



UTIs: Wee have the will and the way

How to treat the toughest bugs and prevent recurrence in an outpatient setting

Objectives

By the end of this session, the audience will be able to

- Describe a framework for categorizing UTIs
- State the empiric treatment of choice for UTIs
- State treatment options for drug resistant UTIs in the outpatient settings
- Describe prevention options for recurrent UTIs

FRAMEWORK

~ COMPLICATED ~



Symptoms

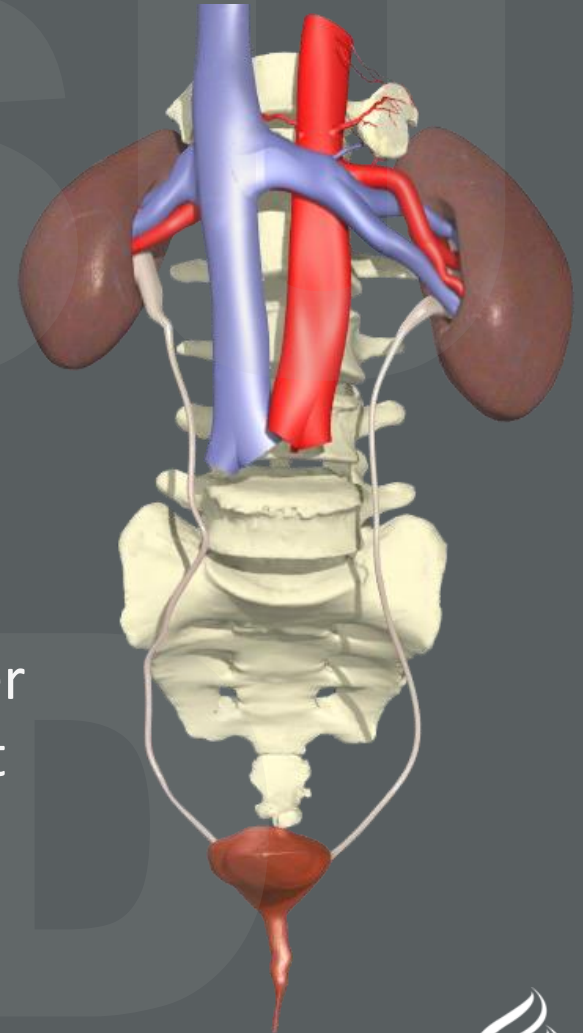
- Pyelonephritis
 - Fever
 - Flank pain
 - +/- frequency, dysuria, urgency
- Cystitis
 - Frequency
 - Dysuria
 - Urgency
 - Suprapubic discomfort
- Prostatitis
 - Acute: pain, fever, obstructive symptoms
 - Chronic: subtle
- Urethritis
 - Dysuria



Upper
tract



Lower
tract



Complicating Factors

History of MDR Urine Isolate

Use of Quinolone, Bactrim, BSBL

Travel to area with high rates MDR

Inpatient stay at HC Facility



Case 1: E.C.

Ms. EC is a 45 yo cisgender woman with a past medical history of hypertension presents with 3 days of dysuria, frequency, hesitancy and fever. On exam she has a temp of 102F, HR98, BP 160/94, pO2 98%. She has suprapubic and flank tenderness. Urinalysis shows 50 WBC, + leuk esterase, + nitrite, no squames. Urine culture grows >100k e.coli (Resistant to cefazolin). What is the best treatment choice?

- A. TMP-SMX x 5 days
- B. Ciprofloxacin x 7 days
- C. Nitrofurantoin x 10 days
- D. Ceftriaxone x 14 days

Table 1: EMPIRIC MANAGEMENT OF URINARY TRACT INFECTIONS

Uncomplicated/ Lower		Complicated/ Upper	
Cystitis		Pyelonephritis	
Low risk MDR	High risk MDR	Low risk MDR Mild-Mod Illness	High risk MDR Critical Illness*
Culture <i>Optional</i>	Culture	Culture	Culture
Nitrofurantoin x 5 d	Nitrofurantoin	Quinolone	Pip-tazo
Bactrim x 3 d (if resistance <20%)	Fosfomycin	Bactrim <u>if</u> susceptible	Cefepime
Fosfomycin x 1		Ceftriaxone	Carbapenem (don't forget ERTA)

Always tailor regimen based on culture data!

* May consider double coverage until culture results return

§ History of MDR urine isolate; Inpatient stay at health care facility; Use of quinolone, bactrim or broad spectrum betalactam; Travel to area with high rates of MDR organisms (India, Israel, Spain, Mexico)



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OHSU OUTPATIENT ADULTS (January 1, 2020 – December 31, 2020)

	Gram Negative Aerobes						Gram Positive	
	Pseudomonas aeruginosa (123)	Enterobacter cloacae complex (51)	E. coli (1221)	Proteus mirabilis (103)	Klebsiella pneumoniae (152)	Klebsiella oxytoca (33)	Enterococcus faecalis (154)	All Staphylococcus aureus (583)
Ampicillin	-	-	65	85	-	-	99	-
Amoxicillin/clavulanate	-	-	88	98	95	88	-	-
Cefazolin	-	-	94	91	97	41	-	75
Cefepime	98	100	99	99	99	100	-	-
Ceftriaxone	-	88 ^b	96	99	97	88	-	-
Ciprofloxacin	90	98	89	92	98	100	89 ^a	-
Clindamycin	-	-	-	-	-	-	-	79
Erythromycin	-	-	-	-	-	-	-	-
Gentamicin	89	100	96	96	99	97	-	-
Levofloxacin	90	100	89	92	98	100	91 ^a	-
Meropenem	95	98	100	100	100	100	-	-
Nitrofurantoin ^a	-	35	97	-	30	76	99	-
Oxacillin (nafcillin)	-	-	-	-	-	-	-	75
Piperacillin/tazobactam	96	94	98	100	96	91	-	-
Tetracycline	-	85	82	-	84	91	31 ^a	95
Tobramycin	97	98	97	96	97	97	-	-
Trimethoprim/sulfamethoxazole	-	88	82	85	90	91	-	95



OHSU INPATIENT ADULTS (January 1, 2020 – December 31, 2020)

	Gram Negative Aerobes									Gram Positive		
	<i>Serratia marcescens</i> (38)	<i>Pseudomonas aeruginosa</i> (184)	<i>Enterobacter cloacae</i> (116)	<i>Klebsiella aerogenes</i> (34) (formerly <i>Enterobacter aerogenes</i>)	<i>E. coli</i> (572)	<i>Proteus mirabilis</i> (78)	<i>Klebsiella pneumoniae</i> (186)	<i>Klebsiella oxytoca</i> (75)	<i>Stenotrophomonas maltophilia</i> (48)	<i>Streptococcus pneumoniae</i> (35) ^c	<i>Enterococcus faecalis</i> (248)	<i>Enterococcus faecium</i> (58)
Trimethoprim/ sulfamethoxazole	100	-	85	97	73	83	91	92	98	80	-	-
Vancomycin	-	-	-	-	-	-	-	-	-	-	100	71

W Ciprofloxacin for 7 days versus 14 days in women with acute pyelonephritis: a randomised, open-label and double-blind, placebo-controlled, non-inferiority trial

Torsten Sandberg, Gunilla Skoog, Anna Bornefalk Hermansson, Gunnar Kahlmeter, Nils Kuylenstierna, Anders Lannergård, Gisela Otto, Bo Settergren, Gunilla Stridh Ekman

	7 days N (%)	14 days N (%)	Difference (90% CI)	P value
<i>E. coli</i>	64 (88)	79 (95)	-	-
Bacteremia	16 (22)	26 (32)	-	-
Cure	68 (93%)	78 (93%)	-0.3% (-7.4 to 7.2)	0.015
Clinical failure or recurrent UTI sx	5 (7%)	6 (7%)	-	-

Seven Versus 14 Days of Antibiotic Therapy for Uncomplicated Gram-negative Bacteremia: A Noninferiority Randomized Controlled Trial

Dafna Yahav,^{1,2} Erica Franceschini,³ Fidi Koppel,⁴ Adi Turjeman,^{2,5} Tanya Babich,^{2,5} Roni Bitterman,⁴ Ami Neuberger,^{4,6} Nesrin Ghanem-Zoubi,⁴ Antonella Santoro,³ Noa Eliakim-Raz,^{1,2} Barak Pertzov,⁵ Tali Steinmetz,⁵ Anat Stern,⁴ Yaakov Dickstein,⁴ Elias Maroun,⁴ Hiba Zayyad,⁴ Jihad Bishara,^{1,2} Danny Alon,⁷ Yonatan Edel,^{2,8} Elad Goldberg,⁹ Claudia Venturelli,³ Cristina Mussini,³ Leonard Leibovici,^{2,5} Mical Paul^{4,6}; for the Bacteremia Duration Study Group^a

Included:

- GNB bacteremia at day 7 IF afebrile and stable x 48hrs
- UTI, Intraabdominal, CVC
- SSTI, unknown source
- Community or Hospital Acquired

Excluded:

- Other sources
- Uncontrolled source
- Polymicrobial growth
- Brucella, salmonella
- Neutropenia, HSCT
- HIV

GNB Bacteremia 7 vs 14 days

	7 days	14 days
Bacteria type	N (%)	N (%)
- E.coli	186 (60.8)	194 (65)
- Klebsiella spp	47 (15.3)	33 (11.1)
- Other enterobacteriaceae	40 (13.1)	43 (14.4)
- Acineto/Pseudomonas spp	30 (9.9)	34 (8.0)
Source of Bacteremia		
- UTI	212 (69.3)	199 (66.8)
- Primary bacteremia	23 (7.5)	28 (9.4)
- Abdominal	37 (12.1)	34 (11.4)
- Respiratory	14 (4.6)	10 (3.4)
- Other	20 (6.5)	27 (8)

Primary Outcomes for GNB Bacteremia 7 vs 14 d

Outcome	7d 306 (%)	14d 296 (%)	P Value
Primary Outcome	140 (45.8)	144 (48.3)	.527
90d all cause mort	36 (11.8)	32 (10.7)	.702
Readmissions	119 (38.9)	127(42.6)	.363
Distant complications	2	1	
Relapse	8 (2.6)	8 (2.7)	.957
Suppurative complications	16 (5.2)	10 (3.4)	.257
14 d mortality	7 (2.3)	4 (1.3)	2.88
28 d mortality	15 (4.9)	13 (4.4)	.753

What Antibiotics Were Used?

Type of IV antibiotics ^a	Short arm (306 patients)	Long arm (298 patients)
Cephalosporins	157 (51.3)	167 (56.0)
Beta-lactam beta-lactamase inhibitors	72 (23.5)	63 (21.1)
Quinolones ^b	15 (4.9)	14 (4.7)
Aminoglycosides	39 (12.7)	36 (12.1)
Carbapenems	23 (7.5)	16 (5.4)
Trimethoprim-sulfamethoxazole	0	2 (0.7)

Type of ORAL antibiotics ^a	Short arm (196 patients)	Long arm (242 patients)*
Quinolones	151 (77.0)	172 (71.1)
Beta-lactams	28 (14.3)	50 (20.7)
Trimethoprim-Sulfamethoxazole	17 (8.7)	20 (8.3)

Treatment Take home

- UTI categorization is now lower vs upper tract with MDR considerations
- Upper tract infections can be treated for 7 days (quinolones)
- Enterobacteriaceae bacteremia in setting of UTI can be treated for 7 days

Case 2: Mr. M.DR

Mr. Michael Don Rivera is a 65 year old cisgender man with a history of BPH who presents with dysuria, frequency, and flank tenderness. He has a temp of 101.3F, HR 85, BP 146/84, RR12, Pox1000% RA. Exam is notable for suprapubic and flank tenderness. Labs show a WBC of 16, Hb 15, Plt 450k, Creat 1.0 and all others within normal limits. Urinalysis shows +25WBC, no RBC and culture grows e.coli resistant to cefazolin and ceftriaxone. What is the best option below.

- A. Treat with pip-tazo x 14 days
- B. Treat with Trimethoprim-sulfamethoxazole x 10 days
- C. Treat with nitrofurantoin x 5 days

CDC's 2019 AR Threats Report: **PREVENTION WORKS.**

↓ **18%** fewer deaths from antibiotic resistance overall since 2013 report

↓ **28%** fewer deaths from antibiotic resistance in hospitals since 2013 report

AND DECREASES IN INFECTIONS CAUSED BY:

↓ **41%** Vancomycin-resistant *Enterococcus*

↓ **33%** Carbapenem-resistant *Acinetobacter*

↓ **29%** Multidrug-resistant *Pseudomonas aeruginosa*

↓ **25%** Drug-resistant *Candida*

↓ **21%** Methicillin-resistant *Staphylococcus aureus* (MRSA)

STABLE Carbapenem-resistant Enterobacteriaceae (CRE) & drug-resistant tuberculosis (TB disease cases)

Despite these gains, CDC's 2019 AR Threats Report shows additional actions are needed to protect people.

2.8M+ antibiotic-resistant infections each year

35k+ deaths from antibiotic resistance each year

Plus: 223,900 cases and 12,800 deaths from *Clostridioides difficile*

**AND INCREASES
IN INFECTIONS
CAUSED BY:**



315%

Erythromycin-resistant
invasive group A strep



124%

Drug-resistant
Neisseria gonorrhoeae



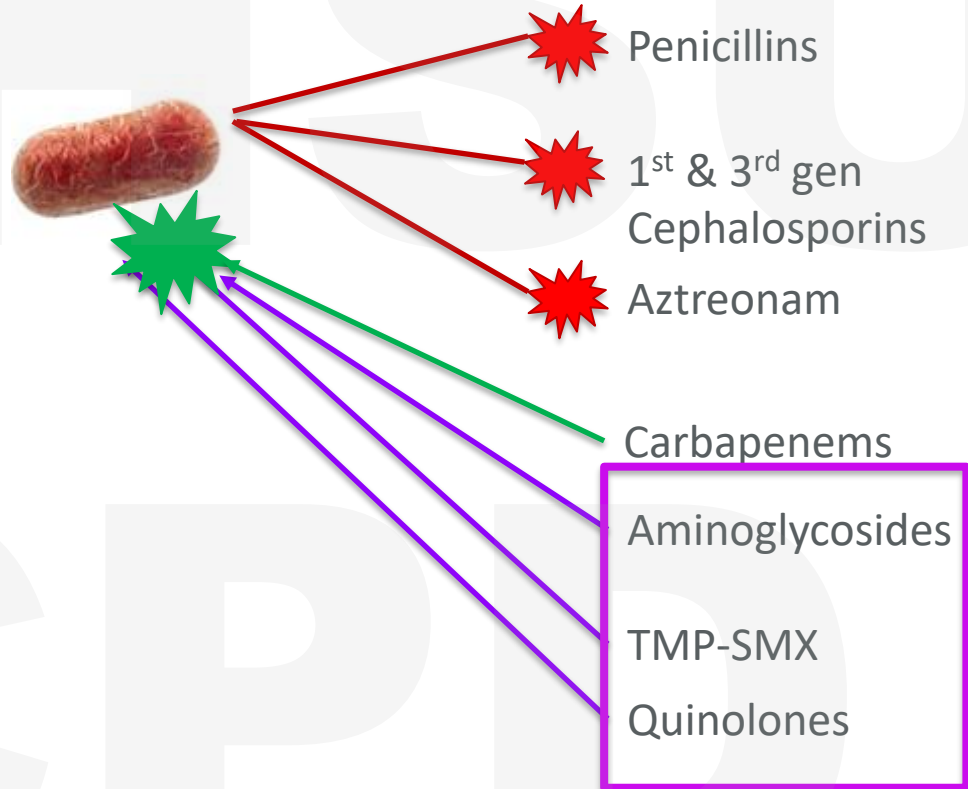
50%

ESBL-producing
Enterobacteriaceae

What is an ESBL?



53%
2012-2017



What to use for Lower Track UTI with ESBL?

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Fosfomycin x 1	Fosfomycin	Ceftriaxone x 10-14	Carbapenem (don't forget ERTA) x 10-14
Pivmecillinam	Pivmecillinam??		
Always tailor regimen based on culture data!			

What about Fosfomycin?

JAMA | **Original Investigation**

Effect of 5-Day Nitrofurantoin vs Single-Dose Fosfomycin on Clinical Resolution of Uncomplicated Lower Urinary Tract Infection in Women A Randomized Clinical Trial

Angela Huttner, MD; Anna Kowalczyk, MS; Adi Turjeman, MSc; Tanya Babich, MSc; Caroline Brossier, RN; Noa Eliakim-Raz, MD; Katarzyna Kosiek, MD, PhD; Begoña Martínez de Tejada, MD, PhD; Xavier Roux, MD; Shachaf Shiber, MD; Ursula Theuretzbacher, PhD; Elodie von Dach, PhD; Dafna Yahav, MD; Leonard Leibovici, MD; Maciek Godycki-Ćwirko, MD, PhD; Johan W. Mouton, MD, PhD; Stephan Harbarth, MD

- Clinical response: 70% with Nitrofurantoin vs 58% Fosfomycin
- Microbiologic resolution: 74% (nitro) vs 63% fos
- Cost: \$5 Nitro course vs \$75 for one sachet

Fosfomycin

Huttner A, et al. JAMA 2018;319:1781

The Newby: Pivmecillinam



- Penicillin with extended GM spectrum
- Only for UTI - Acute simple cystitis
- Low risk of selecting for resistant organisms
- Agent of choice in many Nordic countries due to low resistance
- Some activity against ESBL and carbapenemases
- Well tolerated – mild GI AE
- Dose varies by region/country – 185mg PO TID x 3-7days

Treatment for Upper UTI due to ESBL-E

Carbapenems

- Ertapenem
- Meropenem
- Imipenem

Quinolones

- Levofloxacin
- Ciprofloxacin

TMP-SMX

Key Points

- We still need to be mindful of drug resistance
- For ESBL-E (resistance to Ceftriaxone), **Bactrim** and nitrofurantoin are great for lower track
- Pivmecillinam is a **NEW** option in the US for cystitis
- For ESBL-E upper tract – **Bactrim** and quinolones

Case 3: Ms. De L'eau

Ms. De l'eau is an 65 year old cisgender woman with a history of recurrent urinary tract infections. She is currently on nitrofurantoin daily but continues to have UTIs. She had a urologic evaluation and does not have any anatomic abnormality to address. What would you suggest?

- A. She should start vaginal estrogen
- B. She should start 20mg of Proanthocyanidin daily
- C. She should drink a liter of water a day
- D. She should switch to cephalexin prophylaxis

Check for Modifiable Factors

Diabetes

Optimize glucose control

Immunosuppression

Decrease as able

Stones

Work with urology

Reflux

Work with urology

Catheter

Remove if possible

Post/peri
menopausal

Vaginal Estrogen!

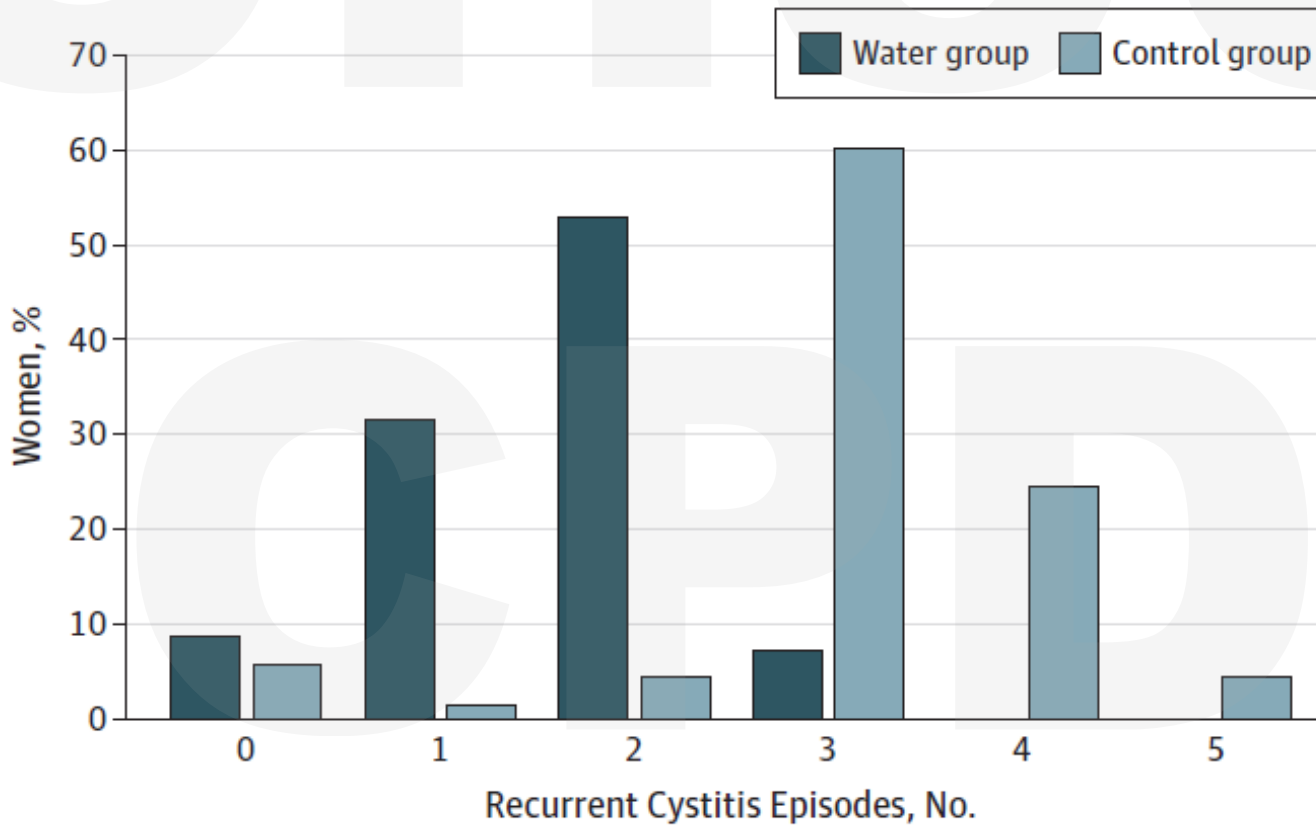


BAG
— OF —
TRICKS



Increased water decreased UTI

Figure 2. Recurrent Cystitis Episodes by Study Group



Vaginal estrogen



- Raz et al., NEJM 1993:
estrogen (0.5) vs placebo (5.9) episodes/person/year
- FPMRS 2021:

UTI events	Placebo	Estrogen	P value
Intention to Treat	16/17	9/18	0.041
Per Protocol	10/11	8/15	0.036

NEJM. 1993;329:753-6

Female Pelvic Med Reconstr Surg 2021;27: 112–117

Effectiveness of Estriol-Containing Vaginal Pessaries and Nitrofurantoin Macrocrystal Therapy in the Prevention of Recurrent Urinary Tract Infection in Postmenopausal Women

R. Raz,^{1,4} R. Colodner,² Y. Rohana,⁵ S. Battino,³ E. Rottensterich,⁵ I. Wasser,⁵ and W. Stamm⁵

- 9 months; 86 pessary vs 85 nitrofurantoin
- 85 episodes in pessary group vs 30 with NM
- 2 episodes per person/yr vs 0.8 in NM group
- Pessary may not be as effective as cream

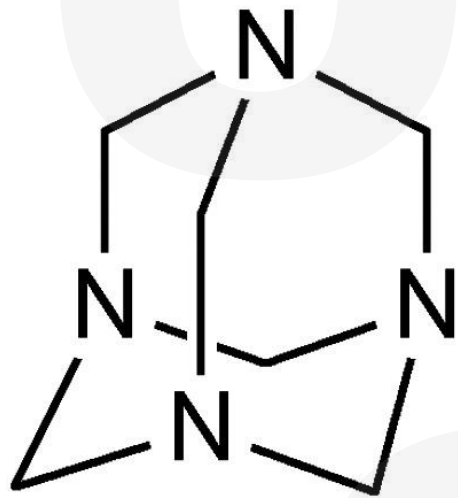
Efficacy of different antibiotics

Organism	No drug	Sulfa	Methenamine	TMP-SMX
E.Coli	24	10	10	0
Klebsiella	2	2	1	0
Citrobacter	1	0	0	0
Enterococcus	5	9	2	1
GBS	1	1	0	0
Totals	33	22	13	1

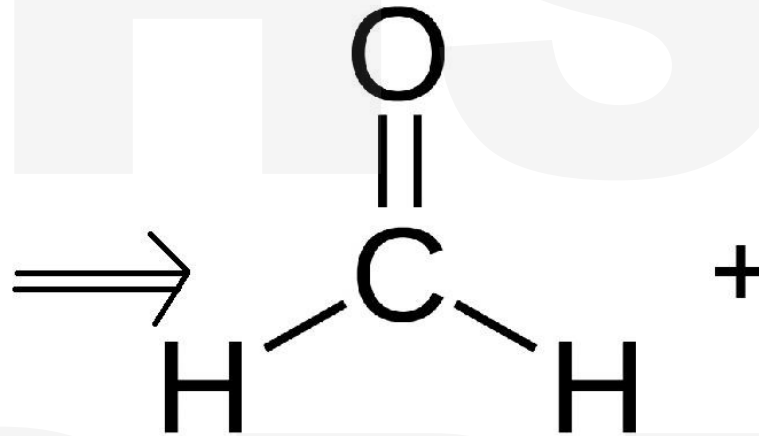
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Totals	33	22	13	1

Now back up, what is methenamine?

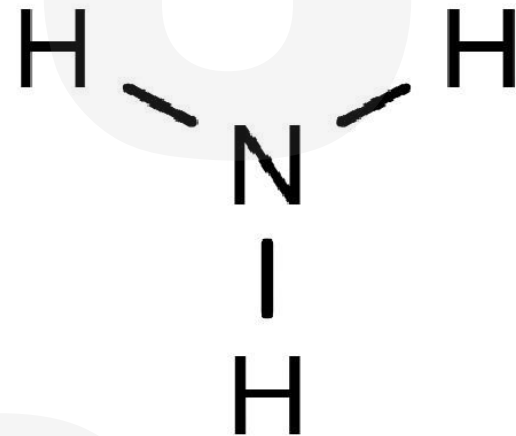


Methenamine



Formaldehyde

+



Ammonia

YES

Methenamine vs Placebo

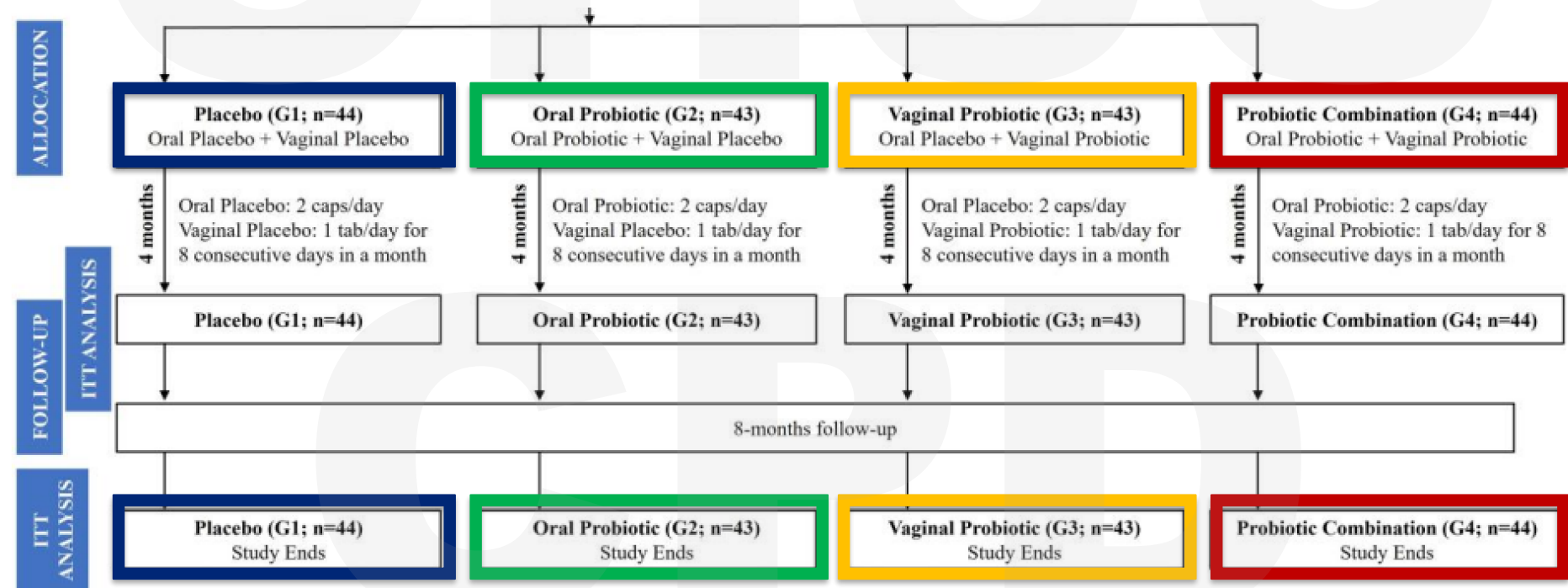
	Methenamine hippurate	Placebo
Cases	11	41
Organisms	E.coli, Proteus, GBS	E.coli, Proteus, Klebsiella, Enterobacter, Enterococcus

Tools & Tricks for UTI Prevention

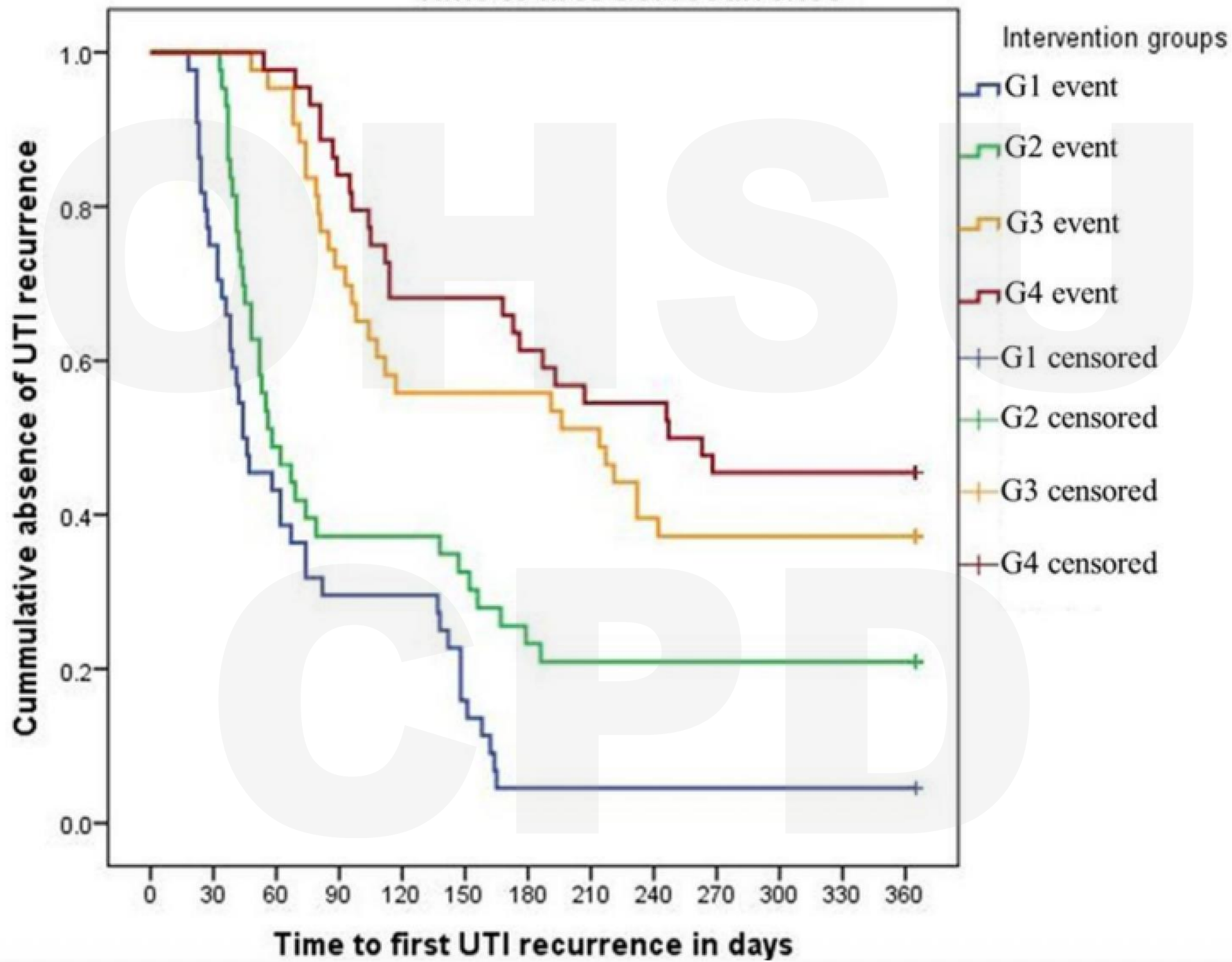
Tool	Mechanism	Evidence It Works?	Considerations
Increased H ₂ O	Flush the system	<i>Maybe</i>	Need more studies
Cranberry Juice	Proanthocyanidin 36mg	YES	
Vaginal Estrogen	Replacement	YES	No increased AE
Methenamine	Formaldehyde	YES	No incontinence, good function
D Mannose	Inhibit adhesion to bladder cells	NO	Too variable
Post-coital or continuous Abx	Bactericidal	YES – sort of	Balance risk of MDR selection, AE
Probiotics	Improve vaginal flora	NO	Too variable

Effectiveness of Prophylactic Oral and/or Vaginal Probiotic Supplementation in the Prevention of Recurrent Urinary Tract Infections: A Randomized, Double-Blind, Placebo-Controlled Trial

Varsha Gupta,¹ Paola Mastromarino,² and Ritu Garg³



Time to first UTI recurrence



Key Points

- Drinking an additional 1.5L water can reduce UTI frequency
- Vaginal estrogen cream can reduce UTI frequency
 - Possibly more than pessaries
 - No increased AE
- Methenamine 1gram BID can be considered
- The active ingredient in Cranberry juice DOES have evidence
- Ultimately, antibiotic prophylaxis does work... for a time
- Probiotics may now have a role in prevention!

Take Home Points

- Nitrofurantoin is **only** for cystitis
- Bactrim is a great drug for upper, lower, and MDR UTIs
- ESBLs do not necessarily need a carbapenem
- Prevention does not have to mean antibiotics
 - Increase water consumption
 - Vaginal estrogen
 - Consider methenamine (check contraindications first)

Key References



IDSA GNR Guidelines



JAMA UTI 2024 Guidance

OHSU



Thank You

CPD

