction. NUU. 29:4-20.
2. Drake MJ (2014) Do we need a new definition of the overactive bladder syndrome? ICI-RS 2013. NUU. 33: 622-4.

Urinary Microbiome?

Standard urine culture



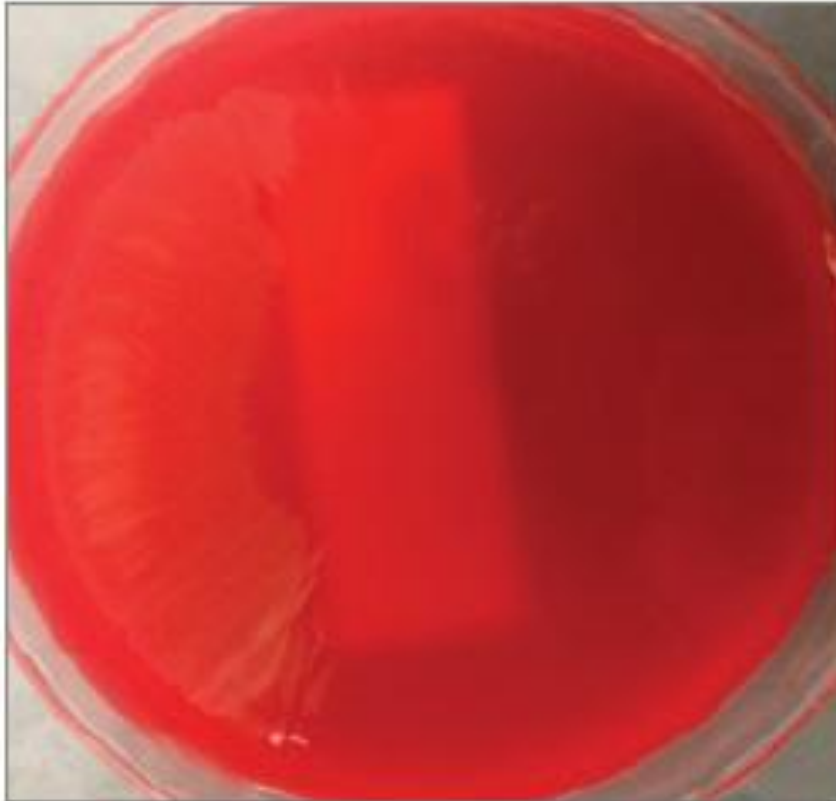
Blood agar, 1 μ L, 24 hours, aerobic

Adapted from June 9, 2016 ASM Microbe presentation by Alan J. Wolfe, PhD: "Urine Is Not Sterile: Why We Should Care."

Urine is not sterile!

This urine is not sterile

Standard urine culture



Blood agar, 1 μ L, 24 hours, aerobic

Enhanced quantitative urine culture



Blood agar, 100 μ L, 48 hours, 5% CO₂

Adapted from June 9, 2016 ASM Microbe presentation by Alan J. Wolfe, PhD: "Urine Is Not Sterile: Why We Should Care."

What is OAB?

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What is OAB?

- “Symptoms of urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence **in the absence of dysbiosis?** or other obvious pathology” ^{1,2}

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Is there a microbial etiology to OAB?



Is there a microbial etiology to OAB?



My Hypothesis:
YES, but in a **subset** (not all OAB)

Objectives

01

Definitions

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Applications for Overactive Bladder

EVOLUTION OF HUMAN MICROBIOME SCIENCE

From Discovery to Precision Medicine: The Gut–Vagina–Bladder Axis



PRE-2010
FOUNDATION ERA



2011
VAGINAL MICROBIOME
DEFINED



2012
URINARY MICROBIOME
DISCOVERED



2014–2019
LINKS TO DISEASE &
FUNCTION



2020–2026
TRANSLATION &
PRECISION MEDICINE



GUT
MICROBIOME

Large-scale characterization of gut microbiome ★

Culture-independent methods
reveal vast microbial diversity
and metabolic potential.

.....
HMP launched in 2007.
(Turnbaugh et al., 2006)

Gut microbiome enters mainstream research

Linked to obesity, metabolism, immunity,
and development.

(Turnbaugh et al., 2009)
(Human Microbiome Project Consortium, Nature, 2012)

Links to disease & function

Associations with IBD, diabetes,
cancer, drug metabolism;
shift from “who is there” to
“what are they doing”.

(Qin et al., Nature, 2014)

Therapeutics & precision nutrition

Microbiome-based therapies,



VAGINAL
MICROBIOME

Early molecular studies

identify previously
uncultured vaginal
bacteria.

Vaginal Community State Types (CSTs) described ★

Five CSTs identified, establishing
modern framework of vaginal
microbiome ecology.

(Ravel et al., PNAS, 2011)

Large-scale characterization
of healthy vaginal
communities by HMP.

*(Human Microbiome Project
Consortium, 2012)*

Links to disease & function

Associations with BV, preterm birth,
HPV persistence, and reproductive
outcomes; host–microbe
interactions defined.

(Serrano et al., Nat Rev Immunol, 2019)

Translational & clinical applications

Microbiome therapeutics for BV,



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Urine considered sterile

Standard culture methods
fail to detect bacteria in
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(Wolfe et al., JCI, 2012)

★ Urinary communities described

Characterization of urinary microbial
communities and associations with
lower urinary tract symptoms.

(Hilt et al., JCI, 2014)
(Thomas-White et al., Nat Rev Urol, 2015)
(Komesu et al., 2018)

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(Komesu et al., 2018)

Links to disease & function

Links to recurrent UTI, urgency
urinary incontinence, overactive
bladder, interstitial cystitis/bladder
pain syndrome, and host–microbe
interactions.

(Vaughan et al., 2021)
(Carnes et al., 2024)



Pre-2010: Gut microbiome era begins
(2005–2007; Turnbaugh et al., Science, 2006)



2011: Vaginal community structure defined
(Ravel et al., PNAS, 2011)



2012: Urinary microbiome discovered
(Wolfe et al., JCI, 2012; Hilt et al., JCI, 2014)





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Welcome to the Duke Microbiome Center