Approccio pratico alla gestione delle infezioni delle vie urinarie

Maddalena Peghin MD PhD
Infectious and Tropical Diseases Unit, Associate Professor
University of Insubria-ASST-Sette Laghi, Varese, Italy

UNIVERSITÀ DEGLI STUDI DELL'INSUBRIA

Rete Nazionale Trapianti

Sistema Socio Sanitario
Regione Lombardia
ASST Sette Laghi
Polo Universitario

The need for improvement in the management of UTI

- Urinary tract infection is one of the most common clinical problems in both the community and healthcare-associated settings
- UTI are one of the most common indications for antibiotics at outpatient visits
- Among infectious disease-related ED visits, upper and lower UTI
  - 12.6% of visits by persons of all ages
  - 25.3% of visits by elderly adults

- Overuse and misuse have contributed to the growing problem of resistance among uropathogenic bacteria

Goto et al. JAGS 64:31–36, 2016
Goebel MC et al. Clin Microbiol Rev 2021

Outline

- Asymptomatic bacteriuria
- Diagnostic challanges
- Treatment tips
- Non antibiotic strategies

Outline

- **Asymptomatic bacteriuria**
- Diagnostic challanges
- Treatment tips
- Non antibiotic strategies

The definition of asymptomatic bacteriuria

- individual without urinary tract symptom and mid-stream sample of urine showing bacterial growth ≥ 105 cfu/mL
  - in two consecutive samples in women
  - in one single sample in men
- 10%-60% of women do not have persistent bacteriuria on repeat screening after an initial positive specimen

Nicolle et al. CID 2019:68 (15 May)

Over-treatment of ABU

- 17 critical-access hospitals 2021-2022; USA
- 891 patients with urine cultures

median time of 7 days (IQR, 3–7)

Hartlage W, et al. Infect Control Hosp Epidemiol. 2024

Inappropriate Management of Asymptomatic Patients With Positive Urine Cultures: A Systematic Review and Meta-analysis

- 4129 cases, 30 articles
- **45% of patients did not require treatment**
- Increased the odds of receiving treatment
  - isolation of gram-negative pathogens (OR, 3.58; 95% CI, 2.12–6.06)
  - pyuria (OR, 2.83; 95% CI, 1.9–4.22)
  - nitrite positivity (OR, 3.83; 95% CI, 2.24–6.54)
  - female sex (OR, 2.11; 95% CI, 1.46–3.06)

- Various interventions, education on diagnostic protocols, provided a significant absolute risk reduction of 33%

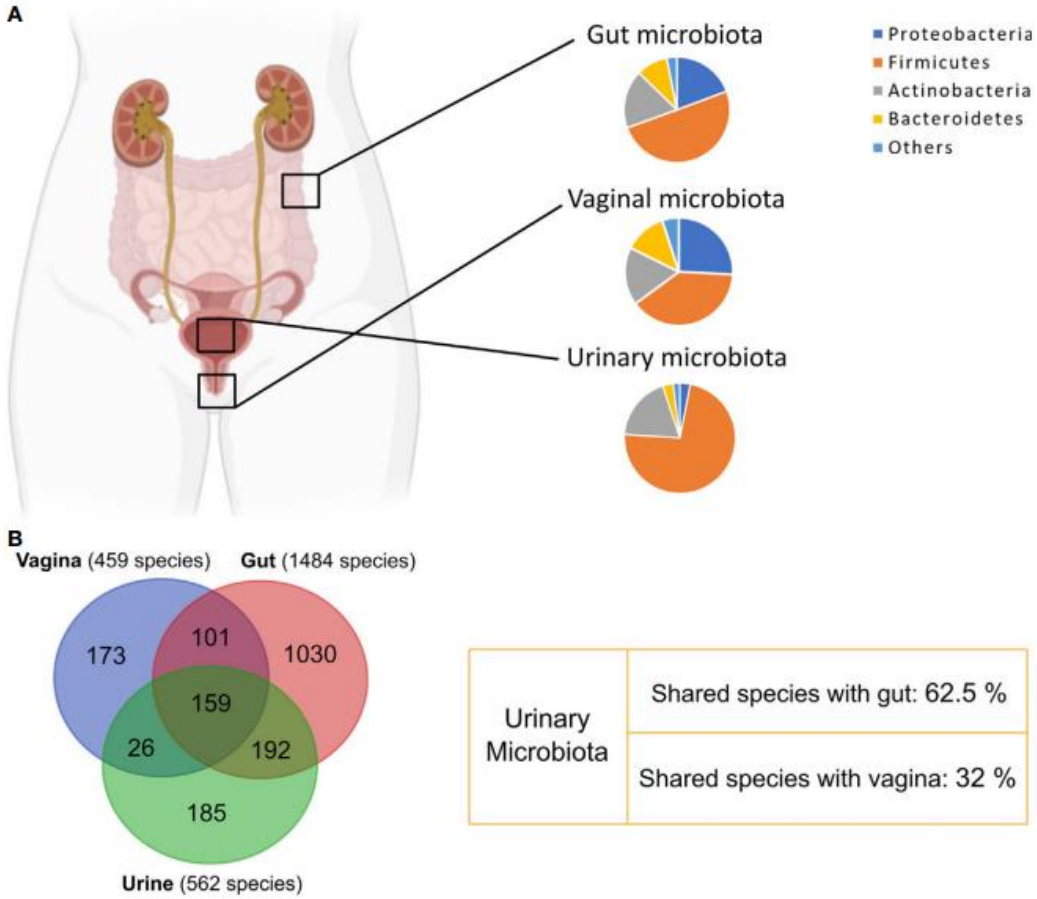
Florkas et al Open Forum Infect Dis 2017;4(4

Epidemiology of ABU

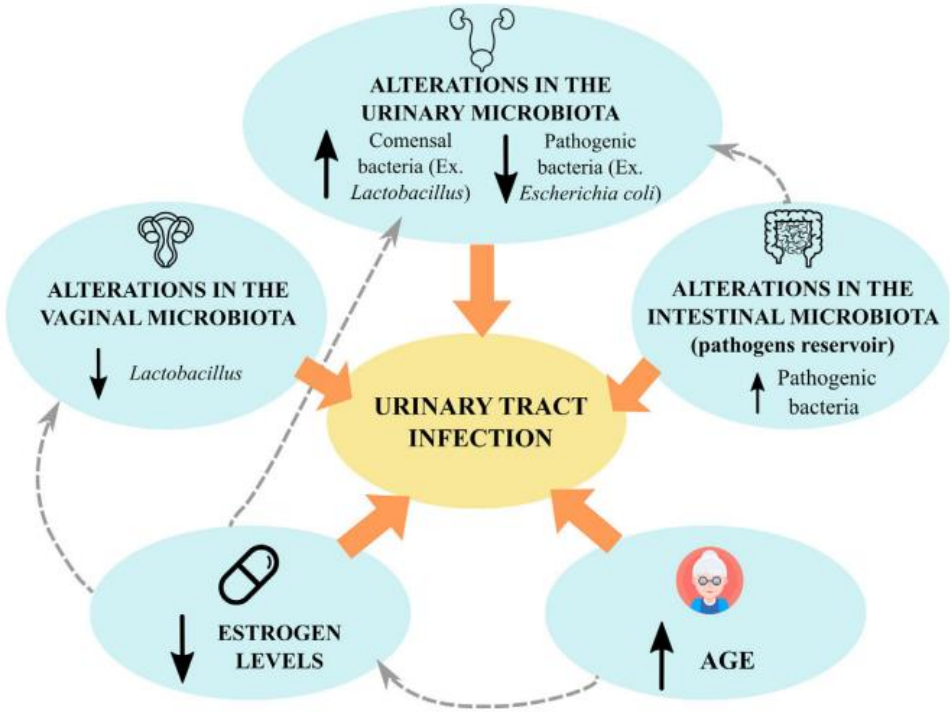
- 1-5% of healthy pre-menopausal females
- 4-19% healthy elderly females and men
- 0.7-27% in patients with diabetes
- 2-10% in pregnant women
- 15-50% in institutionalized elderly populations
- 23-89% in patients with spinal cord injuries
- Uncommon in young men

Perez Carrasco. Frontiers cells 2021

Clinical studies have shown that ABU may protect against superinfecting UTI



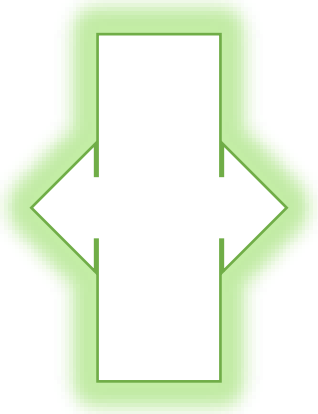
Urinary Microbiota	Shared species with gut: 62.5 %
	Shared species with vagina: 32 %



Perez Carrasco. Frontiers cells 2021

Asymptomatic bacteriuria in adults - Background

- Treatment of ABU should be performed only for proven benefit for the patient
  - to avoid the risk of selecting antimicrobial resistance
  - eradicating a potentially protective ABU strain



Nicolle et al. CID 2019:68 (15 May)

Diagnostic evaluation, pay atention to ABU if …

- persistent growth of **urease producing bacteria** (P.mirabilis) is detected:
  - stone formation in the urinary tract must be excluded

- detected in **younger men** :
  - chronic bacterial prostatitis must be considered and a digital rectal examination has to be performed to investigate the possibility of prostate diseases

Do not screen or treat asymptomatic bacteriuria in the following conditions

- women without risk factors
- patients with diabetes mellitus
- post-menopausal women
- elderly institutionalized patients
- patients with dysfunctional and/or reconstructed lower urinary tracts

Nicolle et al. CID 2019:68 (15 May)

Is treatment of ABU beneficial in recurrent UTI?

Patients with ABU and recurrent UTI, otherwise healthy

- Treatment of ABU increases the risk for a subsequent symptomatic UTI episode, compared to non-treated patients (RR 0.28, 95% CI 0.21 to 0.38; n=673)

- ABU may play a protective role in preventing symptomatic recurrence

Cai et al. Clin Infect Dis, 2012. 55: 771.

Is treatment of ABU beneficial in kidney transplant recipient?

The cumulative incidence of ABU:4-51% after kidney transplantation

Diagnosis and management of asymptomatic bacteriuria in kidney transplant recipients: a survey of current practice in Europe

244 participants in 25 countries

- 72% always screen for asymptomatic bacteriuria in KTRs
- more permissive diagnosis criteria
  - counts <105CFU/ml and/ or by not performing a second culture in women
- 24% would start empirical antibiotics
- fully susceptible microorganism , mostly used antibiotics :
    - fluoroquinolones
    - amoxicillin/clavulanic acid
    - oral cephalosporins

J Coussement et al Nephrol Dial Transplant (2018)

RCT for the treatment of asymptomatic bacteriuria among KTRs

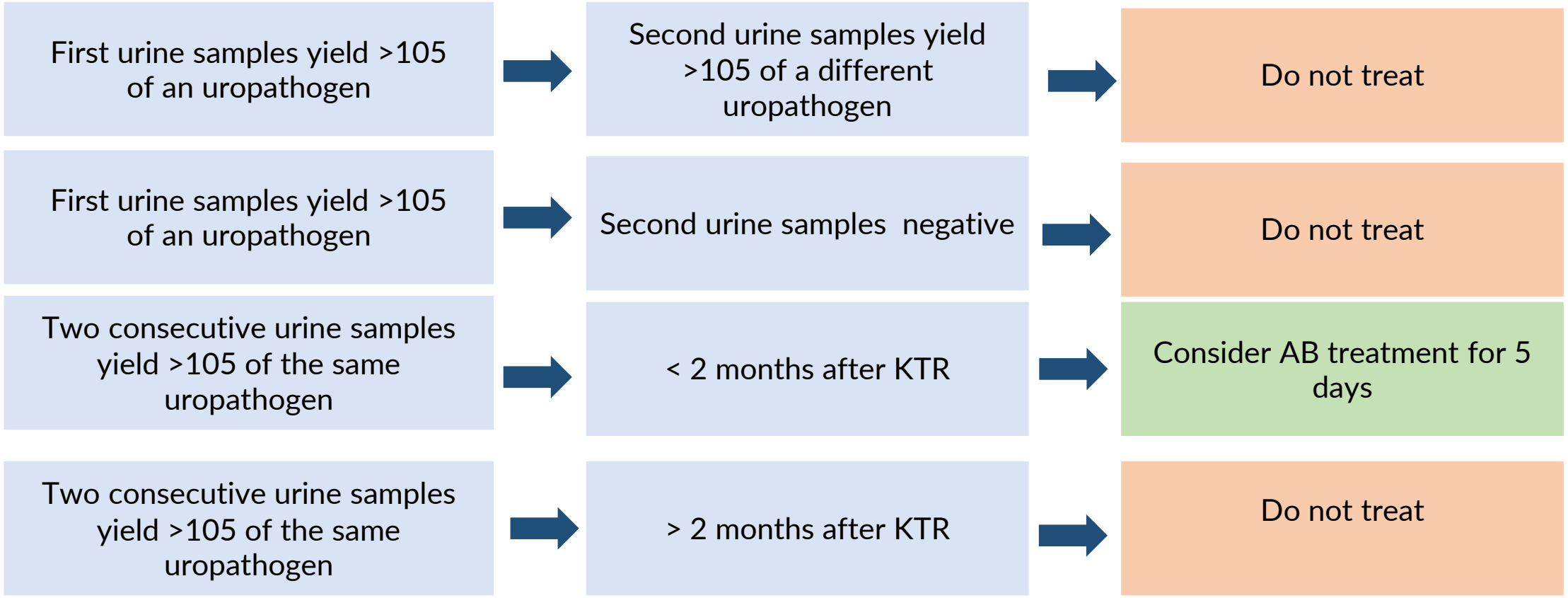
- **For patients > 1–2months after kidney transplantation** and do not have a catheter, treating ASB is not clinically beneficial. No significant effect of antibiotics on the risk of symptomatic UTI or on graft-related outcomes

- **For patients < the first 1–2 months after kidney transplantation**, the optimal management of ASB has not been established. Insufficient data to recommend or discourage the use of a screen-and-treat strategy

Mendoza et al 2022
Coussement et al.2021
Sabe et al.2019
Origüen et al.2016
Moradi et al.2005

Treatment of asymptomatic bacteriuria in KTR

two consecutive urine samples yield >105 of the same uropathogen



Treatment of asymptomatic bacteriuria in KTR

specific pathogens

2 Urine samples yield >105 of an MDR uropathogen → Do not treat

2 Urine samples yield >105 of Candida spp. → Change urinary catether

Exclude obstructing fungal balls or systemic infections → Do not treat asymptomatic candiduria **except** prior to urologic procedures or when the patient is neutropenic

Is treatment of ABU beneficial in prior to surgery?

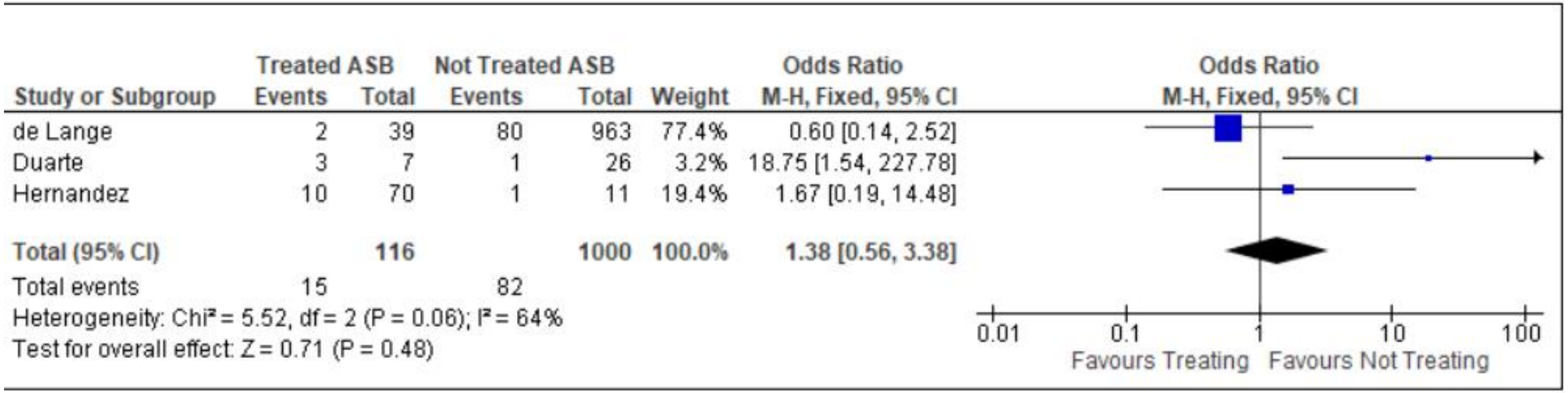
Prior to orthopaedic surgery

- Screening and treatment of bacteriuria **is not recommended** prior to orthopaedic surgery: hip arthroplasty/hemiarthroplasty or total knee arthroplasty

Sousa, R. et al Clin Infect Dis, 2014
Rodriguez-Pardo, D., *et al.* Eur J Clin Microbiol Infect Dis, 2021
Sousa, R. *et al.*. J Arthroplasty, 2019

Prior to cardiovascular surgery

- Meta-analysis
- 1.116 patients: coronary artery bypass grafting (42%), valvular replacements (51%), and thoracic aortic surgeries (7%)



Study or Subgroup	Treated ASB Events	Total	Not Treated ASB Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
de Lange	2	39	80	963	77.4%	0.60 [0.14, 2.52]
Duarte	3	7	1	26	3.2%	18.75 [1.54, 227.78]
Hernandez	10	70	1	11	19.4%	1.67 [0.19, 14.48]
Total (95% CI)		**116**		**1000**	**100.0%**	**1.38 [0.56, 3.38]**
Total events	15		82			

Heterogeneity: Chi² = 5.52, df = 2 (P = 0.06); I² = 64%
Test for overall effect: Z = 0.71 (P = 0.48)

Gomez-Ochoa, S.A., *et al.*. Braz J Cardiovasc Surg, 2018. 33: 641.

Prior to urological surgery

- Diagnostic and therapeutic procedures **not entering the urinary tract**
- Screening and treatment are not considered necessary

AP is not routinely recommended for
- urodynamic exams
- diagnostic cystoscopy
- extracorporeal shock-wave lithotripsy

- Diagnostic and therapeutic procedures **entering the urinary tract and breaching the mucosa**
- Bacteriuria is a definite risk factor

AP is recommended for
- ureteroscopy
- percutaneous nephrolithotomy
- endoscopic resection of bladder tumor
- endoscopic resection of the prostate
- prosthetic or major surgery

Marino et al. Urologia Journal 2024

Outline

- Asymptomatic bacteriuria
- **Diagnostic challanges**
- Treatment tips
- Non antibiotic strategies

Clinical Practice Guideline Definitions of UTI Syndromes

uncomplicated UTIs occur in healthy, non-pregnant women
all other UTIs fall into the category of complicated UTIs

Table 2. Clinical Practice Guideline Definitions of UTI Syndromes in Adults[a]

Defining term(s)	Proposed IDSA	Current IDSA	EAU	AUA, CUA, and SUFU
Complicated UTI and acute pyelonephritis	Any infection beyond the bladder, includes pyelonephritis, CAUTI, febrile or bacteremic patients	Urinary symptoms plus functional or structural abnormalities of the urinary tract. CVA pain and tenderness, often with fever (pyelonephritis)	Dysuria, urgency, frequency, flank pain, CVA tenderness, suprapubic pain, fever, chills, nausea, vomiting; anatomical or functional abnormalities of the urinary tract (eg, obstruction, incomplete voiding due to detrusor muscle dysfunction; presence of diabetes or immunosuppression	Anatomical or functional abnormality of the urinary tract (eg, stone disease, diverticulum, neurogenic bladder); immunocompromised host; multidrug resistant bacteria
Uncomplicated UTI	All other infections not defined as complicated	Frequency, urgency, dysuria, or suprapubic pain in a woman with a normal genitourinary tract	Dysuria, frequency and urgency and the absence of vaginal discharge; limited to nonpregnant women with no known relevant anatomical and functional abnormalities or comorbidities	Dysuria in conjunction with variable degrees of increased urinary urgency and frequency, hematuria, or new or worsening incontinence; female host; no known factors that would increase susceptibility to develop UTI

Nelson et al. JAMA Network Open. 2024;7(11)

Localised UTI (i.e., cystitis)

- Cytistis with typical signs/symptoms (e.g. frequency[1], urgency[2], suprapubic pain[3])
- No signs/symptoms of systemic infection
- Applies to all sexes[4]
- Risk factors may be present and should be addressed

Systemic UTI

- UTI with signs/symptoms of systemic infection (e.g. fever[5], chills[6])
- May also include typical local symptoms (e.g. for pyelonephritis[7] or prostatitis[8])
- Risk factors may be present and should be addressed

Localised UTI[1]
Dysuria (pain, burning, stinging)
Urgency
Frequency
Incontinence
Urethral purulence
Pressure or cramping in the lower abdomen

Systemic UTI[1,2]
Fever or hypothermia
Rigors, shaking chills
Delirium
Hypotension
Tachycardia
Costovertebral angle pain/tenderness

may necessitate blood sampling, imaging, intravenous antimicrobial treatment and hospitalisation

EAU Gudelines 2025

Risk factors that may predispose patients to a severe clinical course or treatment failure

- Male sex > prostatic involvement
- Female sex > pregnancy and pelvic organ prolapse
- Infants
- Immunocompromised state
- Geriatric or frail patients
- Neurourological patients
- Indwelling urinary catheters
- Recent instrumentation
- Post void residual volume
- Anatomic or functional abnormalities of the urinary tract
- Stones obstruction
- Antibiotic use in the past
- MDR organism

Table 3. Diagnostic Testing Performance for Urinary Tract Infections[a]

Test results	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Dipstick				
Positive leukocyte esterase	72-97	41-86	43-56	82-91
Positive nitrite	19-48	92-100	50-83	70-88

absence of pyuria can help rule out infection in most patient populations, but **the positive predictive value of pyuria for diagnosing infection is exceedingly low**

Nelson et al. JAMA Network Open. 2024;7(11)

Table 3. Diagnostic Testing Performance for Urinary Tract Infections[a]

Test results	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Imaging				
Ultrasonography	74.3	56.7	NA	NA
Computerized tomography	81-84	87.5	NA	NA
Magnetic resonance imaging	100	81.8	NA	NA

- **Ultrasonography:**
  - safer and more accessible
  - limited accuracy
  - preferrable first imaging modality in younger patients, pregnancy, and/or KTR
- **CT imaging**
  - if symptoms persist or worsen beyond 72 hours
  - if there are concerns for kidney calculi, kidney abscess, or an alternative focus of infection
- **Magnetic resonance with or without contrast**
  - is less effective for early disease detection and stone visualization
  - KTR advantage in identifying graft infection

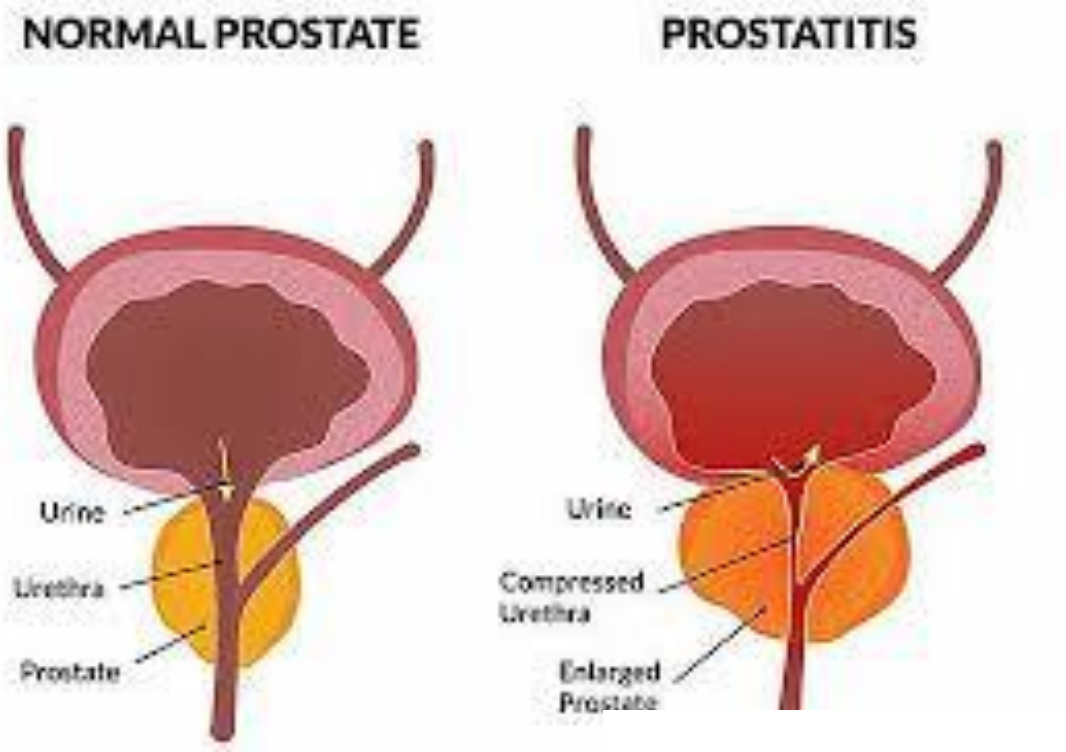
Nelson et al. JAMA Network Open. 2024;7(11)

Outline

- Asymptomatic bacteriuria
- Diagnostic challanges
- **Treatment tips**
- Non antibiotic strategies

Difficult to treat niches

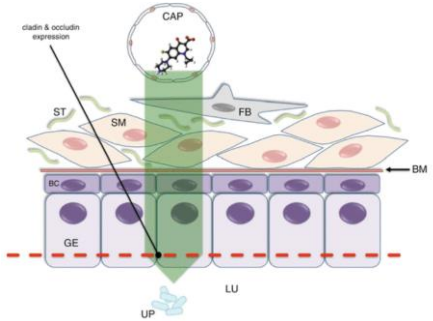
- Recurrent infection after completing therapy is typically caused by the same organism responsible for the original infection

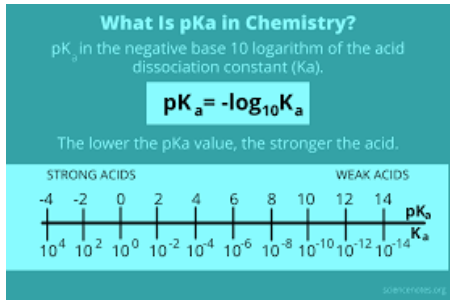


Lam et al. CMI 29 (2023)

Difficult to treat niches

- **Blood prostate barrier** between the microcirculation and the prostate restricts drug penetration:
  - nonprotein- bound, lipophilic antibiotics achieve therapeutic levels within the gland through passive diffusion





- **low pH of prostatic fluid** with achievement of high concentrations of antibiotics with alkaline pKas in prostatic tissue
  - fluoroquinolones and sulfonamides

Holt et al. Am Fam Physician 2016; 93:290–296.

Treatment of Bacterial Prostatitis: Clinico-Pharmacological Considerations

quinolones

sulfonamides

tetracyclines

tobramycin

netilmicin

fosfomicin

nitrofurantoin

macrolids

betalactam drugs

Generally penetrate poorly into prostatic fluid due to their low pKa and poor lipid solubility, except for some cephalosporins

Burillo et al. Curr Opin Infect Dis 2024

What Is the Appropriate Duration of Treatment? Shorter is better

Acute Cystitis

- Nitrofurantoin: 5 days
- TMP/SMX: 3 days
- Fluoroquinolones: 3 days
- Oral fosfomycin: single dose

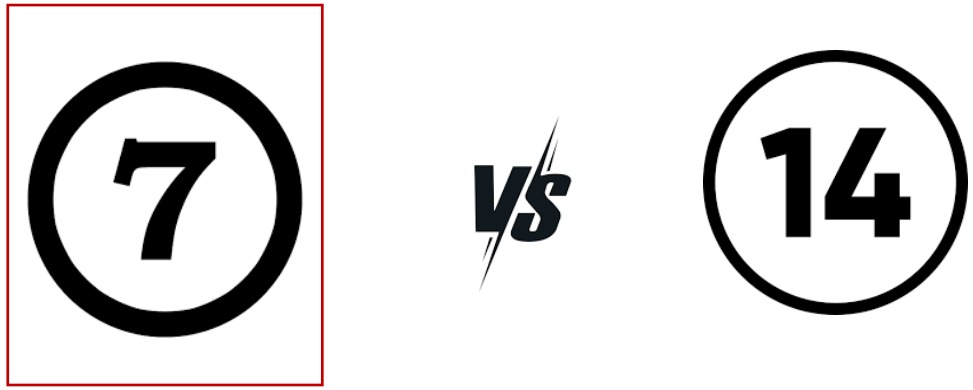
Acute Pyelonephritis and/or Febrile UTI

- Fluoroquinolones: 5 to 7 days
- Dose-optimized β-lactams: 7 days

Nelson et al. JAMA Network Open. 2024;7(11)

What is Appropriate Duration of Treatment for Gram-Negative Bacteremia From a Urinary Source?

- Multiple RCTs comprised patients with GNB bacteremia from predominantly urinary sources
- Noninferiority of 7 days compared with 14 total days of treatment for clinical cure, clinical failure, relapse, and all-cause mortality IF source control is provided
- No specific class of medications can be recommended



Nelson et al. JAMA Network Open. 2024;7(11)

Short versus prolonged antibiotic treatment for complicated UTI after kidney transplantation

- Retrospective study n= 214 kidney transplant recipients
- Duration of treatment : **short (6–10 days) and prolonged (11–21 days)**
- Composite outcome: 30-day readmission/mortality or recurrent UTI at 6 months

	Short treatment *N* = 115	Long treatment *N* = 99	All cohort *N* = 214	*P*-value
Primary outcomes				
Composite outcome	33 (28.7%)	30 (30.3%)	63 (29.4%)	0.797
Relapse of UTI	19 (16.5%)	21 (21.2%)	40 (18.7%)	0.38
Secondary outcomes				
30-day mortality	2 (1.7%)	0	2 (0.9%)	0.500
Readmission 30 days	31 (27%)	30 (30.3%)	61 (28.5%)	0.589
Readmission 90 days	42 (36.5%)	44 (44.4%)	86 (40.2%)	0.239
Days of hospital stay- all cohort, (median, 25–75%)	9 (7–15)	10 (8–18)	10 (8–16)	0.103
Days of hospital stay (alive at day 30), (median, 25–75%)	9 (7–15)	10 (8–18)	10 (8–16)	0.114
Bacteraemia within 30 days	20 (17.4%)	24 (24.2%)	44 (20.6%)	0.216
MDR development within 180 days	26/113 (23%)	23/98 (23.5%)	49/211 (23.2%)	0.937
Creatinine 30 days, *N* = 153 (median, 25–75%)	1.5 (1.01–2.01)	1.47 (1.11–2.12)	1.49 (1.09–2.05)	0.630
Creatinine 90 days, *N* = 147 (median, 25–75%)	1.41 (0.95–2.04)	1.34 (1.01–1.81)	1.41 (0.99–1.87)	0.779

MDR, multidrug resistance.

Avni-Hachman et al. Transpl Int 2021 Dec;34(12):2686-2695

Outline

- Asymptomatic bacteriuria
- Diagnostic challanges
- Treatment tips
- **Non antibiotic strategies**

Ibuprofen versus fosfomycin for uncomplicated urinary tract infection in women: randomised controlled trial

- 42 German general practices . women aged 18-65 with mild to moderate UTI
- randomly assigned to treatment with a single dose of fosfomycin 3 g (n=243) or ibuprofen 3×400 mg (n=241) for 3 days

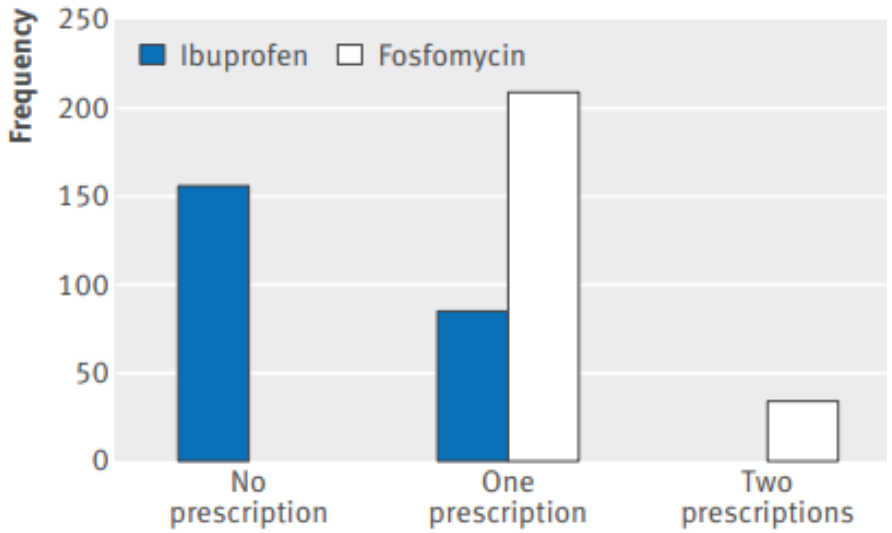


Fig 2 | Total number of antibiotic prescriptions by randomisation group on days 0-28 (range 0-2, intention to treat population)

ibuprofen group reduced the overall number of antibiotic treatment by 67% but had a significantly higher total burden of symptoms, more had pyelonephritis

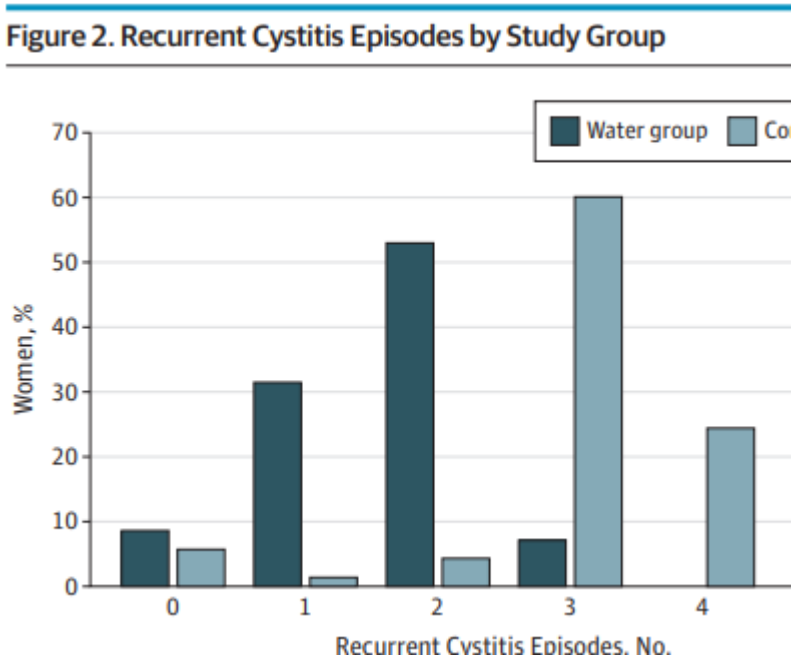
This treatment regimen can be discussed with women who are willing to avoid antibiotics or to accept a delayed prescription

Gagyor et al. : BMJ 2015

Can Water Intake Play a Role in the Prevention of UTIs?

Effect of Increased Daily Water Intake in Premenopausal Women With Recurrent Urinary Tract Infections A Randomized Clinical Trial

- 163 healthy women with recurrent cystitis (3 episodes in past year)
- Participants were randomly assigned to drink 1.5 L of water daily (water group) or no additional fluids (control group) for 12 months



number of cystitis episodes
1.7 (95% CI, 1.5-1.8) in the water group compared with
3.2 (95% CI, 3.0-3.4) in the control group
(95% CI, 1.2-1.8; P < .001)

Hooton et al. JAMA Intern Med. 2018;1

Conclusions

- Symptom-based testing is key to ensure appropriate urine culture testing and proper diagnosis of UTI

- Research gaps for standard definitions, novel diagnostic methods, treatment durations and antimicrobial stewardship strategies

Grazie mille

Rete Nazionale Trapianti

UNIVERSITÀ DEGLI STUDI DELL'INSUBRIA