

Recurrent UTIs post kidney transplantation

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Overview

1. Definitions
2. Incidence and significance of recurrent UTI
3. Asymptomatic bacteriuria
4. Management of recurrent UTIs
5. The role of a dedicated transplant UTI clinic

Definitions

Recurrent UTIs

≥3 UTIs in 12 months (or 2 UTIs in 6 months) resulting from infection with different strains of microbes

Asymptomatic bacteriuria

isolation of a bacterial organism at least 10^5 CFU/ml in a patient without symptoms of UTI

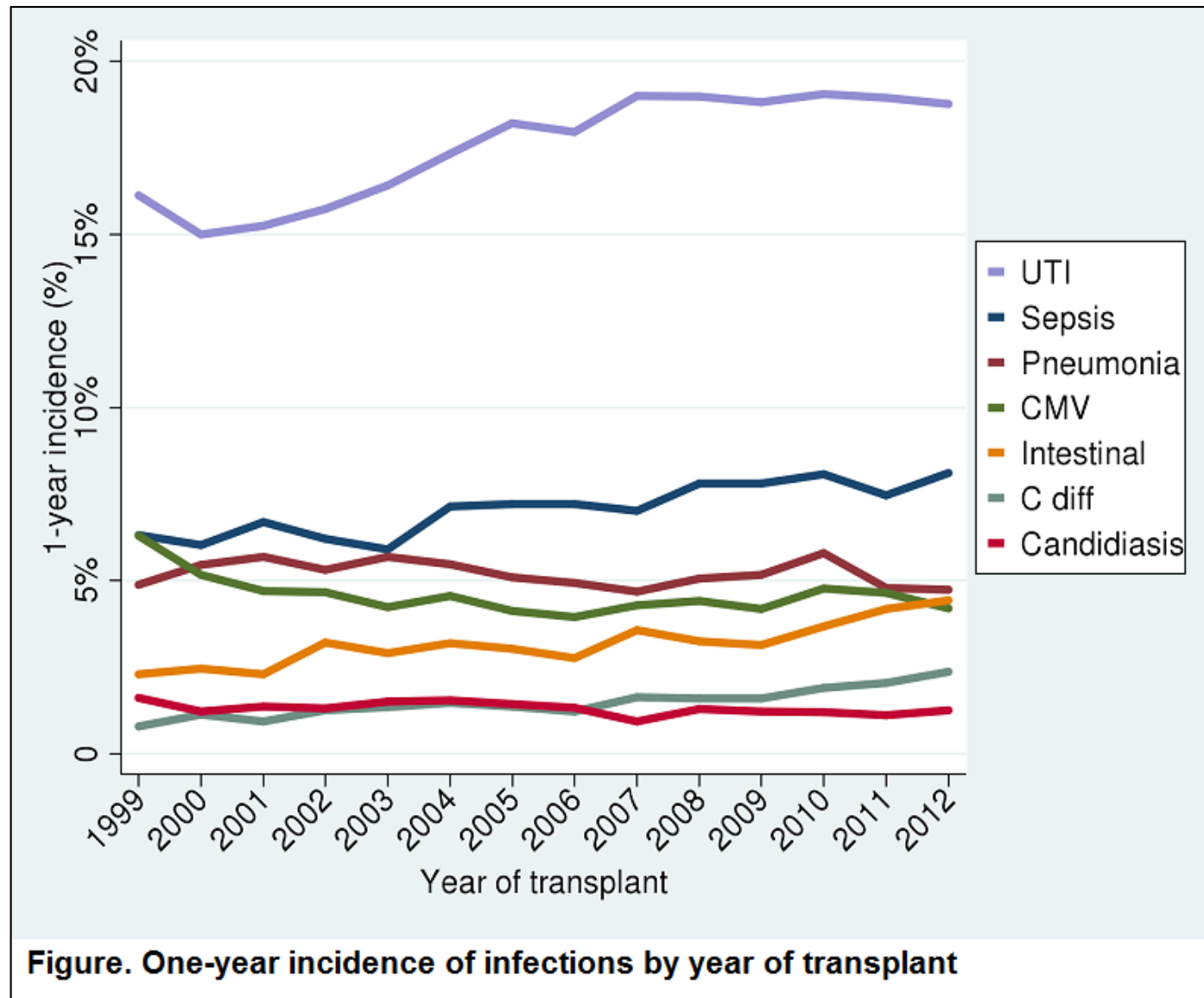


Figure. One-year incidence of infections by year of transplant

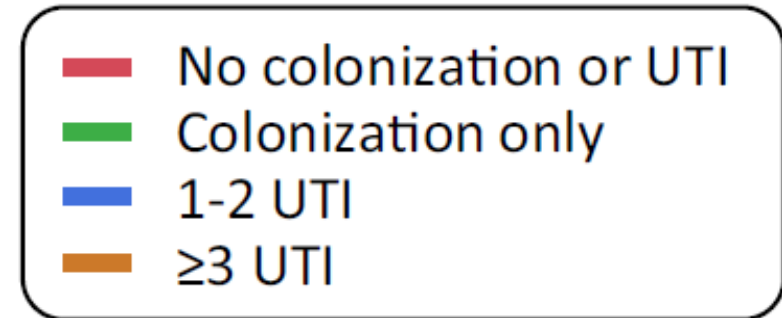
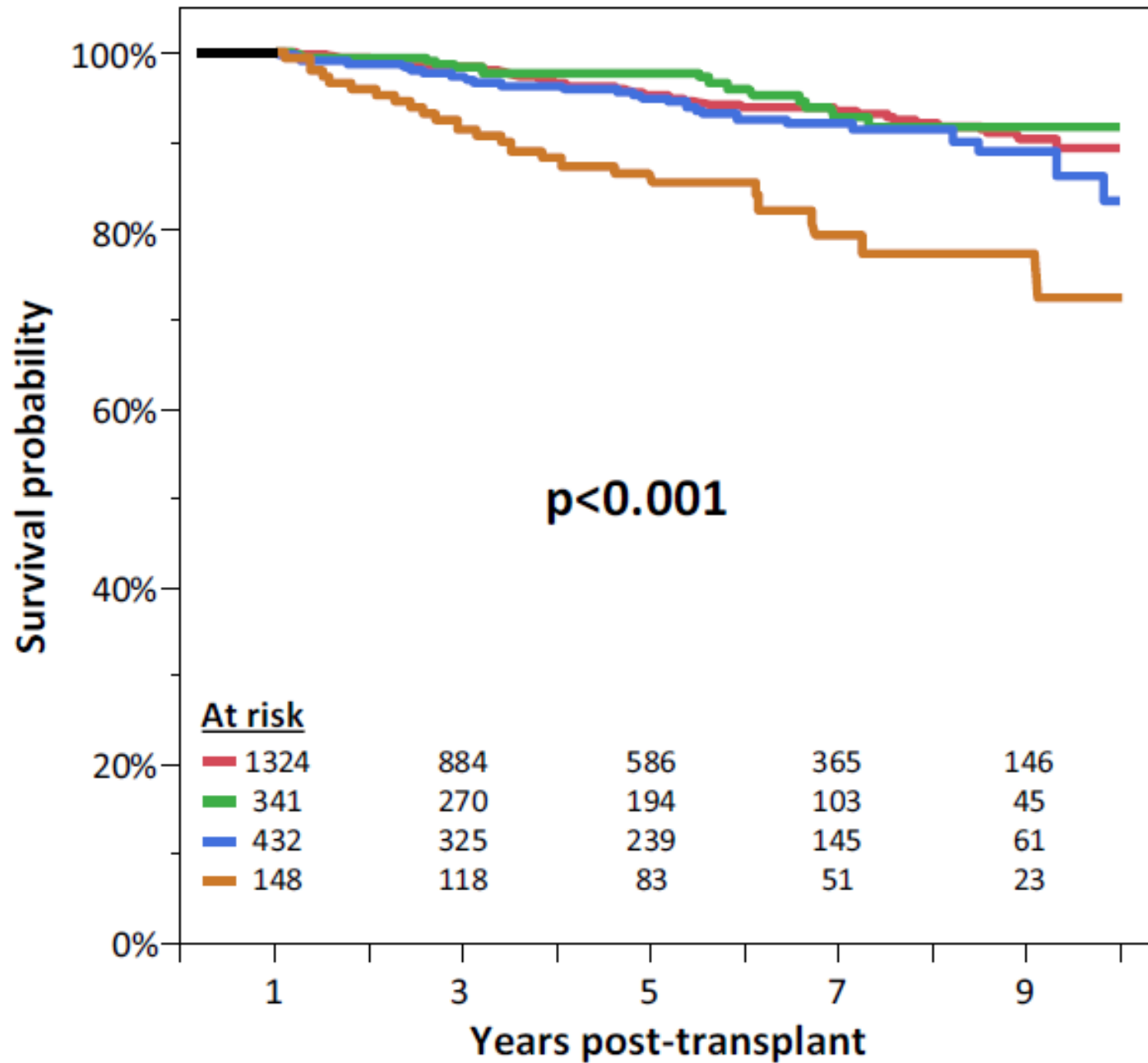
UTI is the commonest infection post Renal Tx

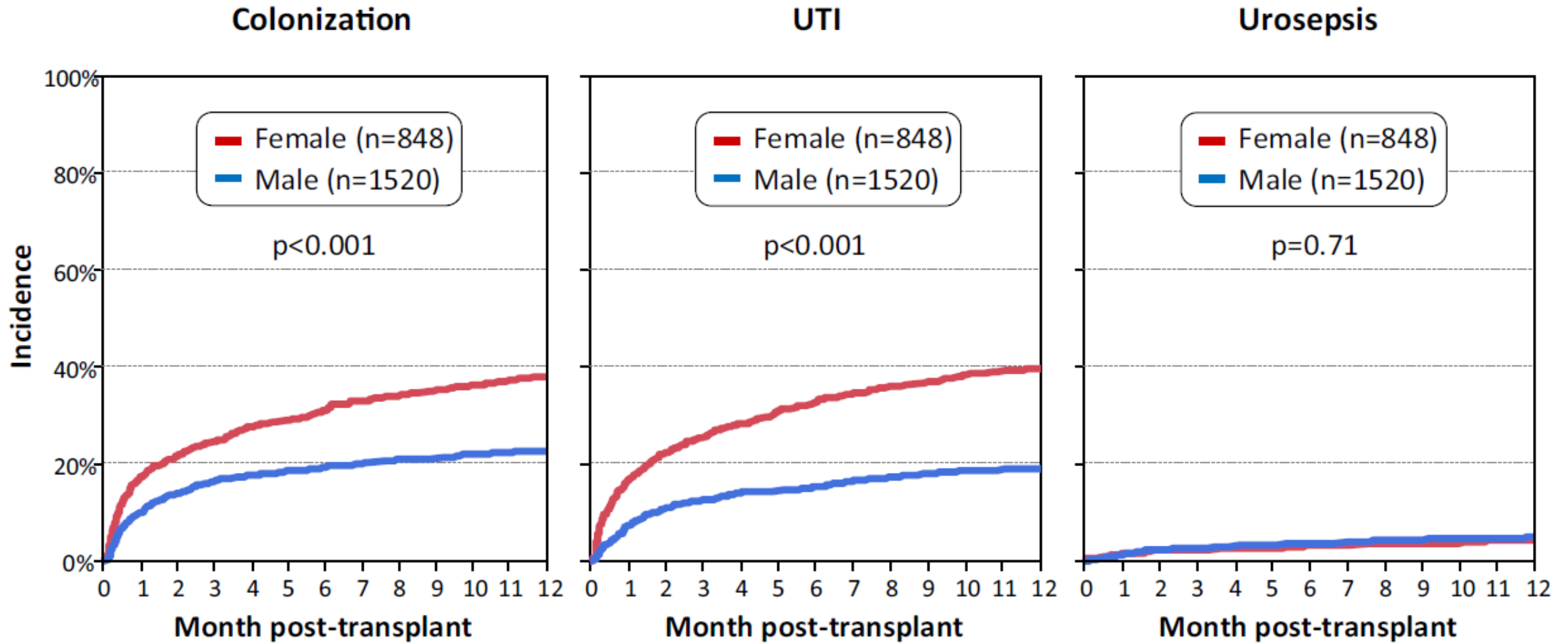
UTI is the commonest infection post Renal Tx

- The incidence of UTIs per 100 transplant-days has been reported as 4.5 in kidney transplant recipients, 2.2 in kidney pancreas recipients
- 7% to 80% with larger studies reporting 1-year incidence around 30%.

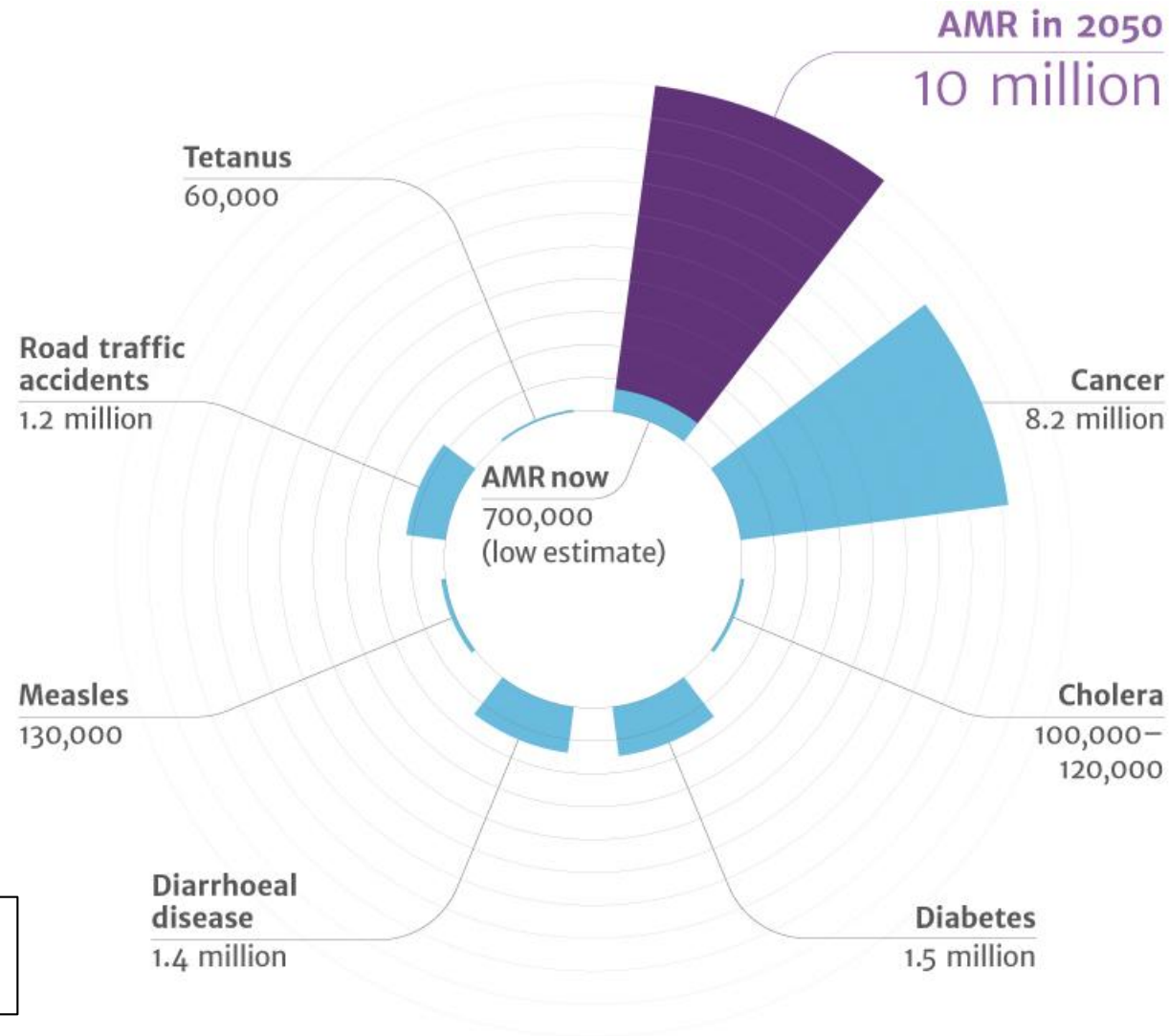
Impact of different urinary tract infection phenotypes within the first year post-transplant on renal allograft outcomes

- recurrent UTI: very strong and independent risk factor for death-censored graft loss, with a HR similar to recurrent rejection (i.e., ≥ 2 rejection episodes within the first-year post-transplant)
- patients in the recurrent UTI group had 7-10 ml/min lower eGFR than the other groups
- colonizations and occasional UTI were not associated with inferior outcomes





Antimicrobial resistance (AMR)



Worldwide WHO figures
Leading causes of death

Antimicrobial resistance (AMR)

- Antimicrobial resistance costs the European Union 1.5 billion in health-care expenses and lost productivity each year
- Infection with antimicrobial-resistant bacteria can lead to more severe infections, longer hospital stays and increased mortality









Asymptomatic Bacteriuria

Asymptomatic bacteriuria isolation of a bacterial organism at least 10^5 CFU/ml in a patient without symptoms of UTI

Treating Asymptomatic Bacteriuria

Are antibiotics effective in reducing symptomatic urinary tract infection in kidney transplant recipients (KTR) with asymptomatic bacteriuria (BiRT) ?



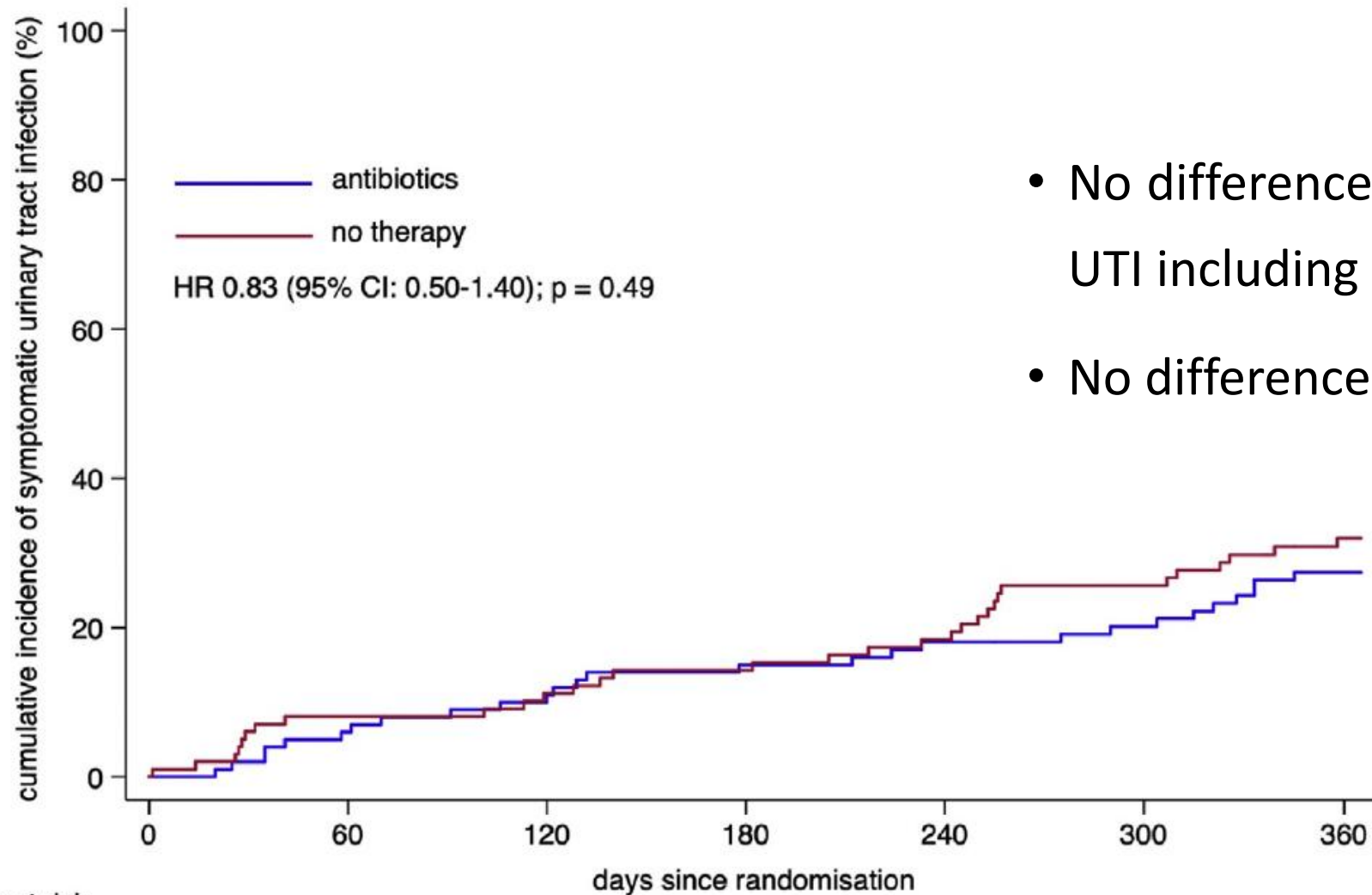
Study Design		Outcomes				
 Multicenter  Open label N=199  ≥2 months post-transplant Kidney transplant recipients	Randomization		Symptomatic UTI 	Antibiotic use (days/person) 	Antibiotic resistant infections 	
		 Antibiotics N=100	12 months follow up	27%	30	18 %
		 No Antibiotics N=99		31%	5	4%

Summary: Applying screen-and-treat strategy for asymptomatic bacteriuria does not reduce the occurrence of symptomatic UTI in ≥ 2 months post kidney transplant recipients. This strategy increases antibiotic use and promotes the emergence of resistant organisms.

Reference: Julien Coussement et al Bacteriuria in Renal Transplantation (BiRT) study group . *Clinical microbiology and Infection. Online Pub.*

Visual Abstract by  @docanjuyadav

Coussement et al *Clinical Microbiology and Infection* 27 (2021) 398-405
 Origuen J et al *Am J Transplant* 2016;16:2943e53.
 Sab_e N. *Open Forum Infect Dis* 2019;6:ofz243.
 Moradi M et al *Urol J* 2005;2:32e5.

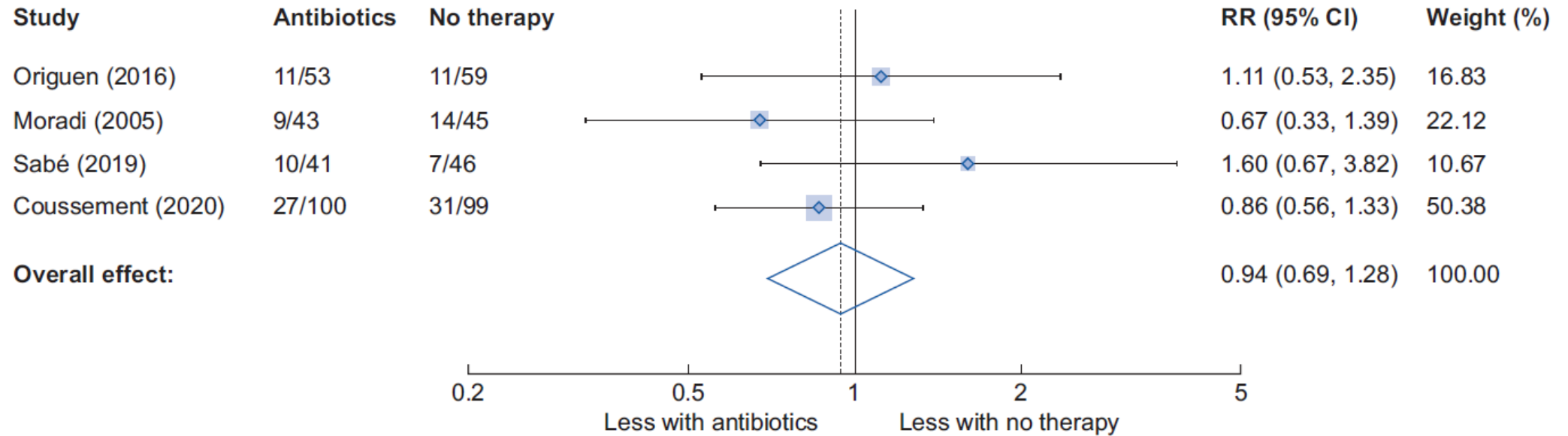


- No difference regarding incidence of UTI including pyelonephritis
- No difference in renal function

Patients at risk

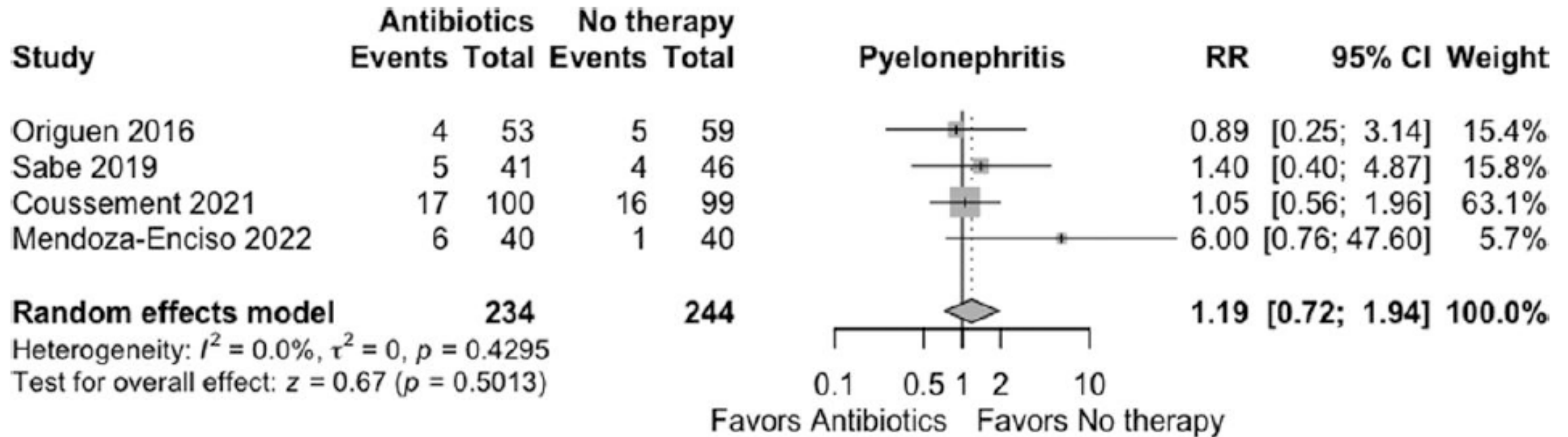
antibiotics	100	94	90	85	80	77	66
no therapy	99	91	86	83	79	72	60

Abx in kidney transplant recipients with asymptomatic bacteriuria



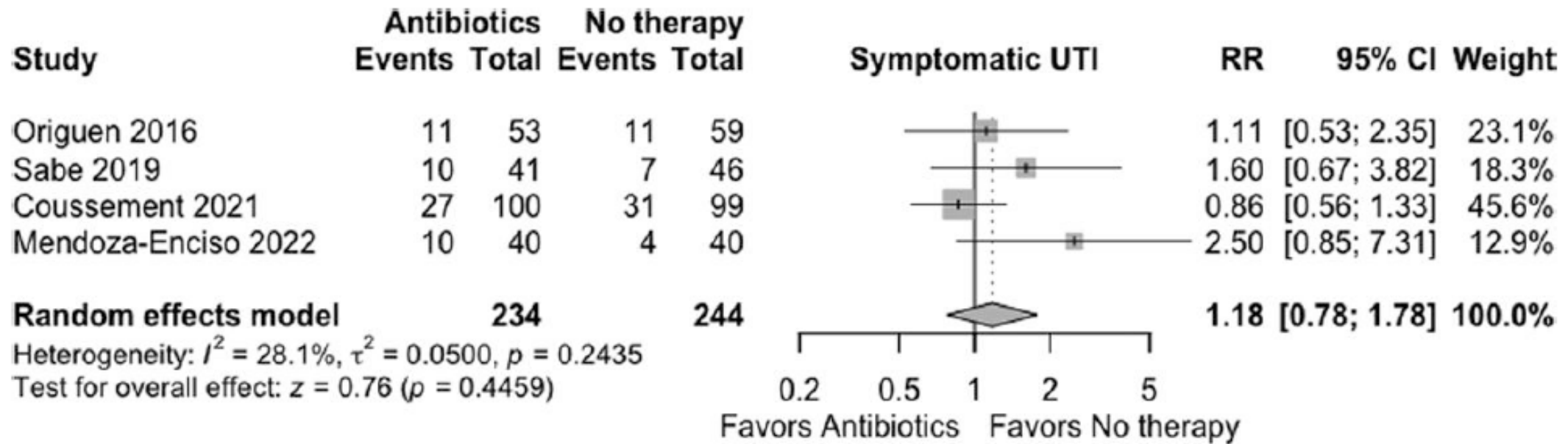
Effectiveness and Safety of Antibiotics in Kidney Transplant Recipients With Asymptomatic Bacteriuria: A Systematic Review and Meta-analysis of Randomized Controlled Trials

Abdullah Tarik Aslan,¹ Lokman Hekim Tanriverdi,² Adrian V. Hernandez,^{3,4} Umut Akova,⁵ Kursat Kutluca,⁶ Samuel Chan,⁷ Julien Coussement,^{8,9} Arreola Guerra Jose Manuel,^{10,11} Julia Origüen,^{12,13} Nüría Sabé,^{14,15} Patrick N. A. Harris,¹ Murat Akova,¹⁶ and David L. Paterson^{17,18}



Effectiveness and Safety of Antibiotics in Kidney Transplant Recipients With Asymptomatic Bacteriuria: A Systematic Review and Meta-analysis of Randomized Controlled Trials

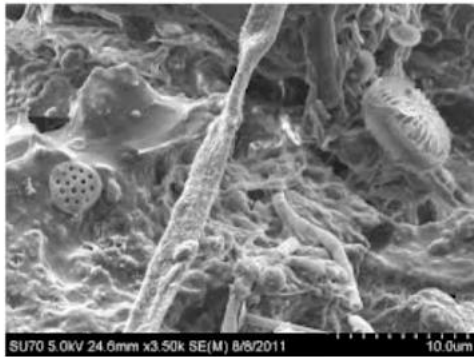
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The biofilm

Sessile
bacteria

Biofilm
"Community of Bacteria"



- Biofilm cells express a radically different phenotype than planktonic bacteria
- Cause of Chronic Infections
- **Can be detected by DNA sequencing only**

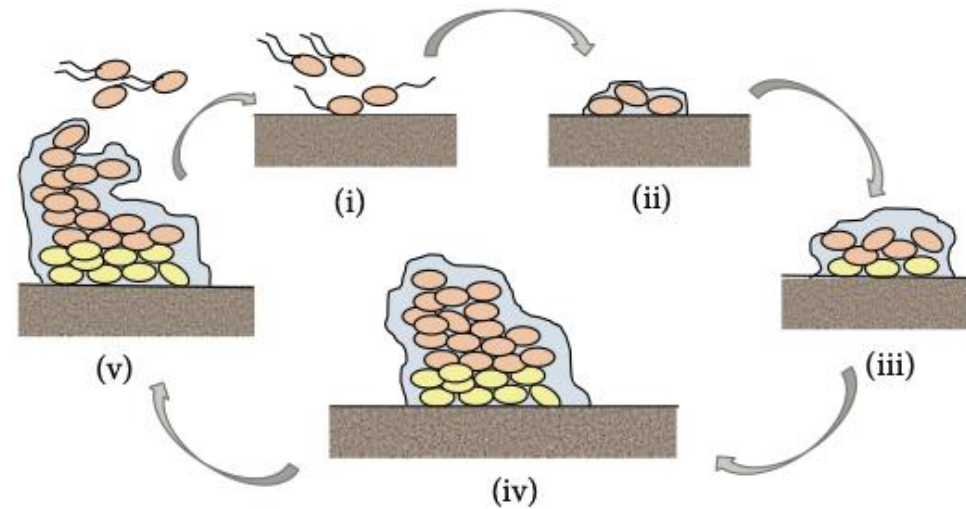
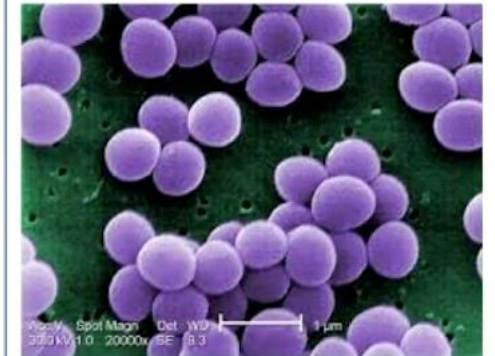


FIGURE 1: Biofilm formation steps. (i) Reversible attachment of planktonic bacteria to surfaces. (ii) Irreversible attachment to surfaces. (iii) Formation of the external matrix. (iv) Biofilms acquire a three-dimensional structure. (v) Biofilm detachment.

Planktonic
bacteria

Planktonic Bacteria
Single Cell

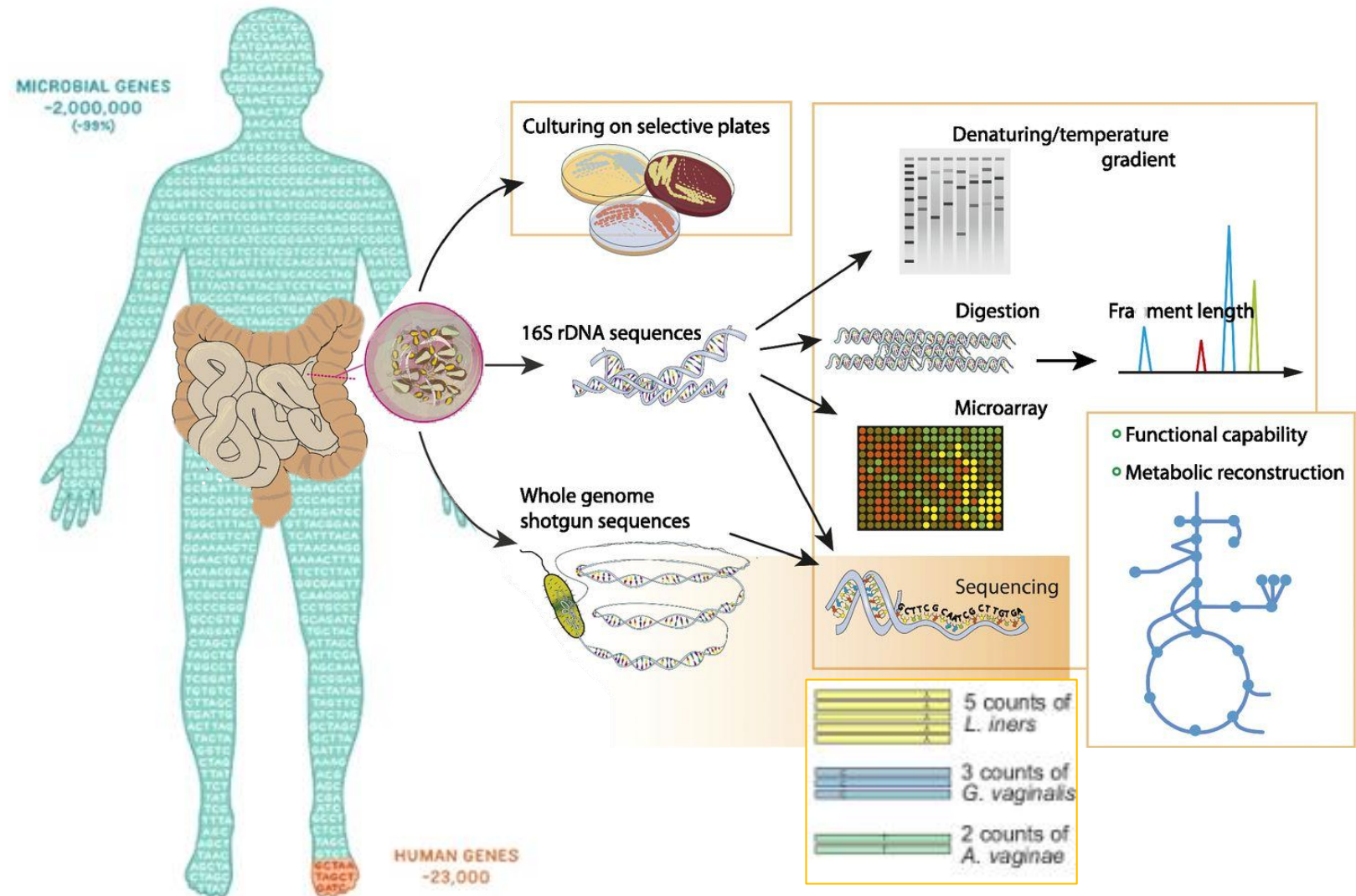


- Cause of Acute Infection
- Will grow in traditional Culture

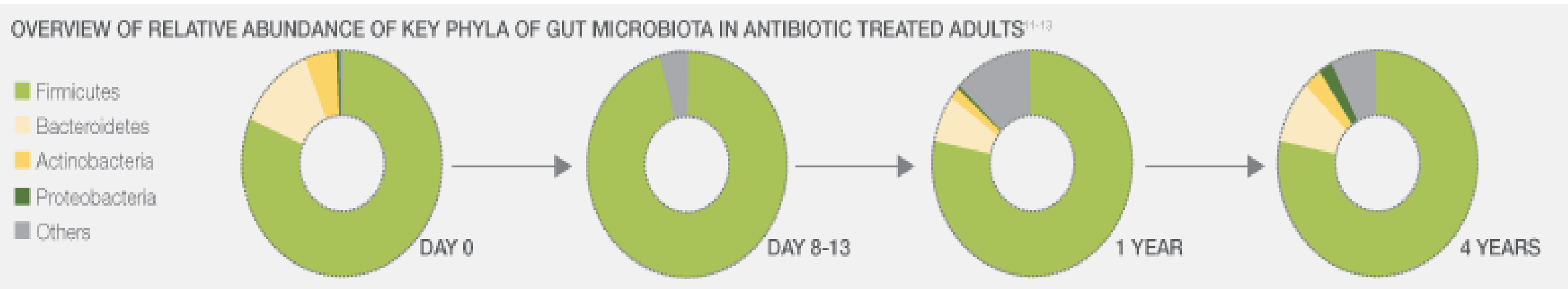
Individual tailored management

Human Microbiome

Each individual has a unique gut **microbiota**, as personal as a fingerprint



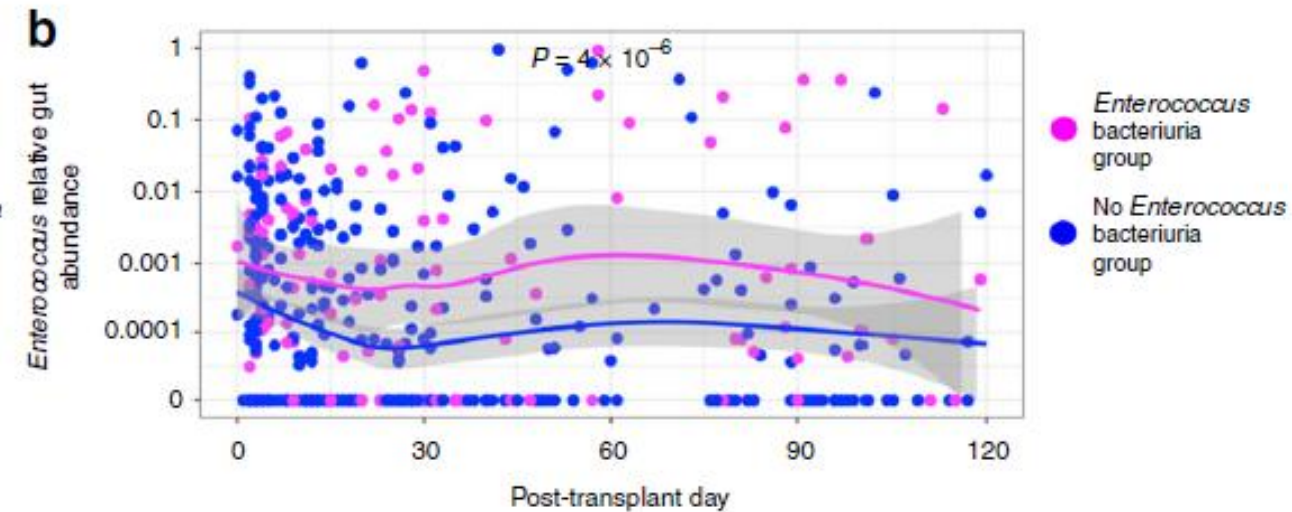
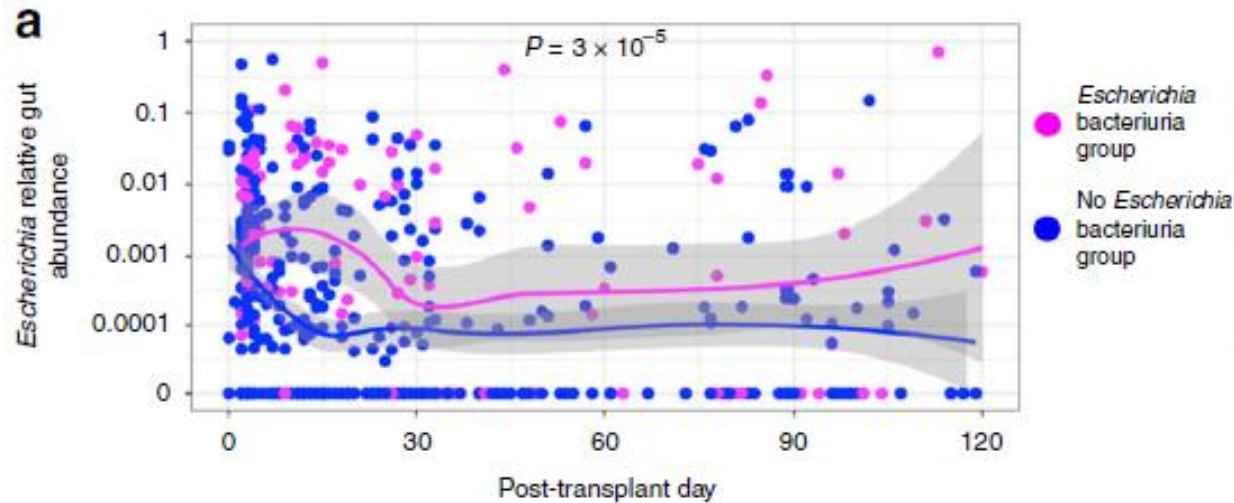
Antibiotics and the gut microbiome



4 years after treatment high levels of the macrolide resistance gene erm(B) were found, indicating that antibiotic resistance, once selected for, can persist for longer periods of time

Gut uropathogen abundance is a risk factor for development of bacteriuria and urinary tract infection

Matthew Magruder¹, Adam N. Sholi¹, Catherine Gong¹, Lisa Zhang¹, Emmanuel Edusei¹, Jennifer Huang¹, Shady Albakry¹, Michael J. Satlin², Lars F. Westblade^{2,3}, Carl Crawford⁴, Darshana M. Dadhania^{1,5}, Michelle Lubetzky^{1,5}, Ying Taur⁶, Eric Littman⁶, Lilan Ling⁶, Philip Burnham⁷, Iwijn De Vlaminc⁷, Eric Pamer⁶, Manikkam Suthanthiran^{1,5} & John Richard Lee^{1,5*}



Precise diagnostics

The Clinical Urine Culture: Enhanced Techniques Improve Detection of Clinically Relevant Microorganisms

Travis K. Price,^a Tanaka Dune,^b Evann E. Hilt,^a Krystal J. Thomas-White,^a Stephanie Kliethermes,^c Cynthia Brincat,^{b,d} Linda Brubaker,^{b,d} Alan J. Wolfe,^a Elizabeth R. Mueller,^{b,d} Paul C. Schreckenberger^a

Department of Microbiology and Immunology, Stritch School of Medicine, Loyola University, Chicago, Illinois, USA^a; Department of Obstetrics & Gynecology and Urology, Loyola University Medical Center, Maywood, Illinois, USA^b; Departments of Medicine and Public Health Sciences,^c Department of Obstetrics & Gynecology and Urology,^d and Department of Pathology,^e Stritch School of Medicine, Loyola University Chicago, Maywood, Illinois, USA

TABLE 1 Summary of urine cultivation protocols for catheterized urine specimens

Protocol	Vol (μl) of urine	Medium or media	Conditions	Incubation(s) (h) for microbial identification	Patient sample identifier ^a
Standard urine culture	1	BAP, MacConkey agar	Aerobic, 35°C	24	1–107
Modified urine culture	1	BAP, MacConkey agar	5% CO ₂ , 35°C	24, 48	108–150
Expanded-spectrum EQUIC	1, 10, and 100	BAP, MacConkey agar	Aerobic, 35°C	24, 48	1–150
		BAP, chocolate agar,	5% CO ₂ , 35°C	24, 48	
		CNA agar			
		CDC anaerobic BAP	Anaerobic, 35°C	48	
		CDC anaerobic BAP ^b	Microaerophilic gas mixture (5% O ₂ , 10% CO ₂ , 85% N), 35°C	48	
Streamlined EQUIC	100	BAP, MacConkey agar, ^c CNA agar	5% CO ₂ , 35°C	48	1–150 ^d

^a Refers to the patient samples on which the corresponding protocol assessed the urinary microbiota. For diagnosis, the standard urine culture protocol was used on patient samples 1 to 107; the modified standard urine culture was used on patient samples 108 to 150. For research, all patient samples were assessed by expanded-spectrum EQUIC.

^b The CDC anaerobic BAP microaerophilic gas mixture condition was used only for samples 10 to 150.

^c The MacConkey 5% CO₂ condition was not part of the expanded-spectrum EQUIC protocol.

^d The streamlined EQUIC protocol was performed using a subgroup of agars/conditions from the expanded-spectrum EQUIC protocol; therefore, it was used on all patient samples.

Optimal detection of uropathogens could be achieved using the following: 100 μl of urine plated onto blood (blood agar plate [BAP]), colistin-nalidixic acid (CNA), and MacConkey agars in 5% CO₂ for 48 h.

This streamlined EQUIC protocol achieved 84% uropathogen detection relative to 33% detection by standard urine culture.

Enhanced quantitative urine culture (EQUIC)

News & Views | Published: 14 September 2018

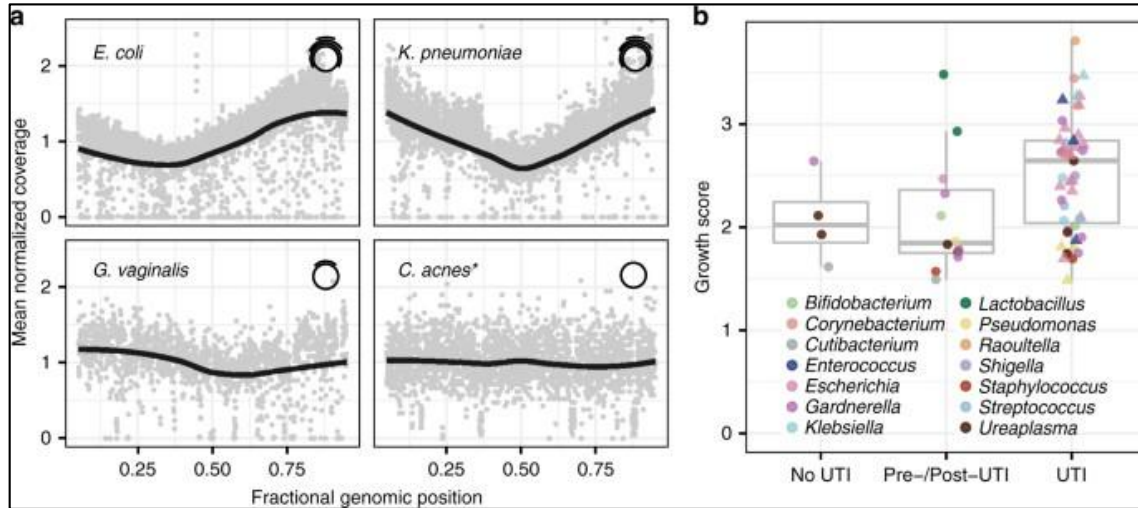
INFECTION

Urinary cell-free DNA and UTI; the age of 'omics'

Rhana Hassan Zakri & Jonathon Olsburgh

Nature Reviews Urology 15, 727–728(2018) | [Cite this article](#)

Refers to Burnham, P. et al. Urinary cell-free DNA is a versatile analyte for monitoring infections of the urinary tract. *Nat. Commun.* 9, 2412 (2018)



New and developing diagnostic technologies for urinary tract infections

Michael Davenport, Kathleen E. Mach, Linda M. Dairiki Shortliffe, Niaz Banaei, Tza-Huei Wang & Joseph C. Liao

Nature Reviews Urology 14, 296–310(2017) | [Cite this article](#)

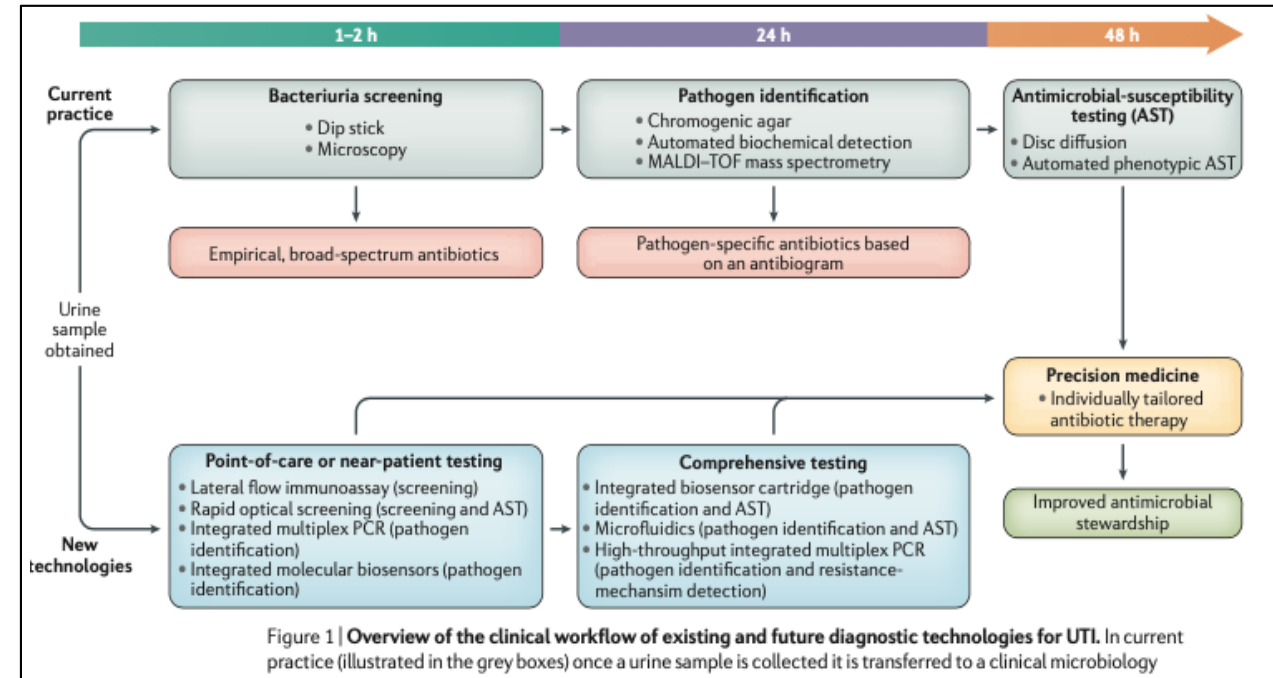


Figure 1 | Overview of the clinical workflow of existing and future diagnostic technologies for UTI. In current practice (illustrated in the grey boxes) once a urine sample is collected it is transferred to a clinical microbiology

Management of recurrent UTIs post kidney transplantation

Non-Abx strategies to prevent UTIs in Tx patients

KTR-focused Strategy	Efficacy in KTRs	Recommendation in KTRs
Early ureteral stent removal (ideally ≤ 14 –21 days, and not later than 3 weeks, when clinically feasible)	Reduces UTI incidence without clear increase in major urologic complications (moderate certainty, meta-analyses) [14,71]	Strong (perioperative practice optimization)
Timing of Foley catheter removal (early vs late)	Uncertain effect on bacteriuria/UTI; evidence very low certainty and outcomes incompletely reported [72,73]	No recommendation (individualize by surgical/urologic risk)
Methenamine hippurate (commonly 1 g BID; requires urinary acidification for activity)	Likely beneficial in recurrent UTI (reduced UTI episodes/antibiotic exposure in observational transplant cohorts) [66,74]	Conditional (selected KTRs with rUTI; antibiotic-sparing option)
Cranberry products (prefer standardized PAC content when available; transplant evidence largely non-standardized formulations)	Possible benefit (limited transplant data; formulation heterogeneity) [61]	Conditional
Urine acidification (L-methionine)	Possible benefit (limited, retrospective transplant data; often evaluated with cranberry) [61]	Conditional
D-mannose (\pm PACs)	No preventive benefit demonstrated in de novo KTR RCT (no meaningful reduction in UTI/ASB) [63]	Not recommended for routine prophylaxis
Vaginal estrogen (postmenopausal women)	No KTR-specific RCTs; efficacy supported in non-transplant rUTI RCTs \rightarrow extrapolation [75,78]	Conditional (postmenopausal KTRs with rUTI, after contraindication review)
Increased water/fluid intake	Commonly advised, but limited KTR evidence for UTI prevention; should be individualized [76]	No recommendation (expert opinion; personalize)
Probiotics (eg, Lactobacillus)	Insufficient KTR-specific evidence for UTI prevention [77,78]	No recommendation

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Prophylactic Ureteric Stents in Renal Transplant Recipients: A Multicenter Randomized Controlled Trial of Early Versus Late Removal

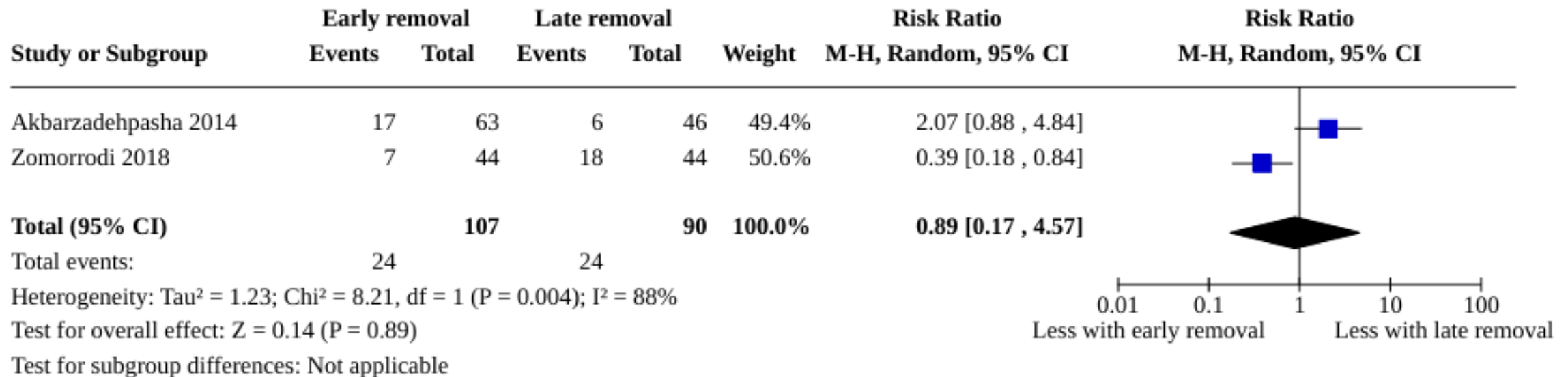
	PP analysis			ITT analysis		
	Late stent removal	Early stent removal	p-value	Late stent removal	Early stent removal	p-value
UTI	31/126 (24.6)	6/79 (7.6)	0.004	23/107 (12.1)	14/98 (14.3)	0.257
Symptomatic UTI	19/126 (15.1)	2/79 (2.5)	0.008	13/107 (12.1)	8/98 (8.2)	0.476
Lower tract UTI only	11/126 (8.7)	2/79 (2.5)	0.128	8/107 (7.5)	5/98 (5.1)	0.662
Upper tract UTI only	4/126 (3.2)	0/79 (0)	0.329	2/107 (1.9)	2/98 (2.0)	0.876
Lower and upper tract UTI	4/126 (3.2)	0/79 (0)	0.259	3/107 (2.8)	1/98 (1.0)	0.655
Asymptomatic UTI	12/126 (9.5)	4/79 (5.1)	0.410	10/107 (9.3)	6/98 (6.1)	0.575

Non-Abx strategies to prevent UTIs in Tx patients

Timing of Foley catheter removal
(early vs late)

Uncertain effect on bacteriuria/UTI; evidence very low certainty and outcomes incompletely reported [72,73]

No recommendation (individualize by surgical/urologic risk)



Goodfellow M et al Early versus late removal of urinary catheter after kidney transplantation. Cochrane Database of Systematic Reviews 2023, Issue 7. Art. No.: CD013788.

Methanamine Hippurate (Hiprex)

- Hydrolysis in acidic urinary environment releasing formaldehyde
- Does not exert selective antimicrobial pressure
- Does not promote resistance
- Non inferior to continuous antibiotic prophylaxis (ALTAR trial)
- Limited data in kidney transplant recipients
- Cannot be given with co-trimoxazole (risk of crystalluria)
- Avoid if eGFR <10 ml/min/1.73m²

Methanamine Hippurate (Hiprex)

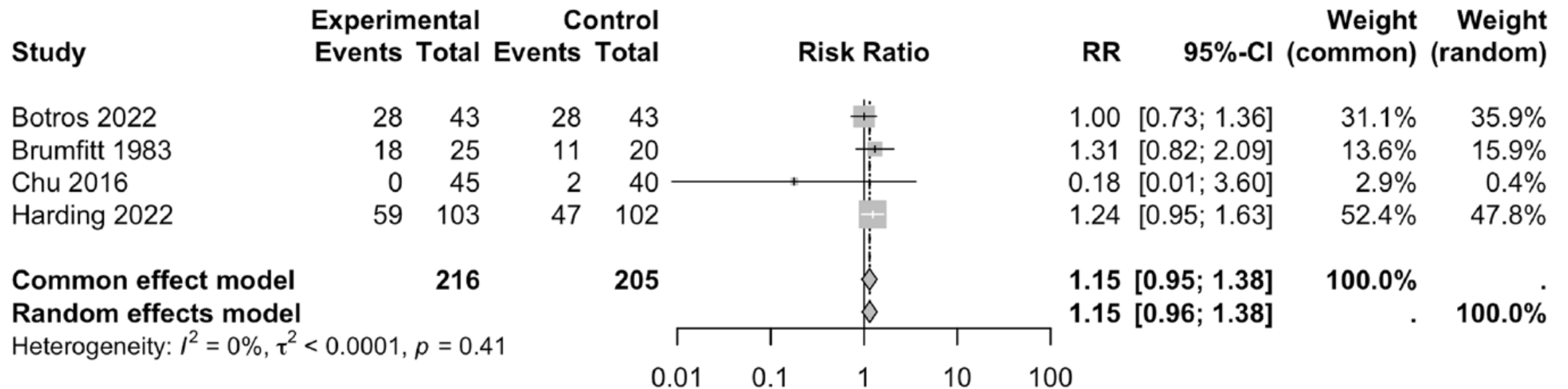


Fig. 2 Rate of symptomatic UTI comparing Methenamine and Antibiotics

Safety and Efficacy of Methenamine Hippurate for the Prevention of Recurrent Urinary Tract Infections in Adult Renal Transplant Recipients: A Single Center, Retrospective Study

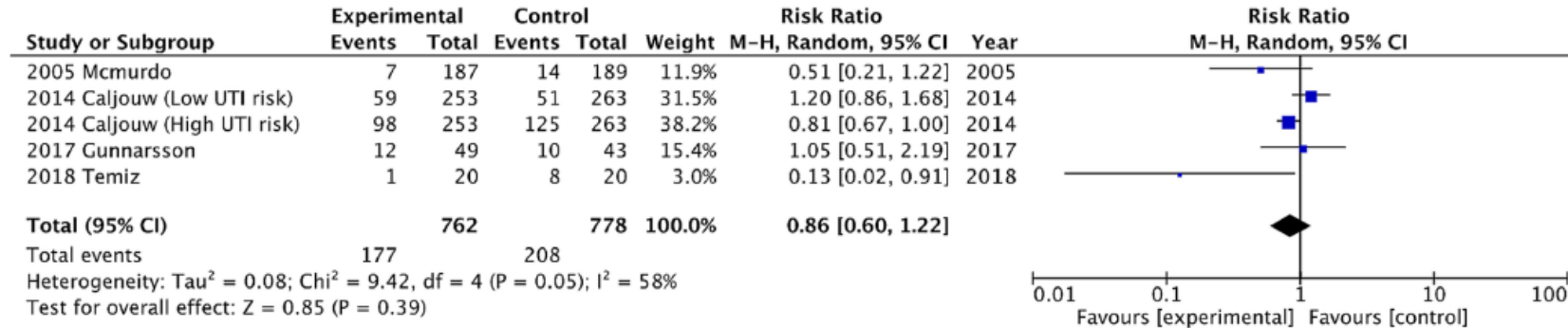
- Follow-up days were 365 (299–365) pre- vs 314 (105–365) post-methenamine.
- *E. coli* and *K. pneumoniae* were the most commonly identified cause of UTI both pre- and post-intervention.
- Drug resistant bacteria (ESBL-producing or VRE) affected 3 patients pre- and recurred in 1 of those patients plus 3 new patients post-methenamine.
- Methenamine had few adverse side effects for patients.

Safety and Efficacy of Methenamine Hippurate for the Prevention of Recurrent Urinary Tract Infections in Adult Renal Transplant Recipients: A Single Center, Retrospective Study

	Pre-methenamine	Post-methenamine	p-value
UTI rate, n/1000 follow-up days	9.16	5.01	0.0001
Length of antibiotic therapy to treat UTI, n/1000 follow-up days	152	88	0.0022
Length of antibiotic suppressive therapy, n/1000 follow-up days	13.7	0	<0.0001
Length of therapy for non-UTI antibiotics, n/1000 follow-up days	69	83	0.8655
TMP-SMX prophylaxis length of therapy, n/1000 follow-up days	849	895	0.7080
Hospitalizations due to UTI, n/1000 follow-up days	2.64	1.07	0.0456
Hospitalizations (other cause), n/1000 patient days	3.72	2.03	0.1244
Untreated ASB, n/1000 follow-up days	0.58	0.85	0.1344
Treated ASB, n/1000 follow-up days	0.66	0.85	0.2290
Culture negative treated UTI, n/1000 follow-up days	0.83	0.96	0.8062
Creatinine, median	1.24	1.21	0.8723
GFR ml/min/1.73m ² , median	50.5	51.0	0.9942
Urinary pH, median	5.50	6.00	0.3203
MDR organisms isolated, % of positive bacteria cultures	0.08	0.07	0.6145

Cranberry products

a Forest plot showing the incidence of UTIs after intervention for cranberry products with an average daily intake of less than 36mg PACs and in the control group



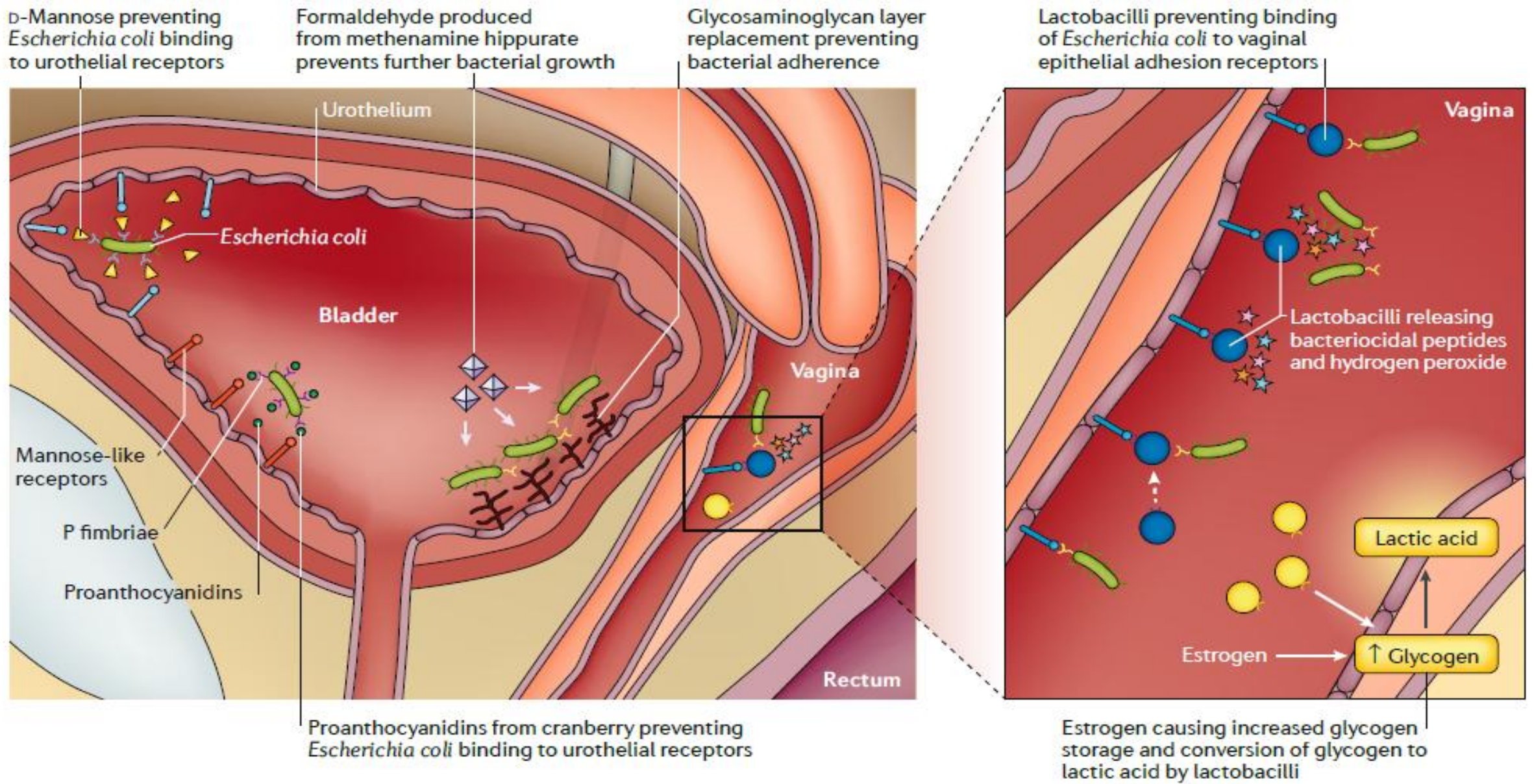
b Forest plot showing the incidence of UTIs after intervention for cranberry products with an average daily intake of at least 36mg PACs and in the control group



- In previous reviews, negative results but most preparations contained <10 to 18mg of PACs
- A minimum effective threshold of 36mg/d, to be taken for at least 12 to 24 weeks
- Aim for 36 mg of PAC per day (DMAC method)

Non-Abx strategies to prevent UTIs in Tx patients

D-mannose (\pm PACs)	No preventive benefit demonstrated in de novo KTR RCT (no meaningful reduction in UTI/ASB) [63]	Not recommended for routine prophylaxis
Vaginal estrogen (postmenopausal women)	No KTR-specific RCTs; efficacy supported in non-transplant rUTI RCTs \rightarrow extrapolation [75,78]	Conditional (postmenopausal KTRs with rUTI, after contraindication review)
Increased water/fluid intake	Commonly advised, but limited KTR evidence for UTI prevention; should be individualized [76]	No recommendation (expert opinion; personalize)
Probiotics (eg, Lactobacillus)	Insufficient KTR-specific evidence for UTI prevention [77,78]	No recommendation

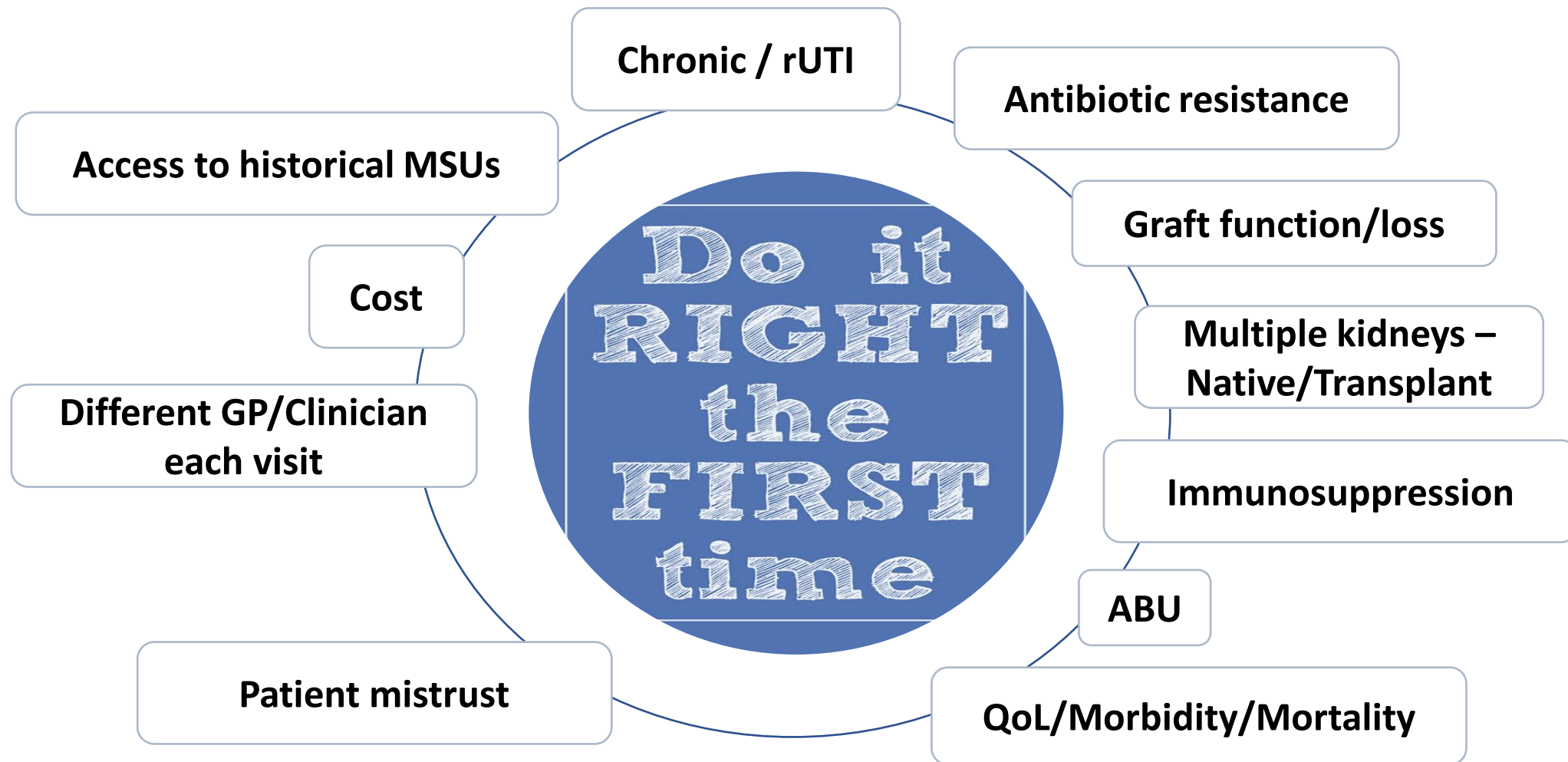


Audit Guy's Hospital

- **29%** - symptomatic UTI in the first 5 years post RTx
- **Cystitis/Pyelonephritis/Number of UTI “hits”** - detrimental effect on Δ graft function at 5 years

Limitations

- **Retrospective observational study**
- **Confounders**
 - **E.g. changes in immune-suppression over 5yrs**
- **Assumptions**
 - **Cystitis – (CRP 0-10 v 10-50)**
 - **“Statistically significant” is “clinically significant”**
- **Need for further multivariate analysis / mixed repeated measure model**



Individual tailored management

Transplant UTI
one-stop clinic

MDT clinic
Tx Urologist
Tx Nephrologist
CNS

Identify all risk factors

Early intervention

Precise diagnostics

Antibiotic stewardship

Individual tailored management – Risk factors

Host factors

Gender
Pre/post menopausal
ESRF cause
UTIs before/after Tx
Bladder function/PVR
Bowel habit
Sexually activity
PMHx: ?DM etc

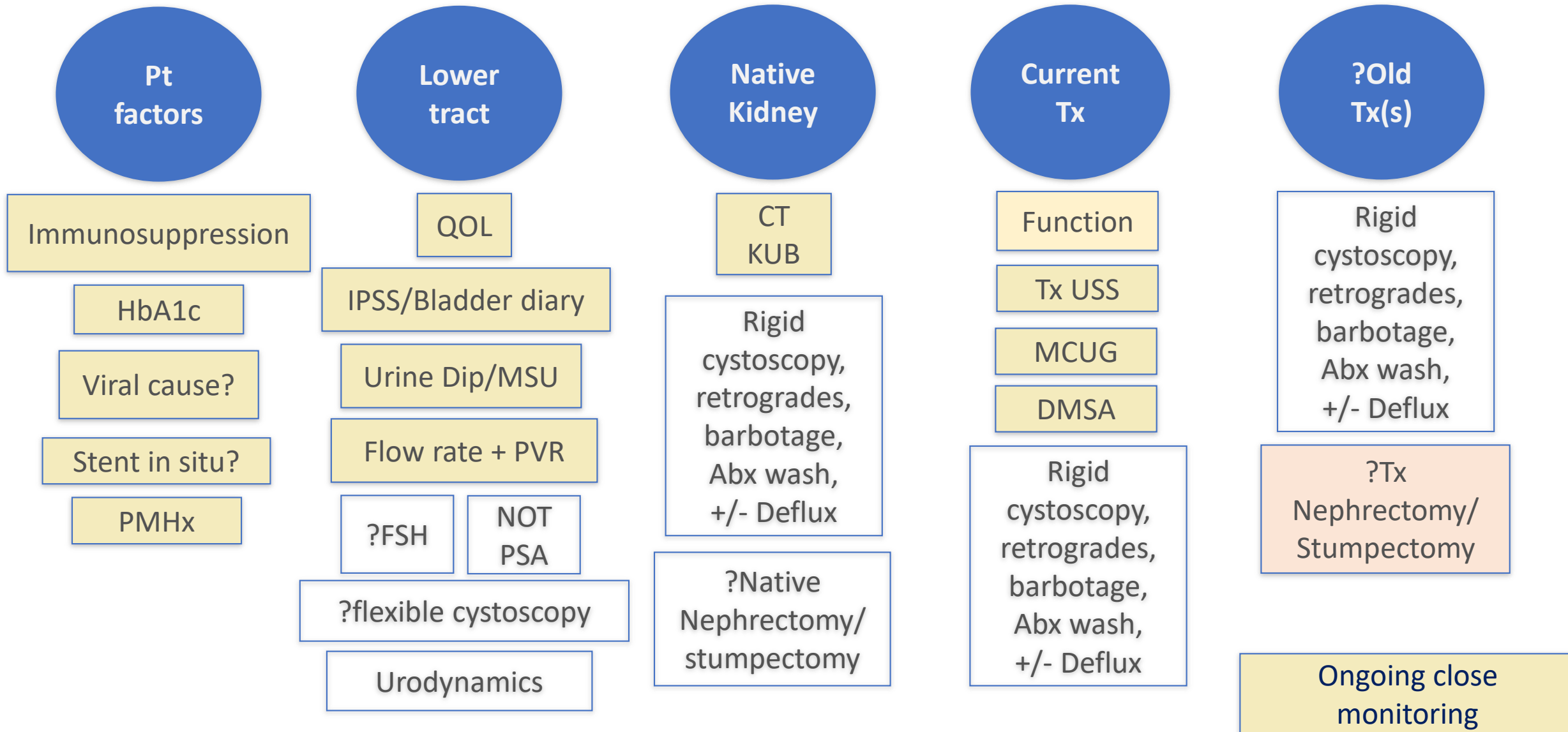
Allograft factors

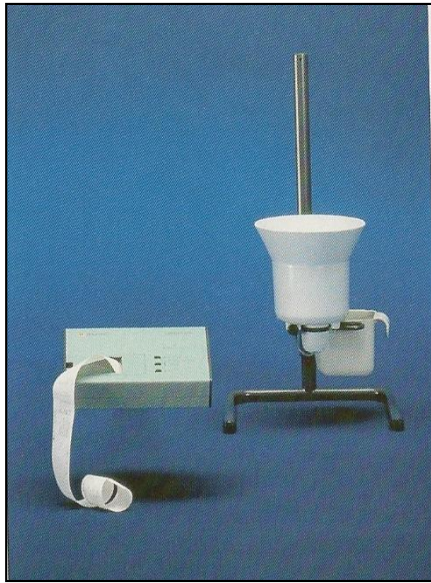
Time since transplant
Previous transplants
In Situ?
?degree of reflux
Episodes of rejection
Immunosuppression

Anatomical factors

Native kidneys ?in-situ
Length of any ureteric
stumps
Urological history

Individual tailored management – Precise diagnostics





Flow Rate

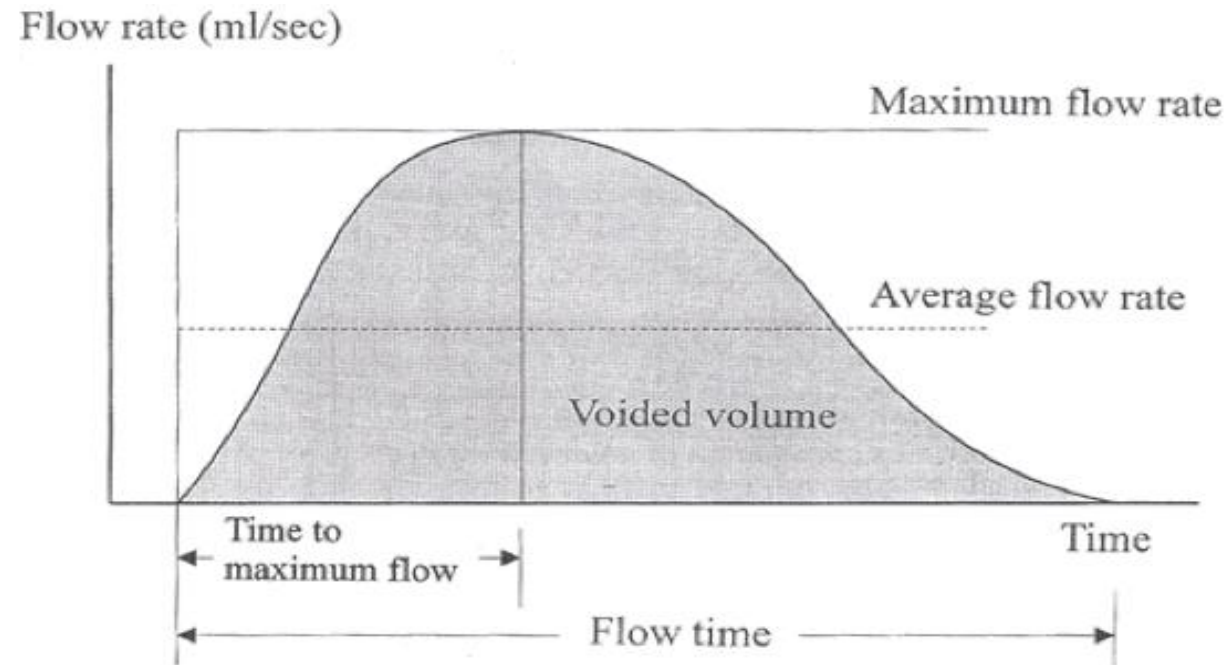
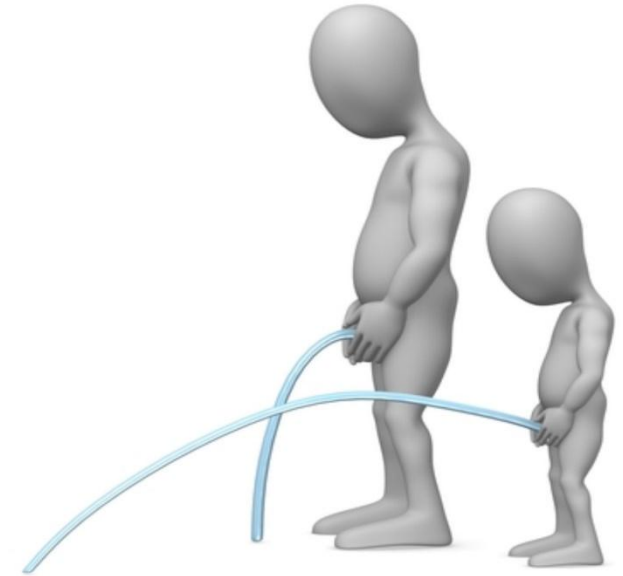
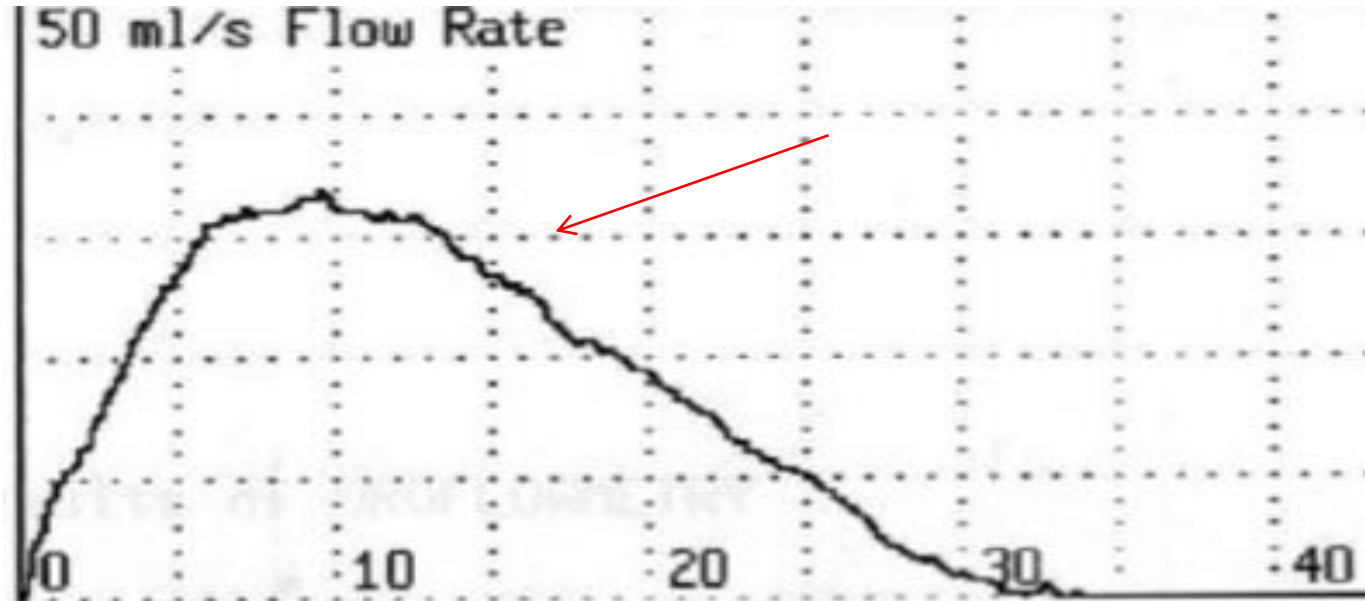


Diagram of a urine flow recording with International Continence Society recommended nomenclature. Basic elements of maximum flow, mean flow, total flow time, and total voided volume.

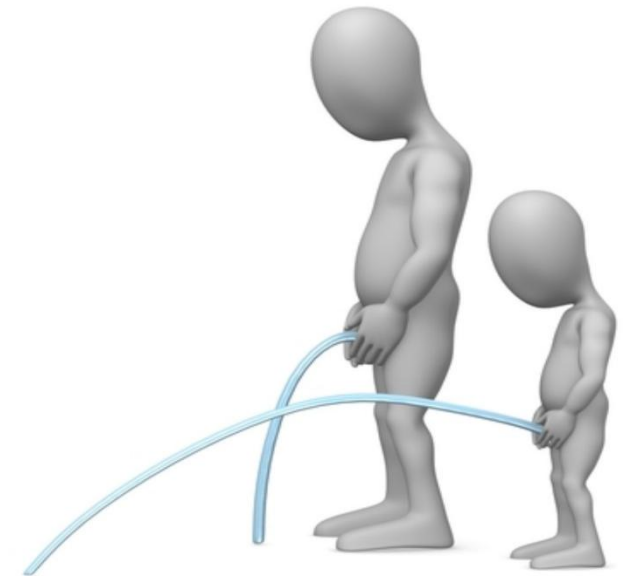


Flow Rate

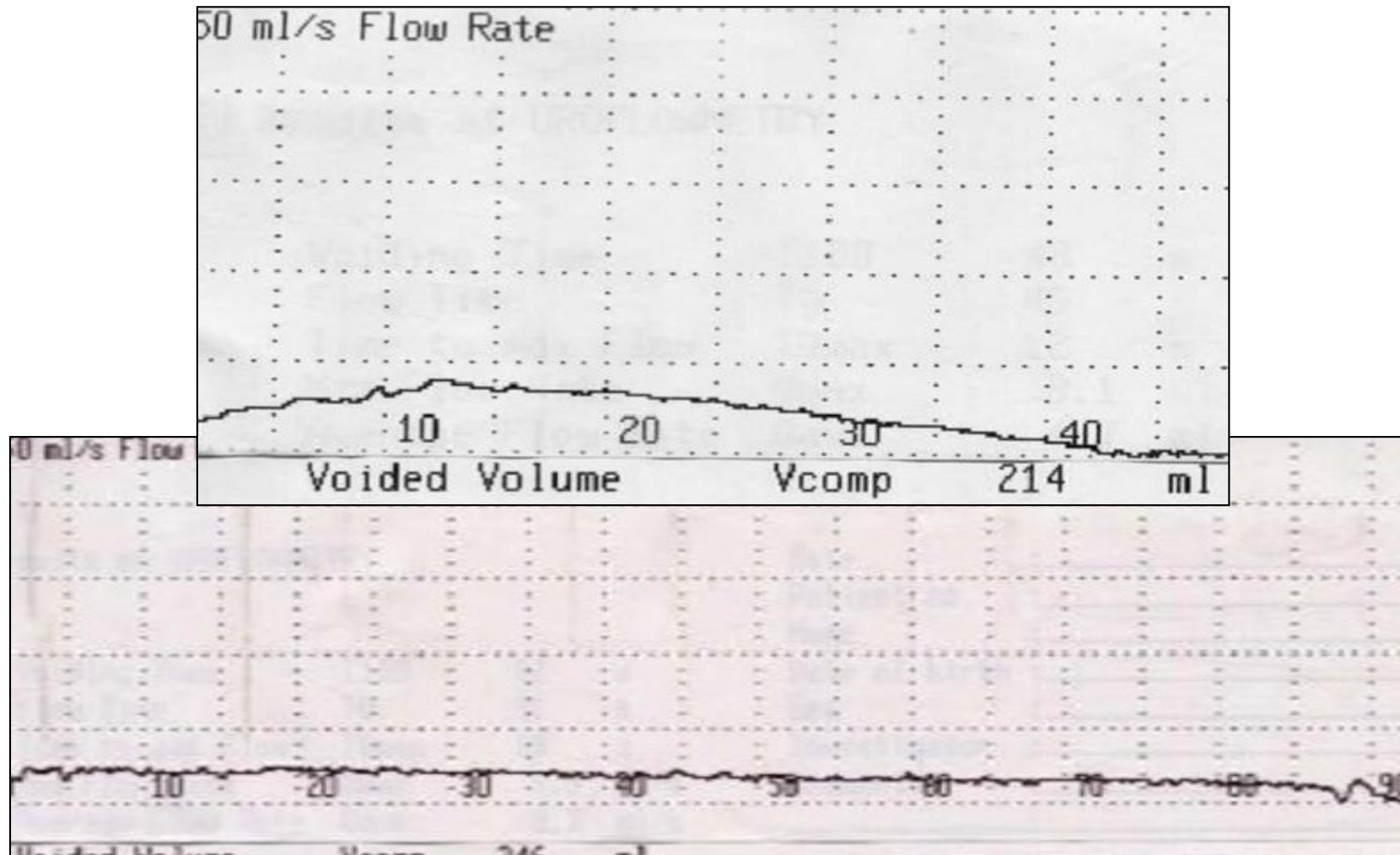


Voiding Time	T100	33	s
Flow Time	TQ	32	s
Time to max Flow	TQmax	9	s
Max Flow Rate	Qmax	33.8	ml/s
Average Flow Rate	Qave	18.6	ml/s
Voided Volume	Vcomp	602	ml

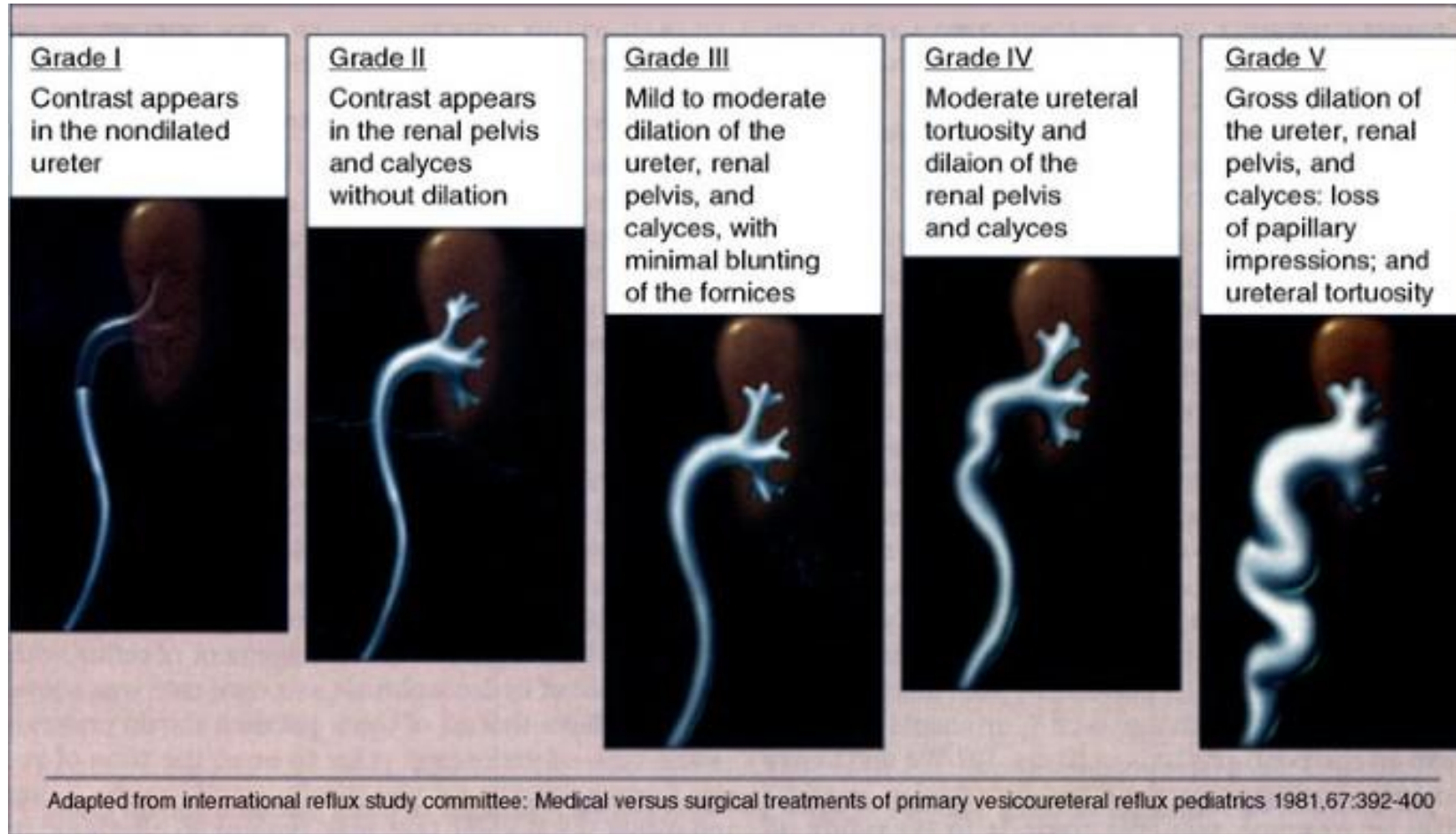
PVR



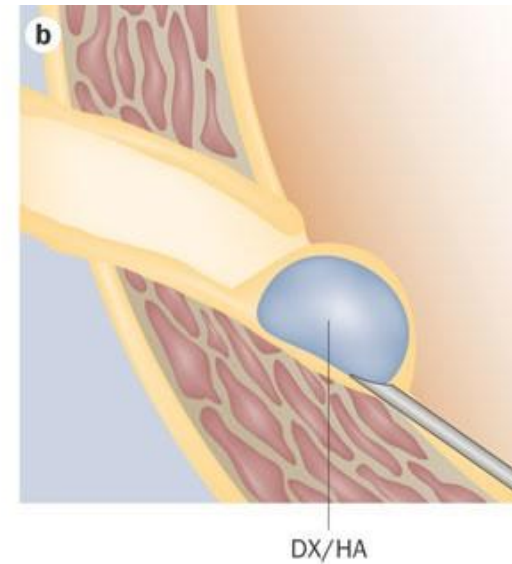
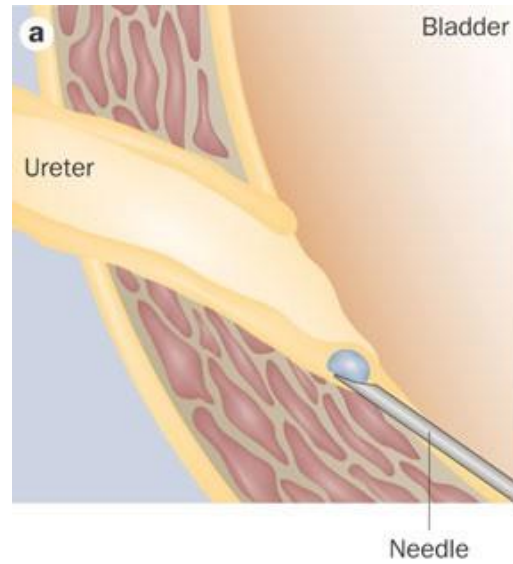
Q-Max



Grades of Reflux



Micturating cystourethrograph (MCUG)



Deflux

Individual tailored management – Armamentarium



(Px) Abx. Rotate



Oestrogen



Ialuril



**Behaviour
Bladder
Bowel – Probiotics**



Fluids



?Vaccines



Cranberry tablets



**Intravesical
Gent**



D-Mannose



Hiprex (methenamine Hippurate)

Hollyer et al *Transpl Infect Dis.* 2019;21:e13063.

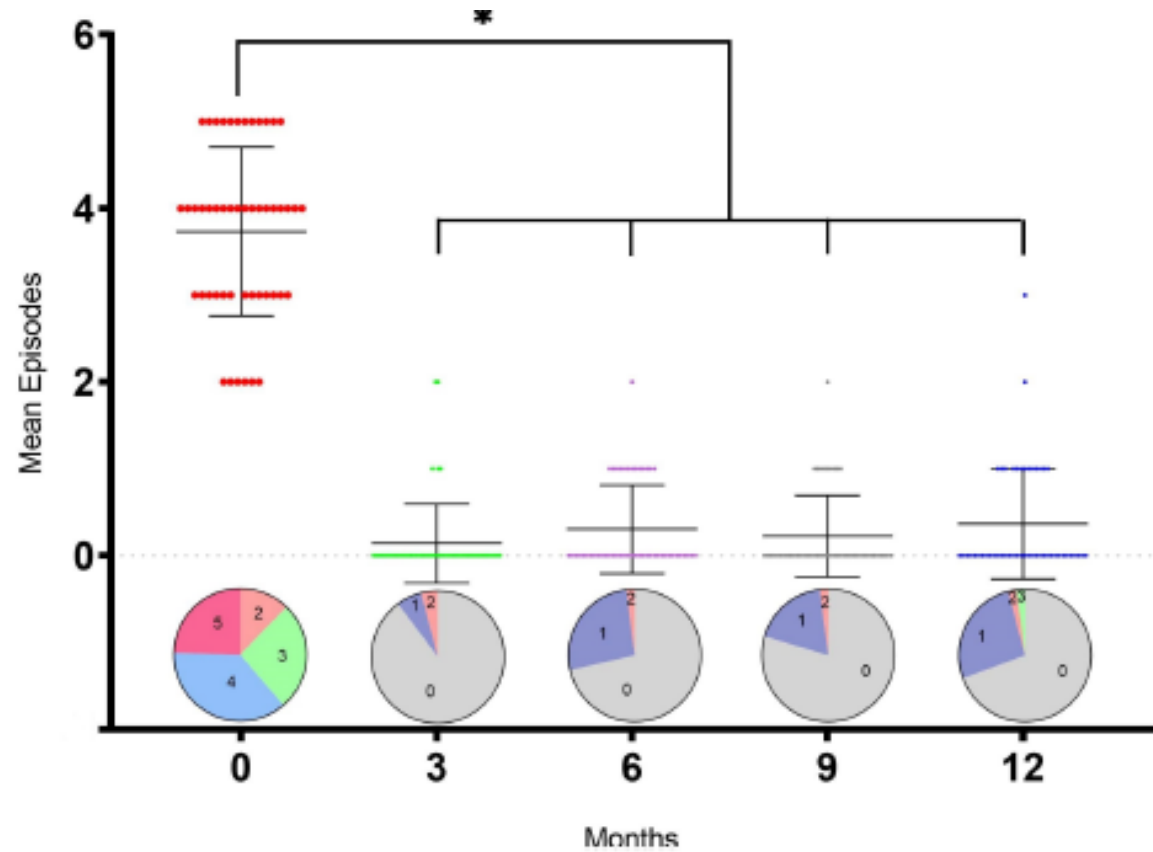
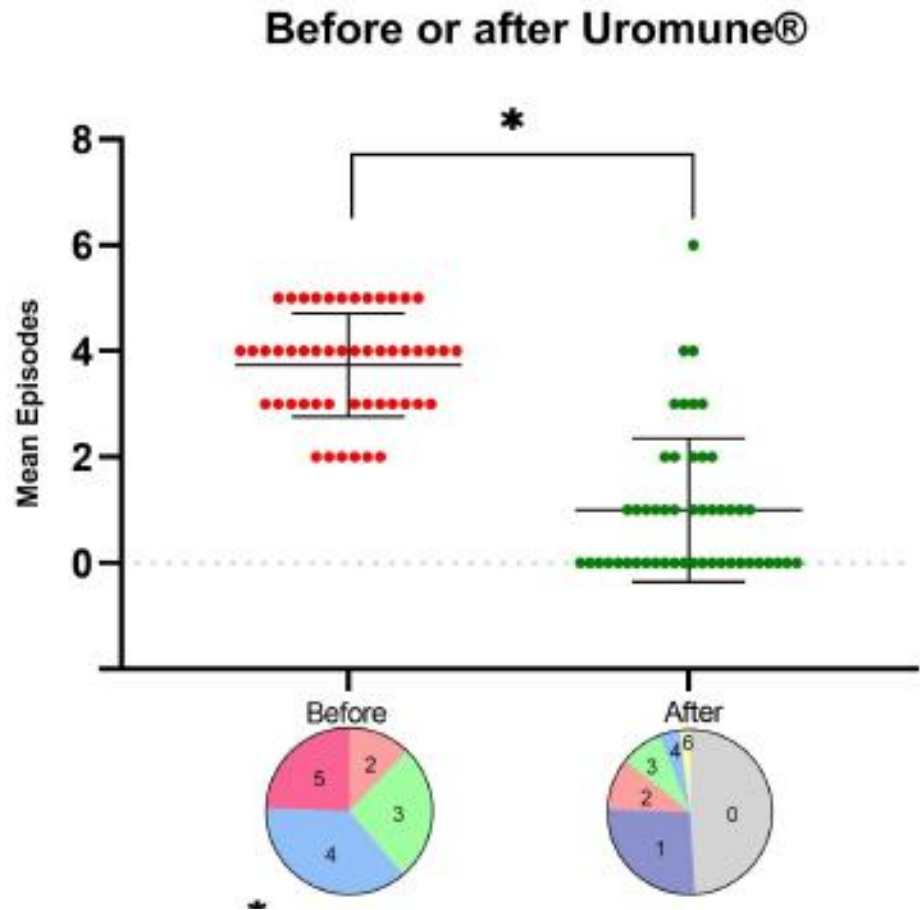
Zgoura et al *Transplantation Proceedings*, 52, 3192e3196 (2020)

Moutzouris et al *Clin J Am Soc Nephrol* 2009 Nov;4(11):1844-57

Other approaches

- Immunostimulants/Vaccines
- Bacteriophage therapy
- Faecal microbiota transplantation

Evaluating the use of Uromune[®] autovaccine in recurrent urinary tract infections: a pilot unicenter retrospective study in Reus, Spain




Clinical and Immunological Response to Sublingual Vaccination for the Prevention of Recurrent Urinary Tract Infections in Kidney Transplant Patients: Results after 1 Year of Follow-up

- 43 kidney transplant recipients with rUTI completed sublingual vaccination with Uromune[®] for 6 months
- The mean incidence of UTI decreased from 4.2 to 2.7 episodes per year (CI 95% 0.9-2.2, $p < 0,001$)
- After one year, 16.3% of patients were completely free from UTI and 46.5% had fewer infections

Safety and Efficacy of MV140 Sublingual Vaccine (Uromune) in Preventing Recurrent Urine Infections Post Renal Transplant: A Case Series

- All but one patient had fewer episodes of UTI in the 12 months post intervention
- No side effects


Transplantation Proceedings
 Volume 52, Issue 10, December 2020, Pages 3192-3196

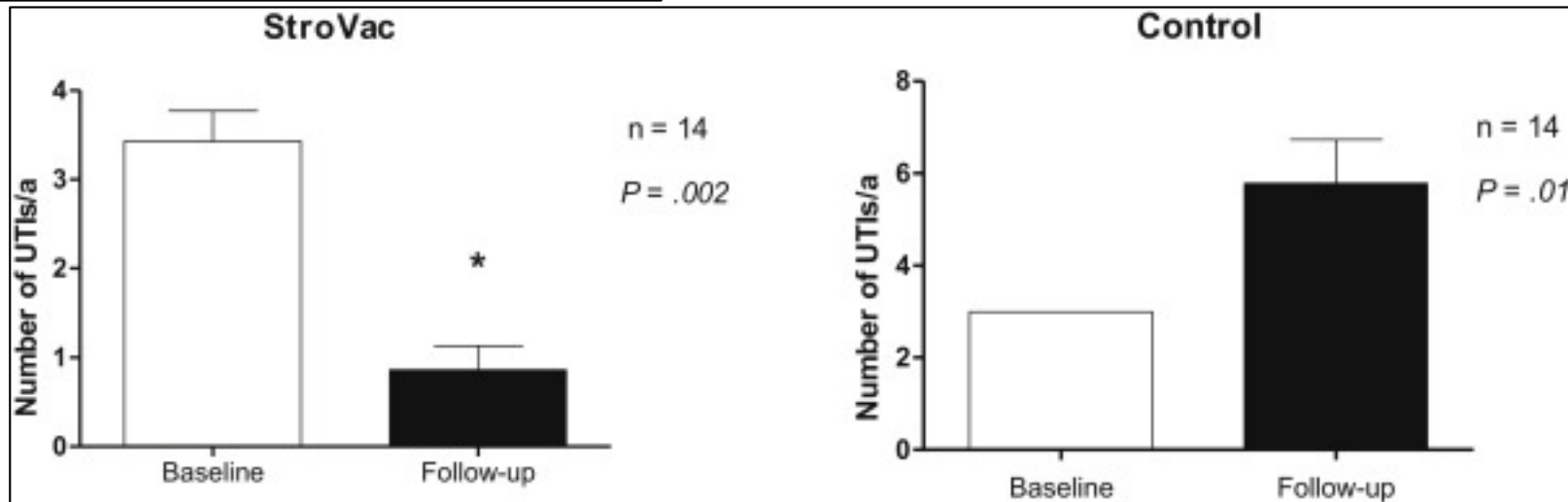
Contributions to Transplantation Science
 Kidney transplantation

Vaccination Against Urinary Tract Infection After Renal Transplantation

Panagiota Zgoura ^a, Christoph Waldecker ^a, Frederic Bauer ^a, Felix S. Seibert ^a, Benjamin Rohn ^a, Peter Schenker ^b, Andreas Wunsch ^b, Sandra Hajt ^b, Richard Viebahn ^b, Nina Babel ^a, Timm H. Westhoff ^a

StroVac contains 10 strains of inactivated bacteria (6 types of *Escherichia coli*, *Proteus mirabilis*, *Morganella morganii*, *Enterococcus faecalis*, *Klebsiella pneumoniae*).

The vaccine is administered 3 times subcutaneously and is supposed to reduce the UTI incidence for about 12 months.



Annual incidence of urinary tract infection (UTI) before (baseline) and after initiation of StroVac vaccination (follow-up). Differences were tested for significance by Wilcoxon test, $P < .05$ was regarded as significant.

Oral Tebipenem HBr Noninferior to IV Imipenem-Cilastatin for Complicated UTI

Jaymin Kang, PharmD | June 4, 2025

- Tebipenem HBr is an investigational oral antibiotic in the carbapenem class.
- The RCT, phase 3 PIVOT-PO trial included 1690 adults with cUTI or acute pyelonephritis. Patients were randomly assigned 1:1 to receive HBr 600mg or IV imipenem-cilastatin 500mg for 7 to 10 days.
- Tx with oral tebipenem HBr was noninferior to IV imipenem-cilastatin based on overall response, defined as a combination of clinical cure and favourable microbiological response. No new safety concerns were reported.

Thank you

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