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Insights into the Impact, Therapeutic Strategies, and Emerging Options in Uncomplicated UTI

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Patient Advocate

On Facebook: "Long-Term Antibiotic Support for Chronic/Embedded UTI" and "CHRONIC UTI - Sharing our Journey"

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Learning Objective 1

Identify the impact of uUTI on patients and the health care system, considering burden, patient QoL, risk factors, and implications of treatment failure

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Learning Objective **2**

Differentiate the types of UTIs, including uUTI, through definitions, classifications, and current evidence-based guidelines for diagnosis and management

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Learning
Objective **3**

Evaluate current and emerging therapies for the therapeutic management of uUTI while considering health care disparities

To Ask a Question

Please select the *Ask Question* tab below the slide viewer.

Please include the faculty member's name if the question is specifically for them.

Defining Uncomplicated UTIs

Classification	Definition
Uncomplicated UTI (uUTI)	A UTI where there are no relevant functional or anatomical abnormalities in the urinary tract, no relevant kidney function impairment, and no relevant concomitant diseases promoting the UTI or risk of developing serious complications
Acute uncomplicated cystitis	A lower UTI in which the acute symptoms involve only the lower urinary tract, for example, urgency, painful voiding (dysuria), pollakiuria, and pain above the symphysis
Acute uncomplicated pyelonephritis	An upper UTI with persistent symptoms including flank pain, flank tenderness, or fever ($> 38^{\circ}\text{C}$)
Asymptomatic bacteriuria	A positive urine culture ($> 10^5$ colony-forming units/ml) in the absence of urinary symptoms
Recurrent uncomplicated UTIs	A recurrent UTI refers to the occurrence of ≥ 2 symptomatic episodes within 6 months or ≥ 3 symptomatic episodes within 12 months

UTI = urinary tract infection

Medina M, Castillo-Pino E. *Ther Adv Urol.* 2019;11:1756287219832172.

UTIs: The Statistics

UTIs affect
150 million
people each year
worldwide

Up to
50%
of the adult female
population will have a
UTI

**UTI is the most
common bacterial
infection**

53%
of older women
experience recurrence
within one year

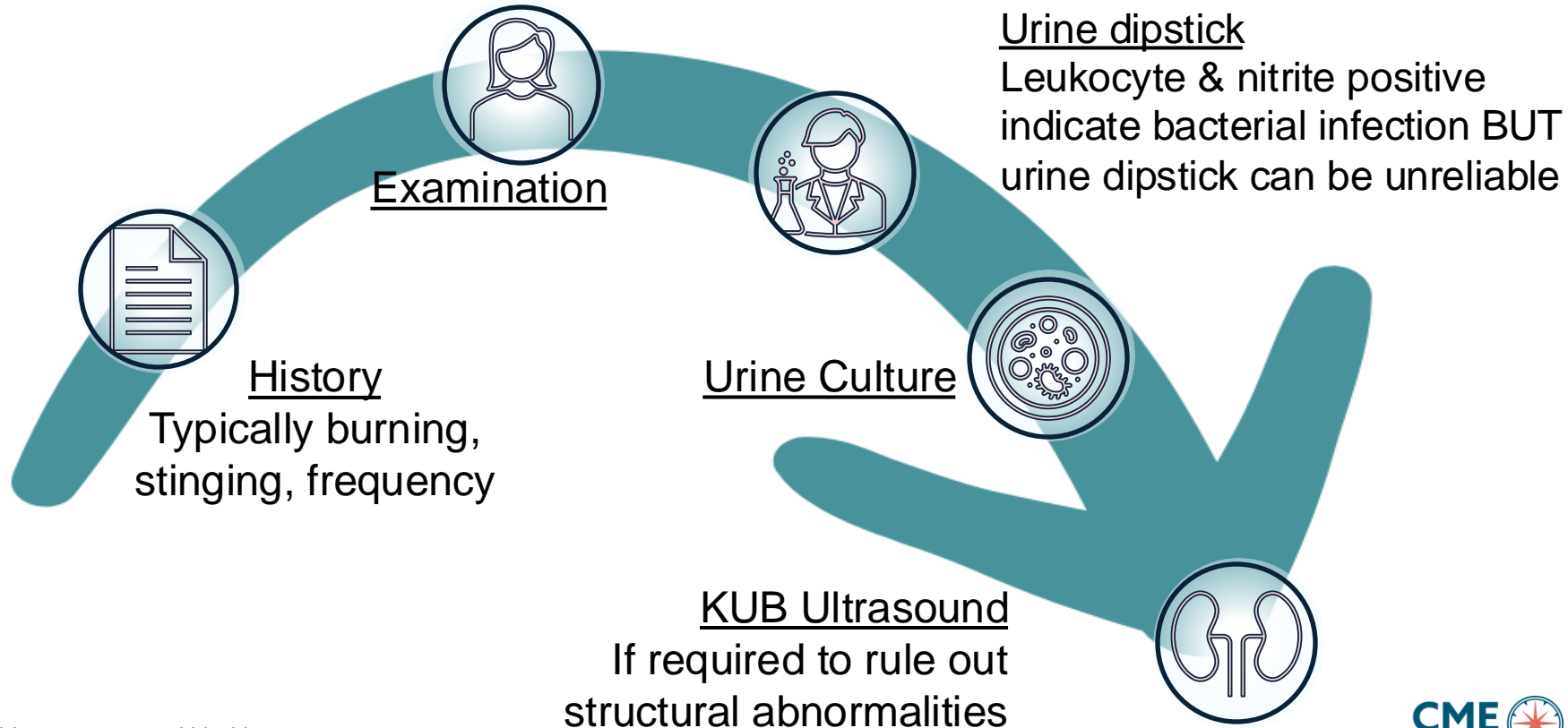
36%
of young women will
experience a
recurrence within one
year

Risk Factors for UTIs

- Female
- Postmenopausal
- Family history and genetics
- Behavior:
 - Pre-coital and post-coital voiding patterns
 - Amount of liquid consumption
 - Frequency of urination
 - Delayed voiding habits
 - Wiping patterns (pediatrics)
 - Tampon use
 - Douching
 - Hot tub use
 - Undergarment material
 - Body mass index



Primary Care: Diagnosis of a UTI



KUB = kidney, ureter, and bladder

Symptoms of UTIs



Do NOT send urinalysis or urine culture

if none of these symptoms are present or there is an alternative cause for the symptom

Signs and symptoms without alternative cause

Fever > 100.5°F

Urgency, frequency, dysuria

Suprapubic pain or tenderness

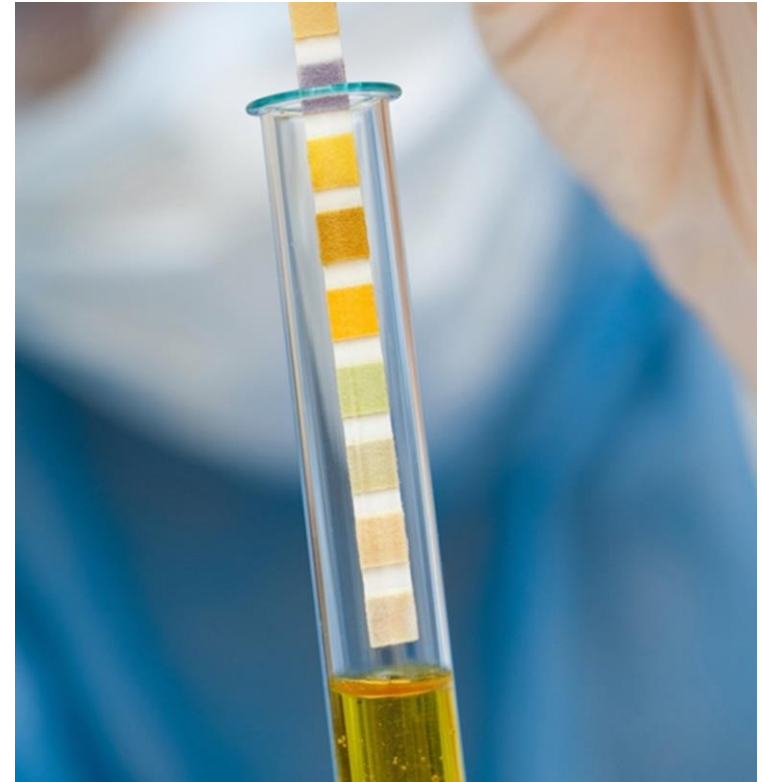
Costovertebral pain or tenderness

New onset mental status changes with leukocytosis (> 10,000 cells/mm³), hypotension (< 90 mmHg systolic), or ≥ 2 SIRS criteria

Acute hematuria

Are You Positive it's Negative?

Urine Dipsticks	Urine Culture	Consider Symptoms
<p>DO NOT rely on dipstick tests alone when diagnosing a UTI</p> <p>40-50% negative on dipstick YET grow bacteria on culture</p>	<p>Diagnosis should be confirmed by urine culture</p> <p>Always send for culture in the following groups:</p> <ul style="list-style-type: none">• Men• Pregnant women• Patients with catheters• Patients > 65 years old	<p>90% probability of a UTI in adult women with dysuria and frequency symptoms</p> <p><u>Recommendation:</u> Empirical antibiotics can be considered, depending on the severity of the symptoms, risk of developing complications, and previous infections and antibiotic use</p>



Traditional Testing



10^5 /mL bacteria in urine = UTI



Anything less reported as 'insignificant growth'



> 2 species of bacteria reported as 'mixed growth'

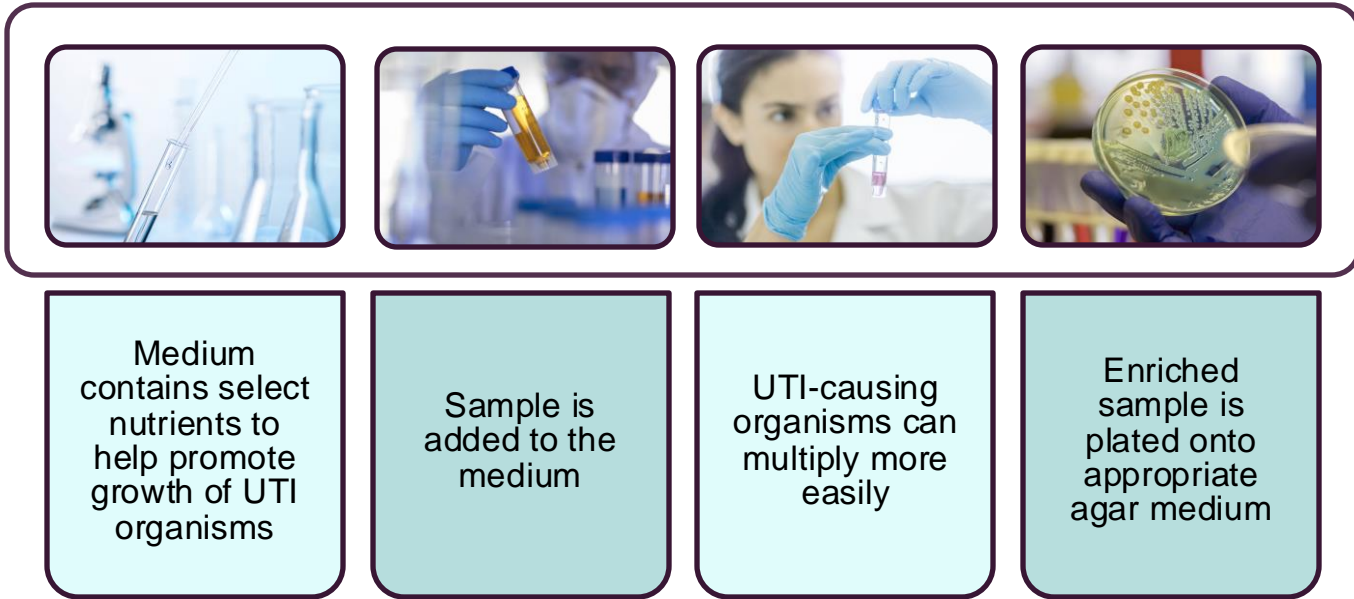


20-40% of acute symptomatic patients have counts of less than 10^5 /mL bacteria



YET they DO respond to antibiotics

Liquid Broth and Enrichment Medium Culture



- Liquid medium better replicates liquid environment in the bladder
- Fluid medium – viable but ‘dormant’ bacteria switch into exponential growth phase, kicked back to the planktonic state
- Uropathogens and normal flora found and reported with advisory

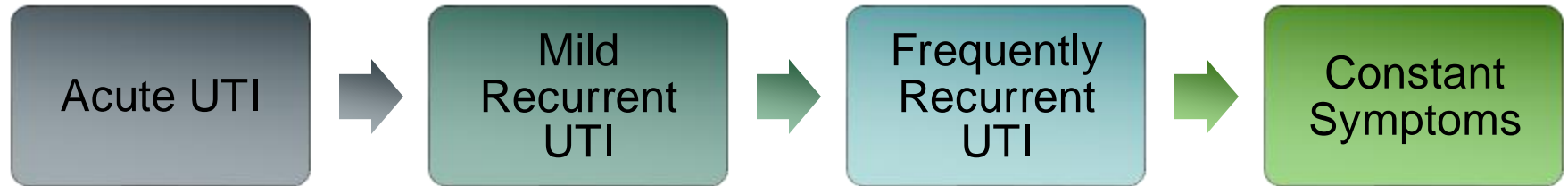
Recurrent & Chronic UTI

Recurrent UTI in adults (age > 16 yrs)

- 2 or more UTIs in the last 6 months
- 3 or more UTIs in the last 12 months

UTI Career often a continuum

- Relapse?
- Persistence?
- Chronicity?



Treatment Failure

Treatment failure associated with:

- Older age
- Pregnancy
- Diabetes
- Renal impairment
- Antibiotic choice and duration
- Increased antibiotic resistance
- UK data reveals microbiological investigation and re-prescription of the same antibiotic given for the initial episode happened in one quarter of UTIs
- Using a treatment with higher efficacy reduces treatment failure, optimizes patient outcomes



Who are We Missing?

- Patients often lost at diagnosis
- Lack of awareness/knowledge, especially amongst HCPs
- Empirical treatment failures
- Misdiagnosis
- Persistently recurrent UTI quality of life likened to end stage renal failure (ESRF) or rheumatoid arthritis (RA)
- Faculty discussion – meeting individual patient needs



Quality of Life for CUTI Patients

Based on anecdotal examples shared by patients with chronic UTIs (CUTI) from across the globe, quality of life for women with this set of symptoms is extremely low. Below are a list of some of daily life activities that are impacted on a regular basis:

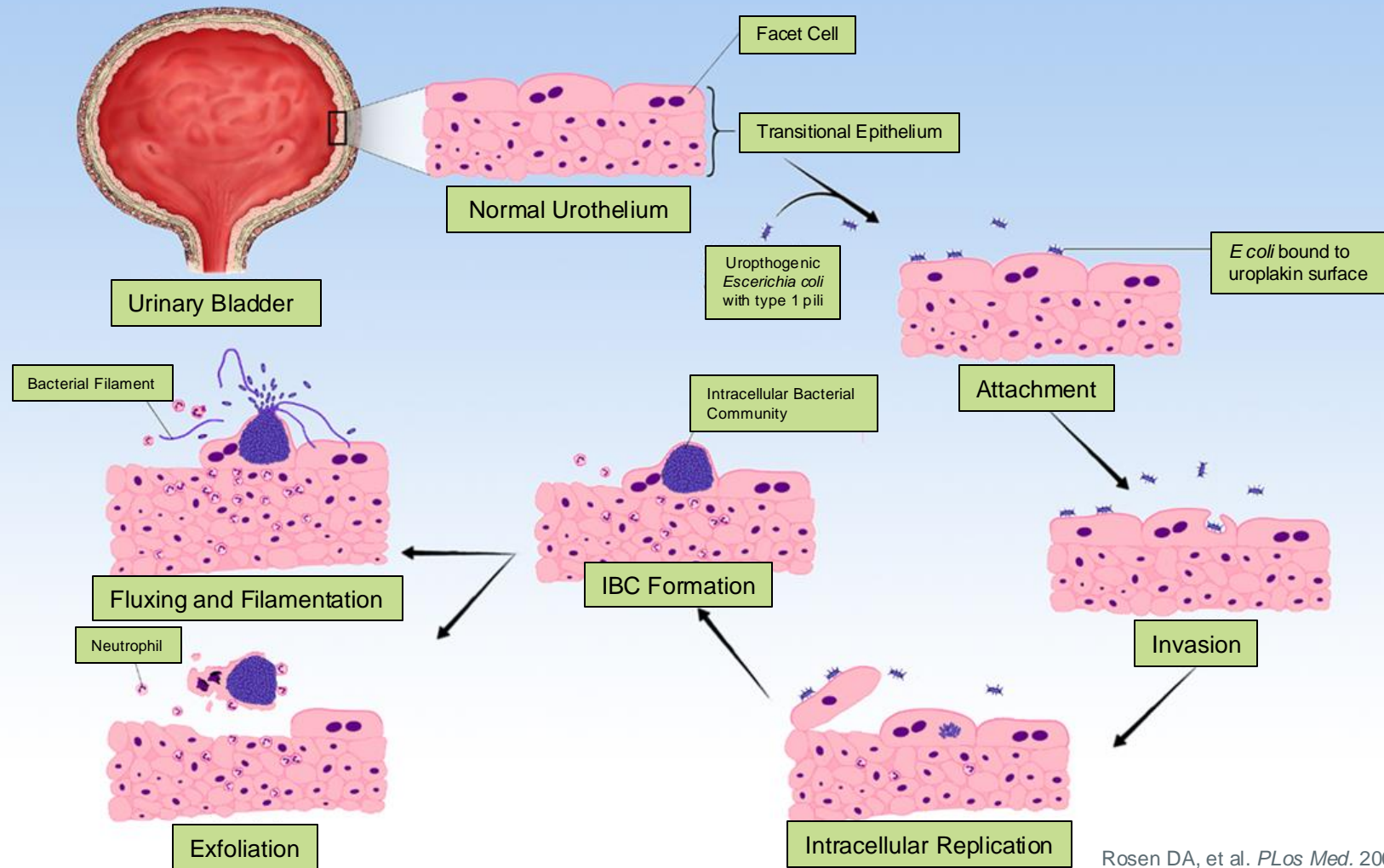
- Fear of doctors due to lack of education of proper treatment, as there are no clear guidelines for chronic UTI treatment
- Expense of medical support, as it is mostly out of pocket
- Lack of intimacy with partner
- Decreased social interactions due to symptoms and inability to partake in normal diet



Quality of Life for CUTI Patients

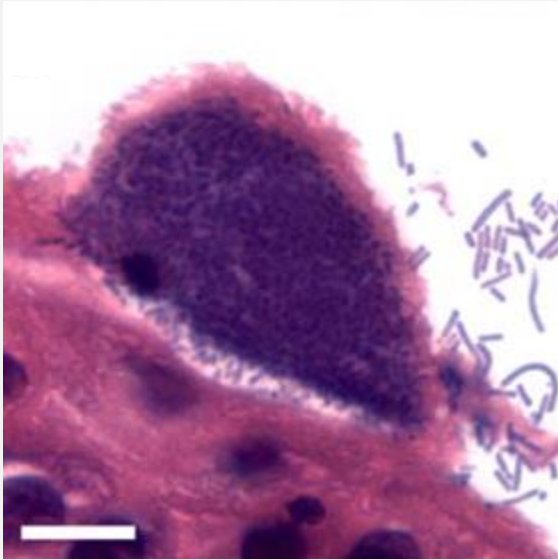
- Decreased work efficiency, or inability to work at all, due to symptomology
- Poor mental health (anxiety and depression)
- Suicidal thoughts and successful attempts
- Inability to plan for travel and social events which further decrease social interactions with friends and family
- Lack of rest due to symptoms



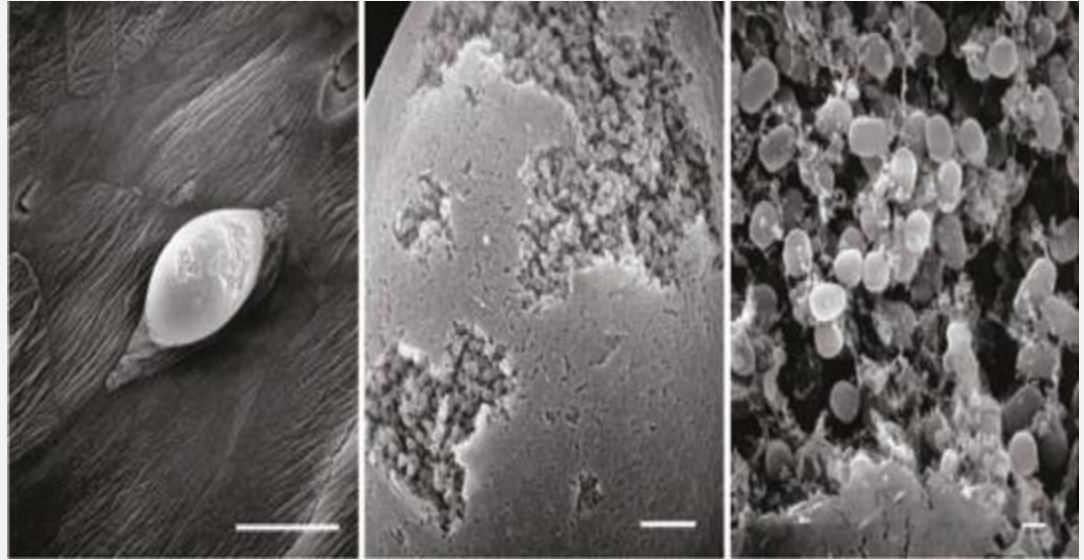


Light and Electron Microscope Images of Intracellular Biofilm-Like Pods in Bladder Mucosa

1.



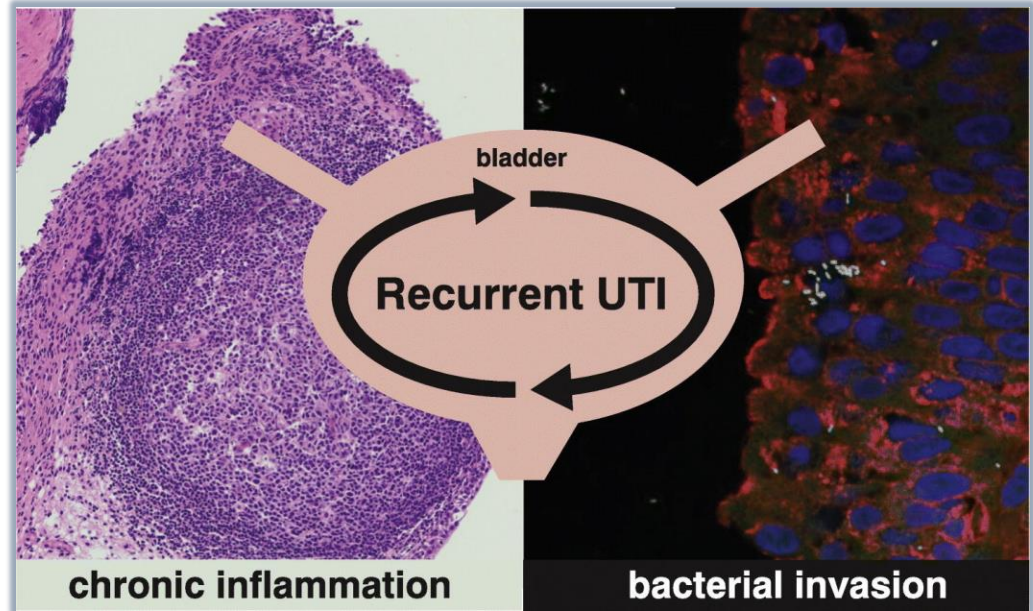
2.



1. Anderson GG, et al. *Microbes Infect.* 2004;6(12):1094-1101.
2. Anderson GG, et al. *Science.* 2003;301(5629):105-107.

Intracellular Bacterial Communities

- Texas study: urine and bladder biopsies
- Postmenopausal women with antibiotic-refractory recurrent UTI
- Direct evidence of embedded bacteria in bladder tissues associated inflammatory response
- Less bacteria found in urine



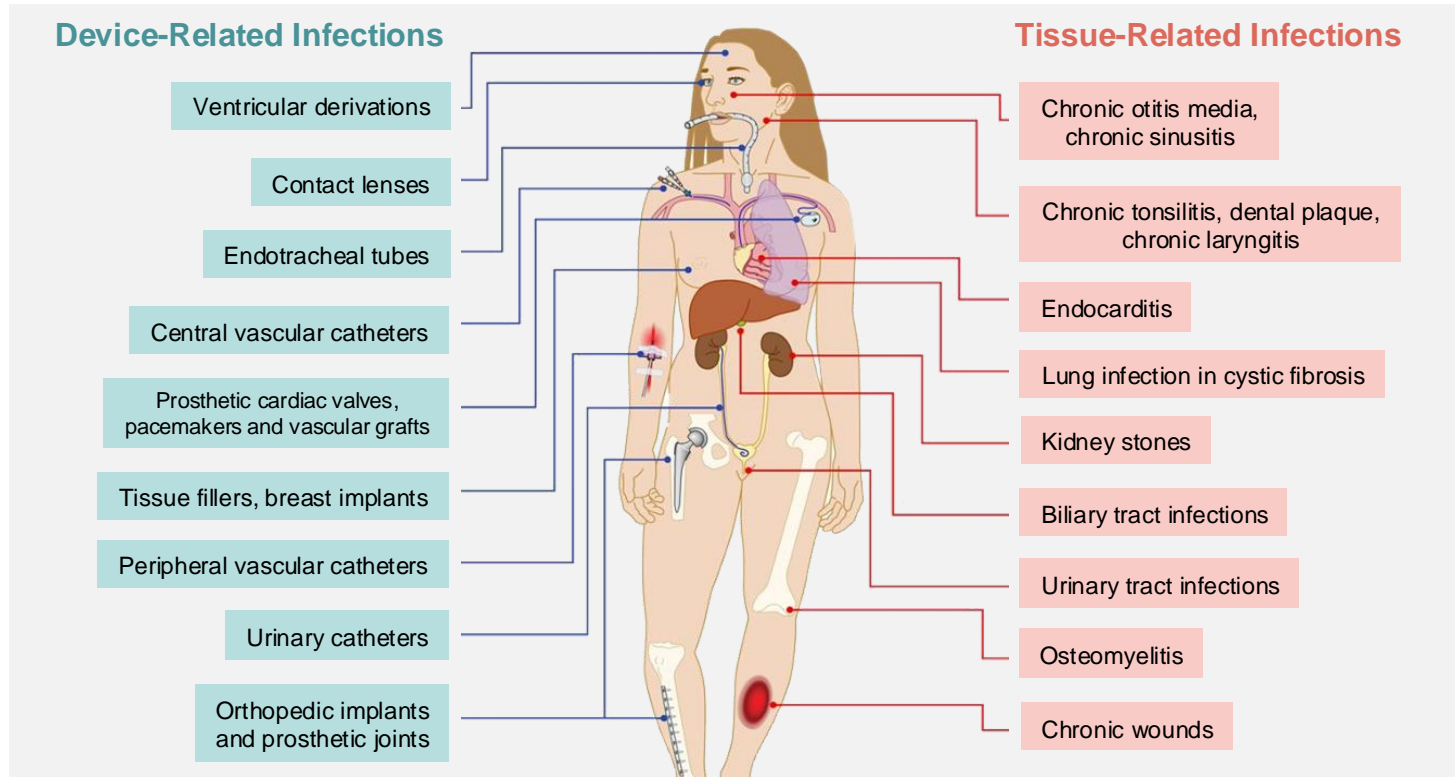
Biofilms



“A structured community of bacterial cells enclosed in a self-produced polymeric matrix and adherent to an inert or living surface”

80% of bacteria in the universe exist in biofilm phenotype

Biotic and Abiotic Sites of Biofilm Medicated Infection/Colonization



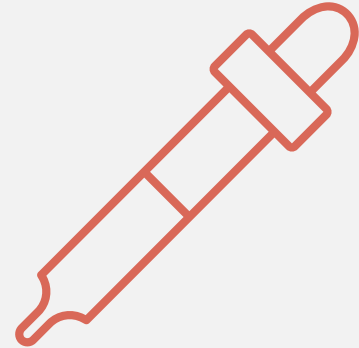
Treatments in Recurrent & Chronic UTI



Adjunct estrogen
(immune modulation)
may help



Bladder instillations
(gag layer replacements,
antibiotics, steroid)



Vaccines; not licensed

Improved Testing Support Validity of Treatment Based on Symptoms

Belgian primary care study:
PCR + culture

220 women UTI symptoms, 86 controls

Symptomatic group:

Control group:

Almost all women with typical urinary symptoms & negative culture had *E. coli* infection

80.9% cultures - positive

95.9% *E. coli* qPCR-positive

10.5% urine cultures - positive

11.6% - *E. coli* qPCR-positive

Treatments in Recurrent & Chronic UTI



Extended courses of abx (akin to other biofilm infections, e.g., osteomyelitis, subacute bacterial endocarditis (SBE), bronchiectasis)



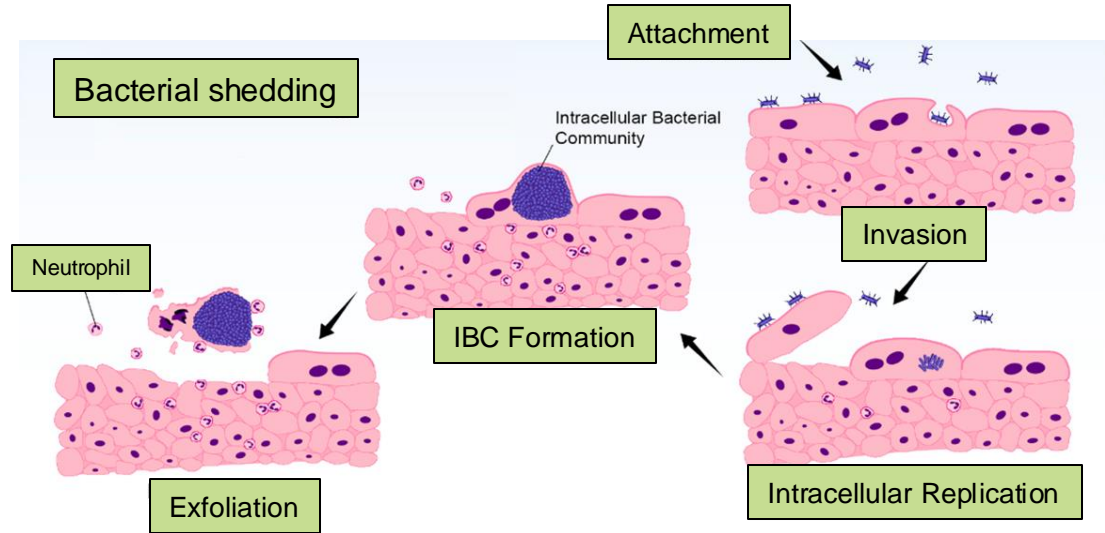
Prophylactic abx



Methenamine hippurate indicated in the prophylaxis of UTIs

Extended Course Antibiotics

- Bladder cells - slow turnover (3 months)
- Bacteria can hide within bladder cells
- It is postulated that a longer courses of antibiotics halt new rounds of infection/invasion



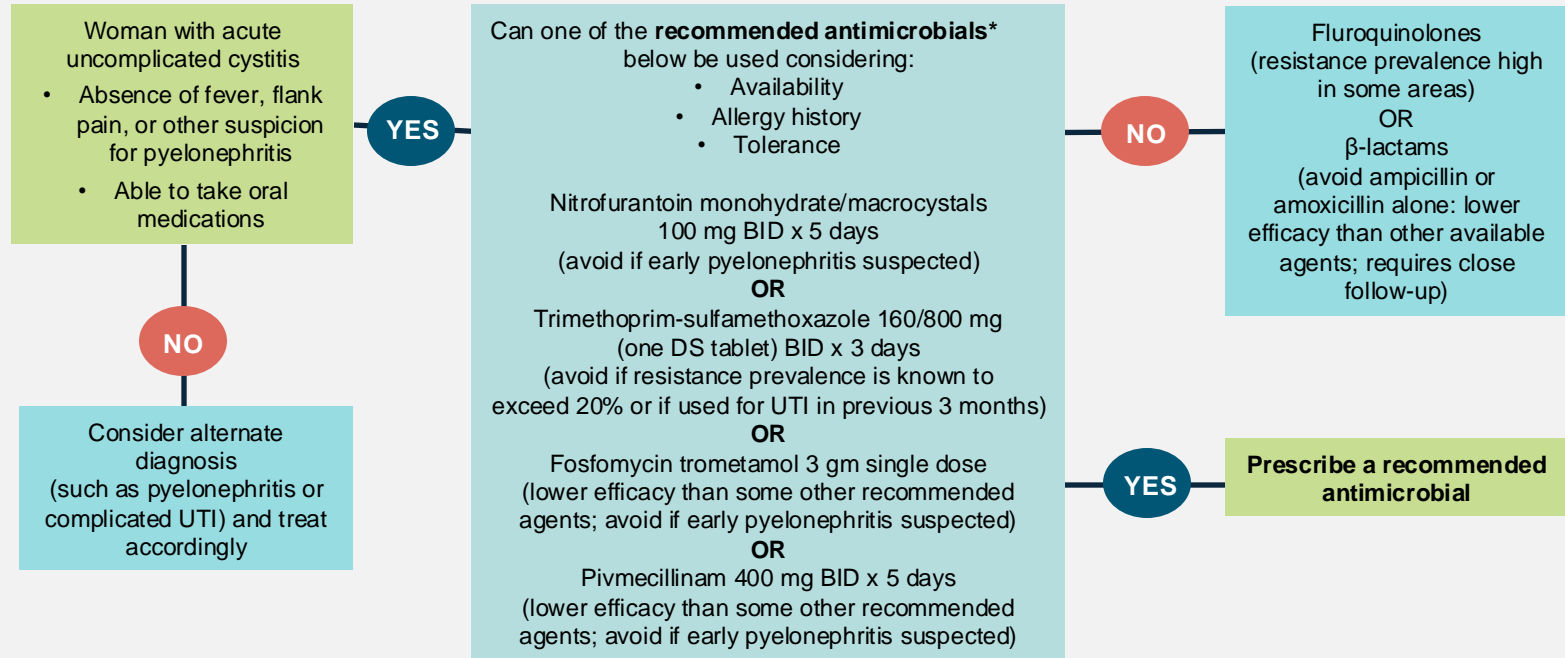
IBC = intracellular bacteria

Scott V, et al. *Urology*. 2015; 86(3):425-431; Rosen DA, et al. *PLoS Med*. 2007. 4(12):e329.

Evidence-Based Guidelines for uUTI Treatment

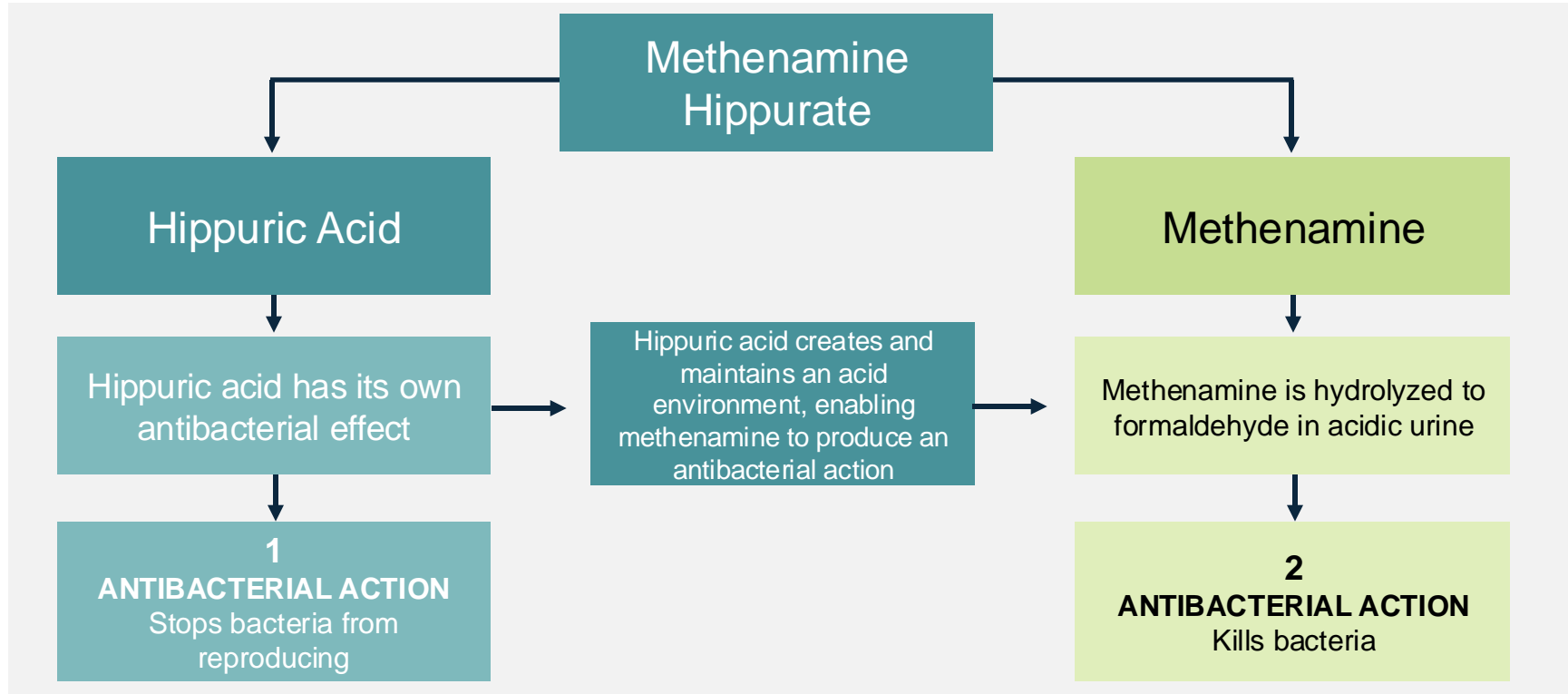
Antibiotic	Duration	Considerations
Nitrofurantoin	5 days	Avoid in CrCl < 30ml/min
Trimethoprim-sulfamethoxazole	3 days	Increasing <i>E. coli</i> resistance
Alternative		
Fosfomycin	1 dose	Cost ~ \$60/dose May not be available at some retail pharmacies May consider extending duration to 3-5 doses
IV beta-lactam or Oral beta-lactam	3-7 days	

IDSA Treatment Algorithm

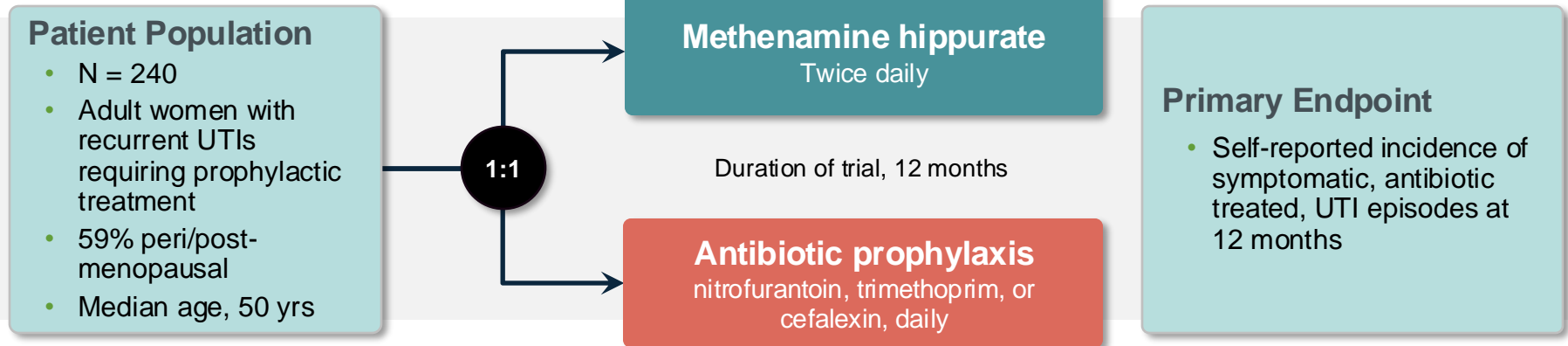


*The choice between these agents should be individualized and based on patient allergy and compliance history, local practice patterns, local community resistance prevalence, availability, cost, and patient and provider threshold for failure.

Methenamine Hippurate Dual Action



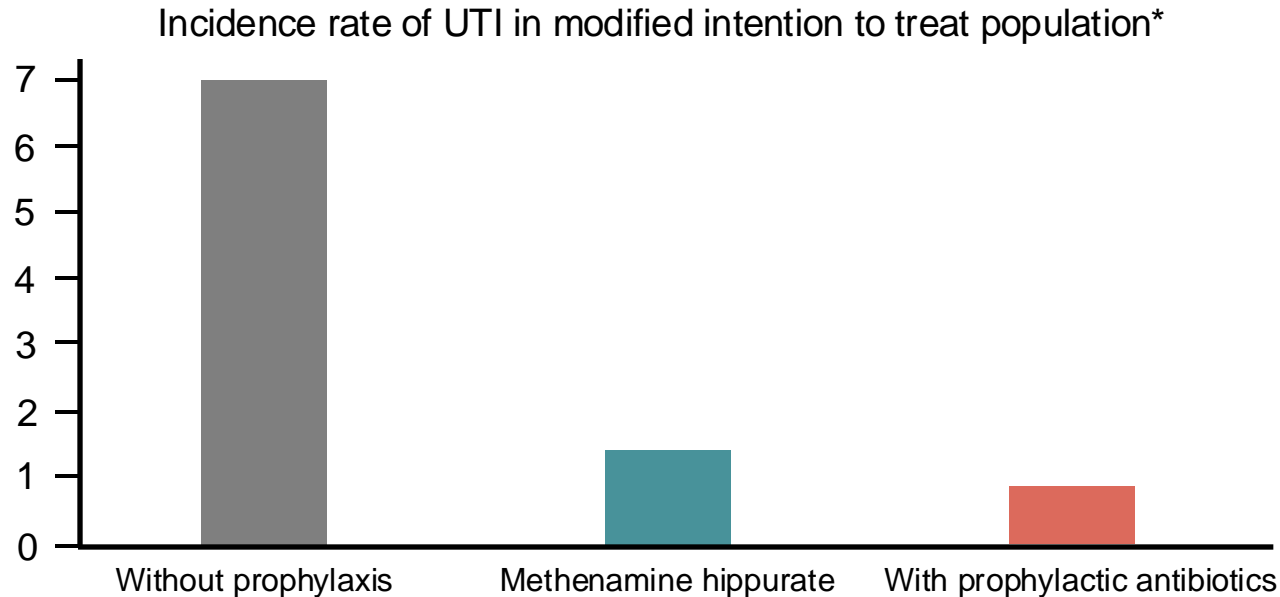
ALTAR Study



Secondary Endpoints:

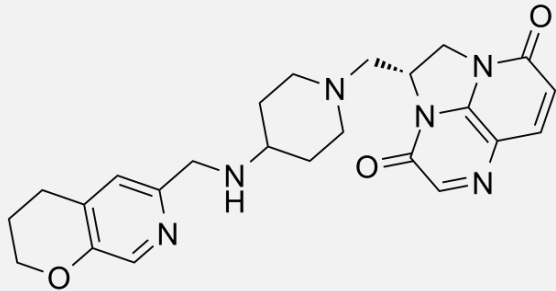
- Incidence of symptomatic, antibiotic treated UTI at 6 months; microbiologically confirmed UTIs; antibiotic resistance profiles in *E coli* isolated from urine and perineal swabs; asymptomatic bacteriuria; total antibiotic use; and hospital admissions due to UTI
- Participant satisfaction with treatment using the treatment satisfaction questionnaire for medication, which assessed treatment satisfaction: effectiveness, side effects, convenience, and global satisfaction

ALTAR Study: UTI Incidence Rates



* Modified intention to treat = primary analysis, including all patients with at least six months of follow-up data analysis according to the original treatment allocation

Gepotidacin

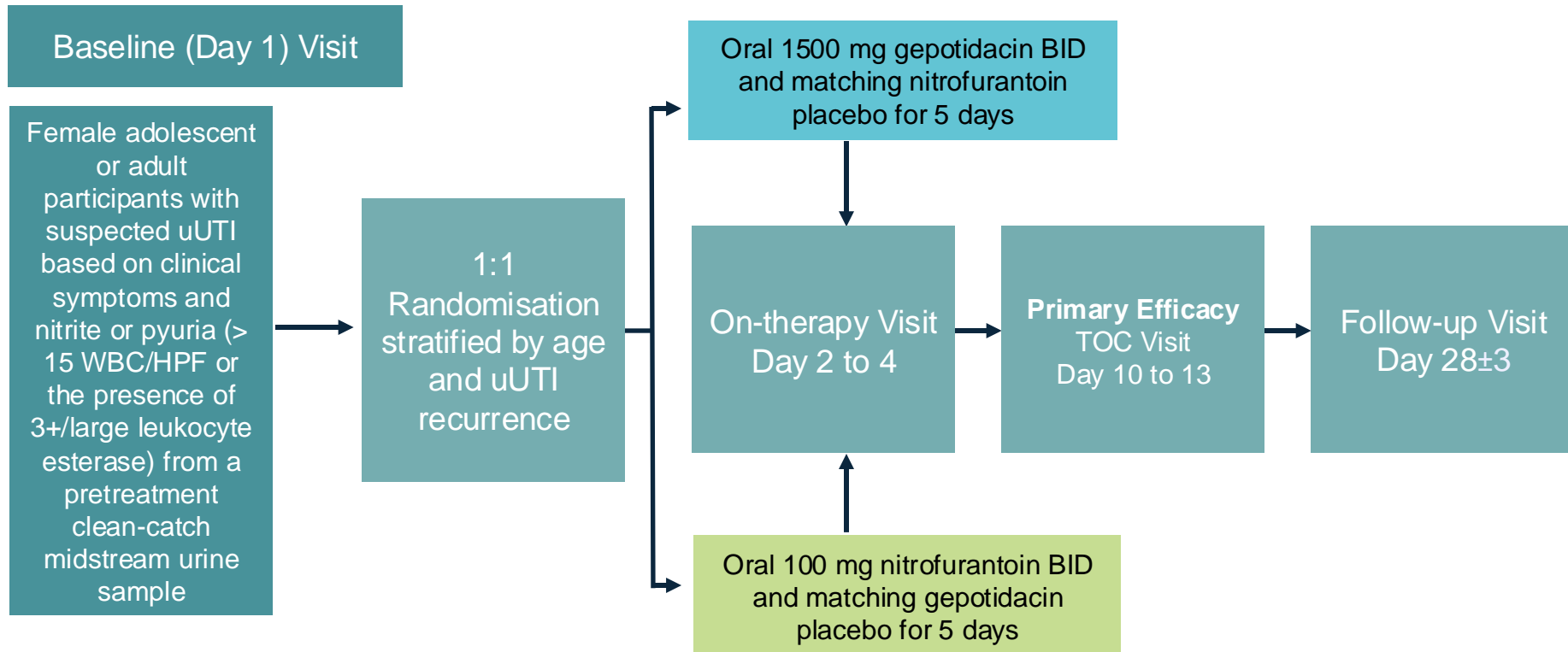


Novel, first-in-class antibiotic which selectively inhibits bacterial DNA replication

In studies, gepotidacin was well-tolerated and more effective than nitrofurantoin

Demonstration of efficacy against the less common but serious uropathogens such as *Proteus sp.*, which is intrinsically resistant to nitrofurantoin, and *Enterococcus sp.*, which is susceptible to only a limited set of oral antibiotics

EAGLE-2/EAGLE-3: Study Design



Primary endpoint: therapeutic success [combined clinical success (i.e., complete symptom resolution) and microbiological success (i.e., reduction of qualifying uropathogens to $< 10^3$ CFU/mL) without other systemic antimicrobial use]

BID = two times a day; CFU = colony forming unit; HPF = high power field; TOC = transition of care; WBC = white blood cells

Wagenlehner FME, et al. *JAC-Antimicrob Resist.* 2023;5(Suppl_3):dlad077.035.

Wagenlehner F. et al. *Lancet.* 2024;403(10428):741-755. Ali ASM, Anderson CS. *Lancet.* 2024;403(10428):702-703.

EAGLE-2/EAGLE-3: Efficacy

Table 1. Therapeutic, clinical, and microbiological response at test-of-cure

Endpoint (number, %)	Gepotidacin 1500 mg BID	Nitrofurantoin 100 mg BID	Treatment difference (95% CI)*
EAGLE-2	N = 320	N = 287	
Therapeutic success	162 (50.6%)	135 (47.0%)	4.3% (-3.6%-12.1%)
Clinical success	210 (65.6%)	187 (65.2%)	1.2% (-6.3%-8.7%)
Microbiological success	232 (72.5%)	194 (67.6%)	5.2% (-2.1%-12.5%)
EAGLE-3	N = 277	N=264	
Therapeutic success	162 (58.5%)	115 (43.6%)	14.6% (6.4%-22.8%)
Clinical success	188 (67.9%)	167 (63.3%)	4.4% (-3.5%-12.3%)
Microbiological success	200 (72.2%)	151 (57.2%)	15.0% (7.2%-22.9%)

Study success rules were based on pre-defined interim analysis rules. Both studies were stopped for non-inferiority as the observed Z statistics of 3.5554 (EAGLE-2) and 5.8838 (EAGLE-3) were greater than the non-inferiority boundaries of the respective studies (2.065 for EAGLE-2 and 2.098 for EAGLE-3). Following pre-specified hierarchical testing strategy, superiority was then demonstrated in EAGLE-3 (observed one-sided P value of 0.0003 less than the superiority boundary [0.018]).

* Calculated using Miettinen–Nurminen test adjusting for age and recurrence history.

These endpoints were evaluated in patients with all qualifying uropathogens determined to be susceptible to nitrofurantoin.

EAGLE-2/EAGLE-3: Safety

Most common AEs were mild gastrointestinal disturbances:

- Diarrhea
- Nausea
- Flatulence

C. diff was rare

	Gepotidacin 1500mg BID (N = 1570)	Nitrofurantoin 100mg BID (N = 1558)
Total number of AEs	1039	589
No. (%) of patients with at least one:		
AE by maximum severity	551 (35)	365 (23)
Grade 1 (mild)	326 (21)	215 (14)
Grade 2 (moderate)	201 (13)	136 (9)
Grade 3 (severe)	24 (2)	14 (<1)
Grade 4/5 (life threatening/fatal)	0	0
Drug-related AE	418 (27)	201 (13)
Leading to study drug discontinuation	71 (5)	20 (1)
AESI	432 (28)	174 (11)
<i>Clostridioides difficile</i>	8 (< 1)	0
Cardiovascular	4 (<1)	3 (<1)
Gastrointestinal	425 (27)	170 (11)
Potential acetylcholinesterase-inhibition (non-gastrointestinal)	9 (<1)	5 (<1)
SAE	7 (<1)	8 (<1)
Drug-related	1 (<1)	1 (<1)
Leading to death	0	0
AE leading to study withdrawal	27 (2)	10 (<1)
AEs reported in ≥ 1% of patients (in any treatment group)		
Diarrhea	258 (16)	51 (3)
Nausea	146 (9)	64 (4)
Flatulence	43 (3)	8 (<1)
Headache	38 (2)	40 (3)
Feces soft	37 (2)	8 (<1)
Dizziness	29 (2)	19 (1)
Vomiting	28 (2)	10 (<1)
Abdominal pain upper	26 (2)	11 (<1)
Urinary tract infection	19 (1)	20 (1)

AE = adverse event; AESI = adverse event of special interest;
SAE = serious adverse event
Wagenlehner FME, et al. *JAC-Antimicrobial Resistance*. 2023;5 (Suppl_3):dlad077.035. Wagenlehner F, et al. *Lancet*. 2024;403 (10128):741-755. Ali ASM, Anderson CS. *Lancet*. 2024;403(10128):702-703

EAGLE-2/EAGLE-3: Summary

- Results of the EAGLE-2 and EAGLE-3 trials provide strong evidence that gepotidacin is an effective and safe oral antibiotic for the treatment of uUTI
- Good news for patients who are resistant to other antibiotics or who are intolerant to other first-line treatments
- Superiority over nitrofurantoin
- Efficacy against the less common but serious uropathogens such as *Proteus* and *Enterococcus* species, which are intrinsically resistant to nitrofurantoin
- Gepotidacin is generally well-tolerated (the most common adverse event was mild or moderate diarrhea)

Alternative Treatments



- Naturopathic treatments, e.g., D-Mannose (NICE supported), uva ursi, oregano oil (carvacrol), etc.
- Lifestyle changes e.g., low carbohydrate diet, increase fluids, reduced caffeine, etc.

The Global Impact of Antimicrobial Resistance (AMR)

700,000



estimated deaths each year globally from antimicrobial resistant infections



10 million predicted deaths by 2050 if we do nothing



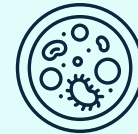
1 Number of new classes of antibiotics discovered since the 1980s



Resistance to **amoxicillin** is now **100%** among urinary isolates of *E. coli* in some countries



34% of UTI samples analyzed were found to be resistant to **trimethoprim**, an increase from 29.1% in 2015



3% of samples analyzed were found to be resistant to **nitrofurantoin**

Impact of AMR



AMR is a global problem that impacts all countries and all people, regardless of their wealth or status



\$100 TRILLION cumulative cost by 2050 if no action is taken



Rise of AMR is creating a new generation of 'SUPERBUGS' which cannot be treated by existing medications

Global Impact of AMR



- In the **United States**, antibiotic resistance contributes to **23,000+ deaths** per year and > 2.0M illnesses
- In the **European Union**, antibiotic resistance contributes to **25,000 deaths** per year and 2.5M extra hospital days
- In **Thailand**, antibiotic resistance causes **38,000+ deaths** per year and 3.2M hospital days
- In **India**, over **58,000 babies died** in one year as a result of infection with resistant bacteria usually passed on from their mothers

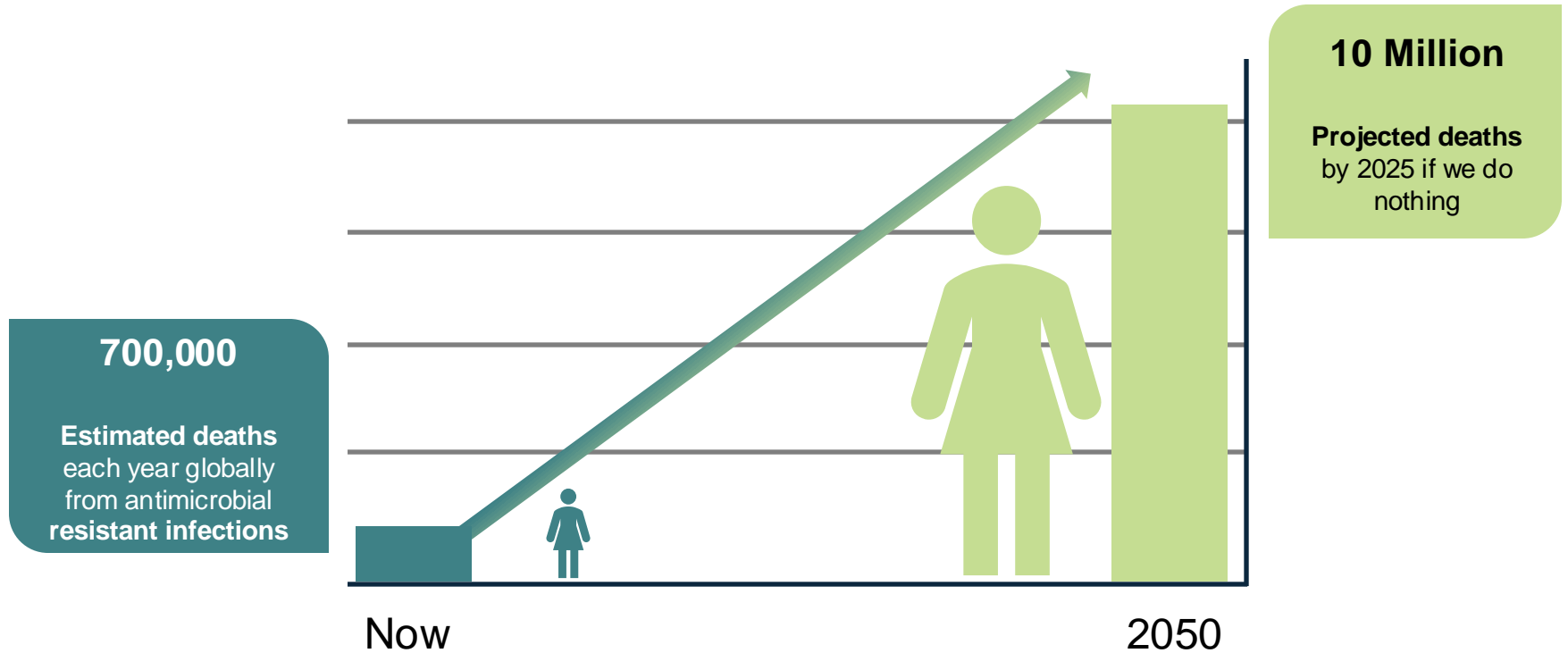
ECDC/EMA Joint Technical Report. 2009.

https://www.ecdc.europa.eu/sites/default/files/media/en/publications/Publications/0909_TER_The_Bacterial_Challenge_Time_to_React.pdf.

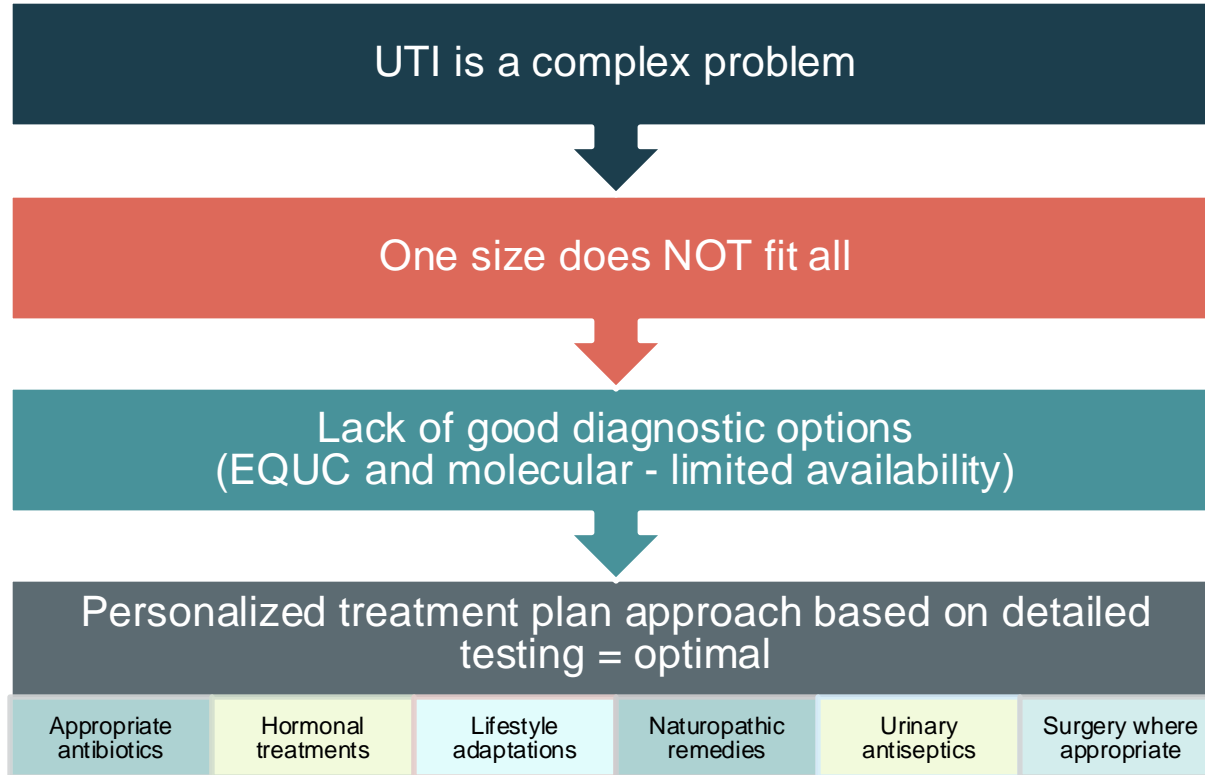
Laxminarayan R, et al. *Lancet Infect Dis*. 2013;13(12):1057-98. Pumar P, et al. *J Health Serv Res Policy*. 2012;6:352-360.

Centers for Disease Control and Prevention [CDC]. <https://www.cdc.gov/antimicrobial-resistance/>.

The Human Cost of No Action

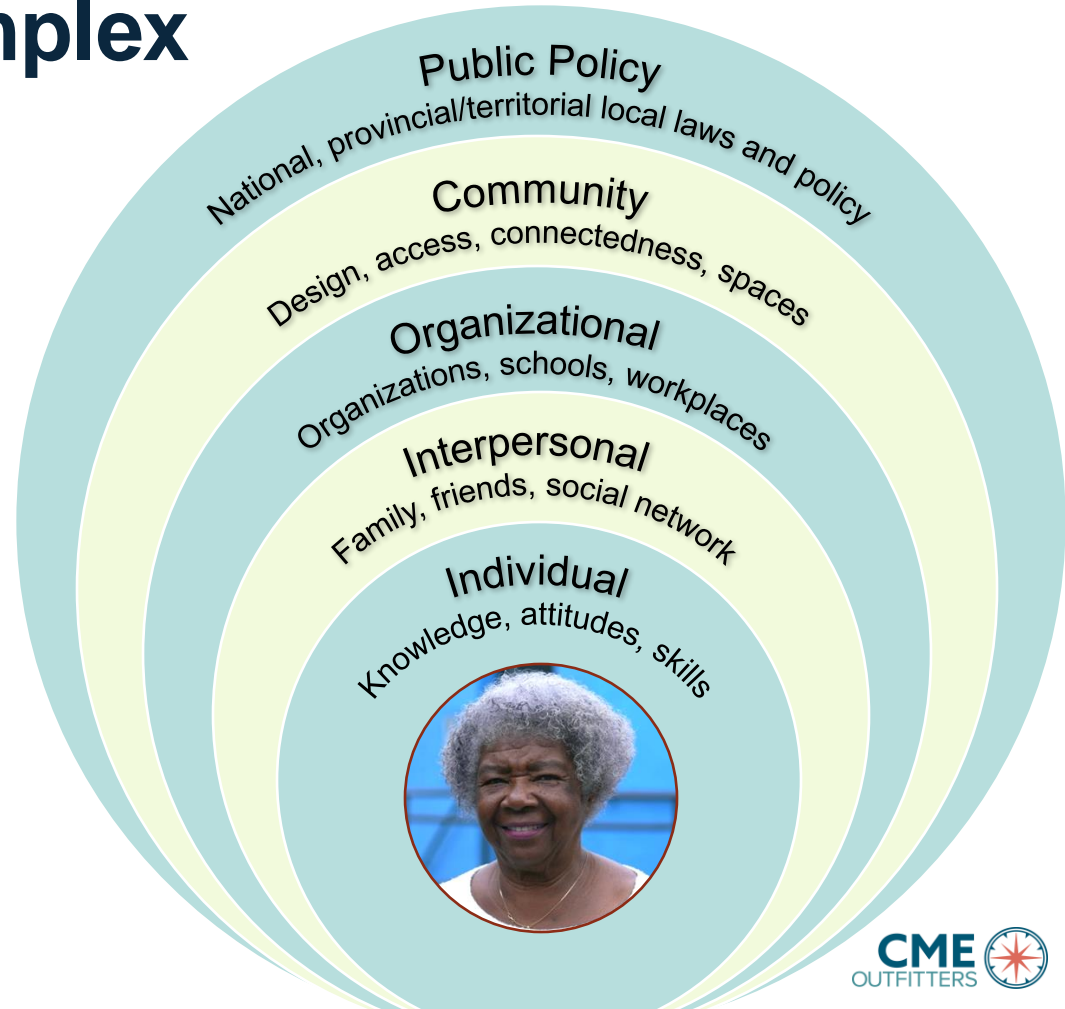


Unmet Needs in Uncomplicated UTI



Disparities Are Complex

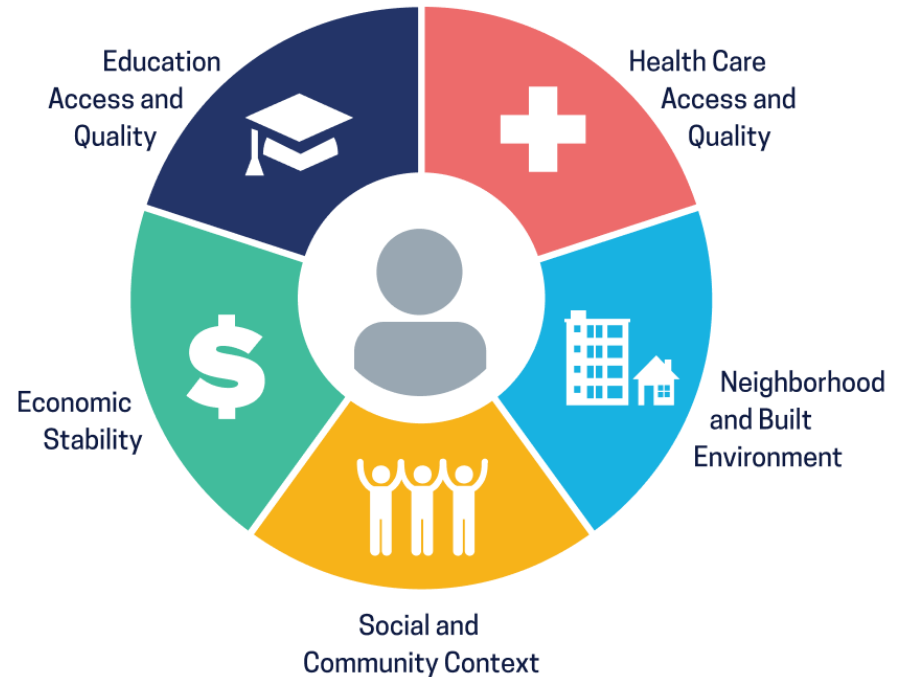
- Structural racism and inequalities
- Social drivers of health (SDoH)
- Geographic barriers to health care
- Unconscious bias



Social Drivers of Health

Health is determined in part by:

- Access to social and economic opportunities
- Resources and supports available in our homes, schools, neighborhoods, and communities
- Conditions in the environments where people are born, live, work, play, worship, and age that affect health, functioning, and quality of life

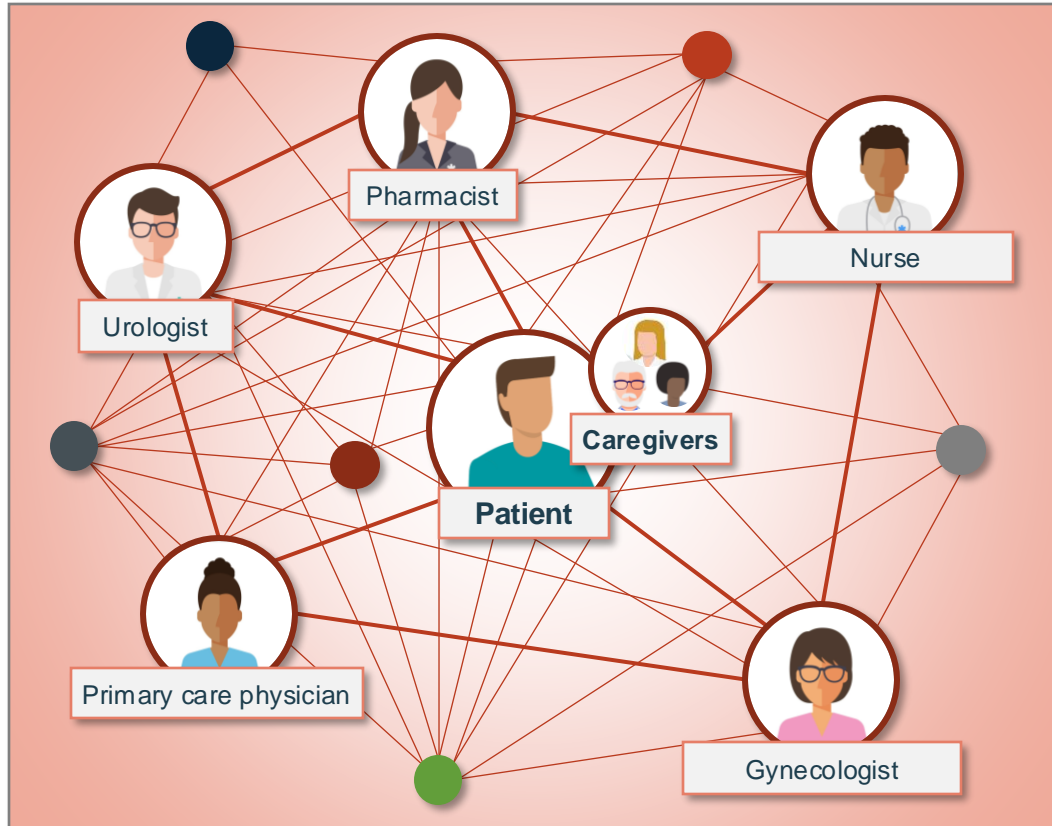


Poverty, culture, and social inequity affect medical conditions

SDoH Associated with Recurrent UTIs

	Risk Factors	← Decreased	Increased →	aRR (95% CI) ¹	rUTI (n, %)
Age group	18-27 (reference)			1.00	2668, 16.7
	28-37			0.92 (0.88-0.96)	1225, 14.7
	38-47			0.88 (0.85-0.92)	2063, 14.0
	48-57			0.90 (0.86-0.93)	2428, 14.4
	58-67			0.94 (0.90-0.98)	2750, 16.6
	68-77			1.03 (0.99-1.08)	2581, 19.5
	≥ 78			1.16 (1.10-1.21)	2122, 24.0
Race and ethnicity	White (reference)			1.00	1476, 13.6
	Black			0.90 (0.86-0.95)	1073, 15.9
	Hispanic			0.97 (0.95-1.00)	7110, 16.2
	Asian/Pacific Islander			0.86 (0.83-0.89)	6616, 18.3
	Other/Unknown			0.95 (0.89-1.02)	452, 15.2
Neighborhood-level income	< \$40,000 (reference)			1.00	567, 15.9
	\$40,000 – < \$60,000			1.02 (0.96-1.09)	2815, 15.9
	\$60,000 – < \$85,000			1.05 (0.99-1.11)	5009, 16.6
	≥ \$85,000			1.08 (1.02-1.15)	8242, 17.0
Medicaid	Medicaid (yes)			1.12 (1.08-1.15)	1777, 19.8
Charlson comorbidity index	0 (reference)			1.00	9183, 14.7
	1 – 2			1.03 (1.00-1.06)	5785, 18.7
	≥ 3			1.12 (1.07-1.18)	1759, 24.9
Specific comorbidities	Diabetes			1.06 (1.03-1.10)	#REF!
	Dementia			1.08 (1.01-1.16)	3277, 20.1
	Immunocompromised			1.10 (1.04-1.17)	461, 27.1
	Oral contraceptives			1.08 (1.03-1.13)	589, 23.7

Optimal Management of uUTI Requires a Multidisciplinary Approach



Communicate respectfully

- Do not blame patients
- Do not assume UTIs are caused by "bad behavior"
- Do not label patients

- Take detailed medical histories
- Listen to your patients
- Foster open discussions
- Involve your patients

Summary



UTI and recurrent UTI are common but complex.

Treatment options available, paucity of EBM



Need for more recognition, understanding, better diagnostics & guidance



Further research studies to aid diagnosis/treatment



Support organizations

SMART Goals

Specific, Measurable, Attainable, Relevant, Timely

- DO NOT rely on dipstick tests alone when diagnosing a UTI; consider the symptoms and confirm diagnosis by urine culture
- Obtain a detailed medical history
- Use the right antibiotic at the right dose for the right amount of time
- Patient communication is key: Avoid labeling, open discussion, listen carefully

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