



ΕΘΝΙΚΟ ΚΑΙ ΚΑΠΟΔΙΣΤΡΙΑΚΟ ΠΑΝΕΠΙΣΤΗΜΙΟ ΑΘΗΝΩΝ

ΙΑΤΡΙΚΗ ΣΧΟΛΗ

Α' ΠΑΘΟΛΟΓΙΚΗ ΚΛΙΝΙΚΗ

Διευθυντής: Καθηγήτρια Ε.Ι. Γκόγκα

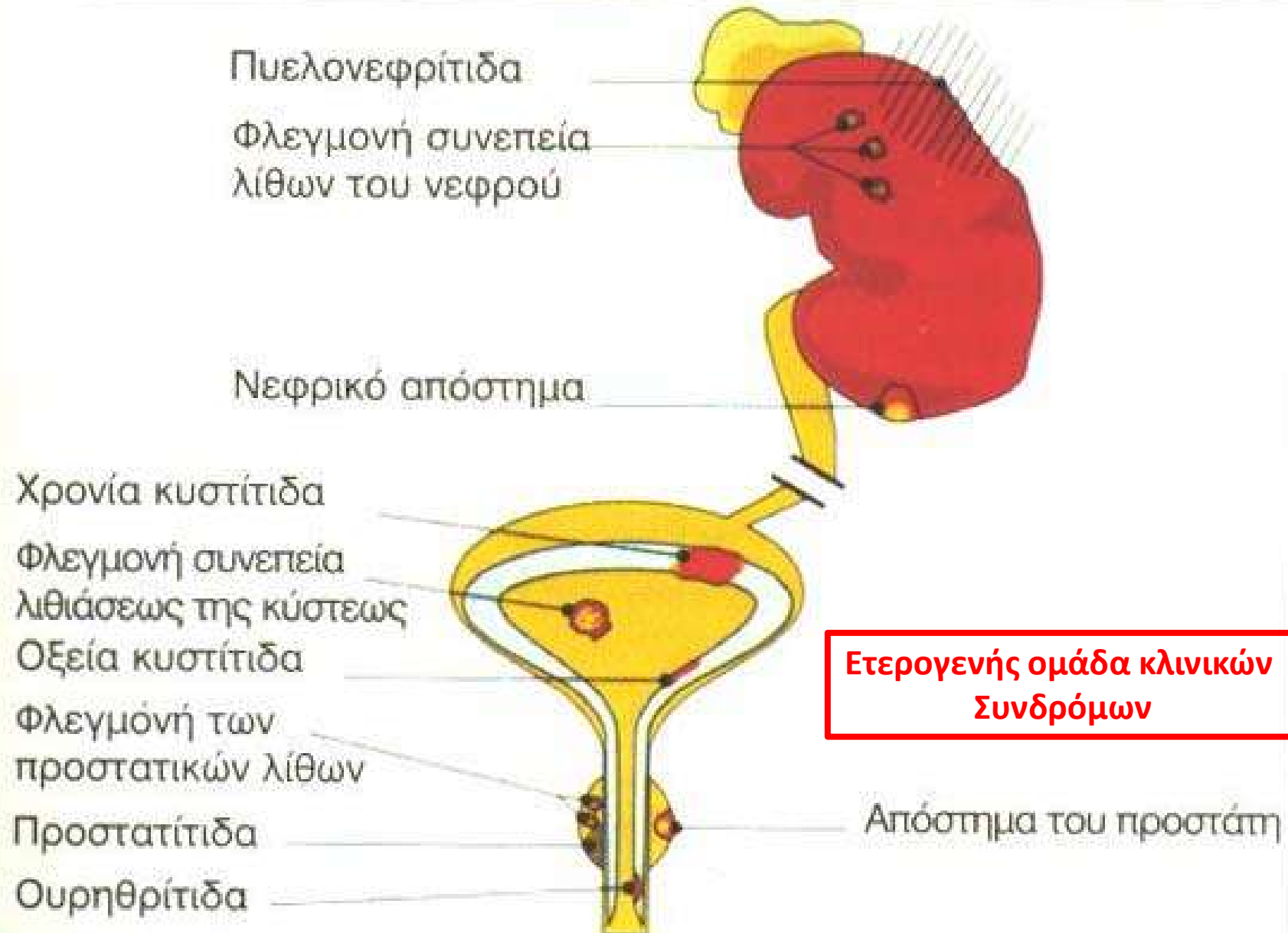


Λοιμώξεις ουροποιητικού

Ειρήνη Κουρμπέτη

Διευθύντρια ΕΣΥ

Σημεία του ουρογεννητικού που συνήθως σχετίζονται με λοίμωξη



Our approach to categorizing UTI in adults and adolescents

Acute simple cystitis*	<ul style="list-style-type: none">▪ Acute UTI that is presumed to be confined to the bladder▪ There are no signs or symptoms that suggest an upper tract or systemic infection (refer to below)
Acute complicated UTI	<ul style="list-style-type: none">▪ Acute UTI accompanied by signs or symptoms that suggest extension of infection beyond the bladder:<ul style="list-style-type: none">• Fever ($>99.9^{\circ}\text{F}/37.7^{\circ}\text{C}$)[¶]• Chills, rigors, significant fatigue or malaise beyond baseline, or other features of systemic illness• Flank pain• Costovertebral angle tenderness• Pelvic or perineal pain in men
Special populations with unique management considerations	<ul style="list-style-type: none">▪ Pregnant women▪ Renal transplant recipients

We categorize UTI as either acute simple cystitis or acute complicated UTI based on the extent and severity of infection. This categorization informs management and differs somewhat from other conventions. Specifically, cystitis or pyelonephritis in a nonpregnant premenopausal woman without underlying urologic abnormalities has traditionally been termed acute uncomplicated UTI, and complicated UTI has been defined for the purposes of treatment trials

Our approach to categorizing UTI in adults and adolescents

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Categorization based on the extent and the severity of infection

Bilsen *Open Forum Infect Dis* 2023; 10: ofad332

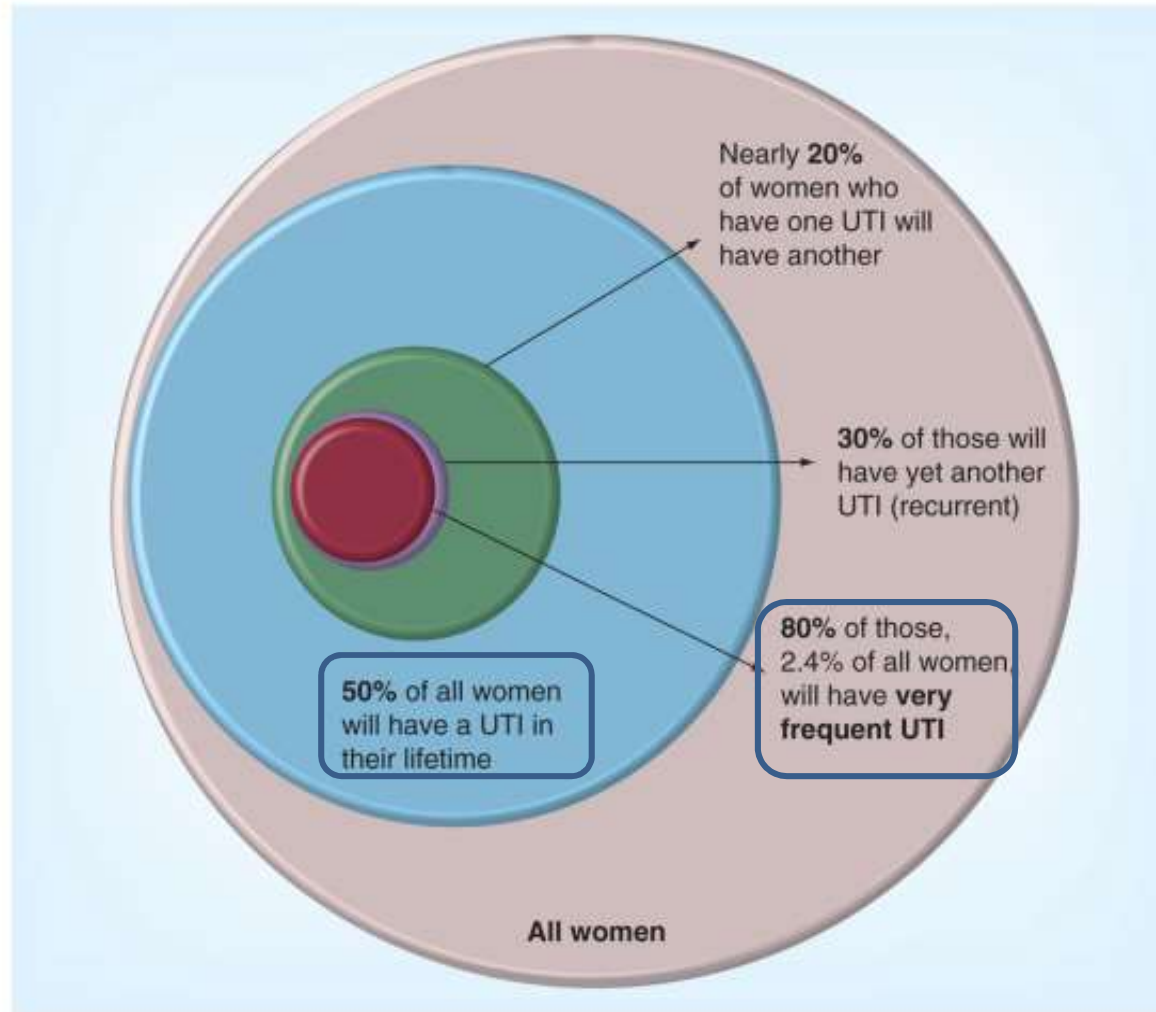
	<ul style="list-style-type: none">• Pelvic or perineal pain in men
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Cystitis is the most common bacterial infection in the ambulatory setting



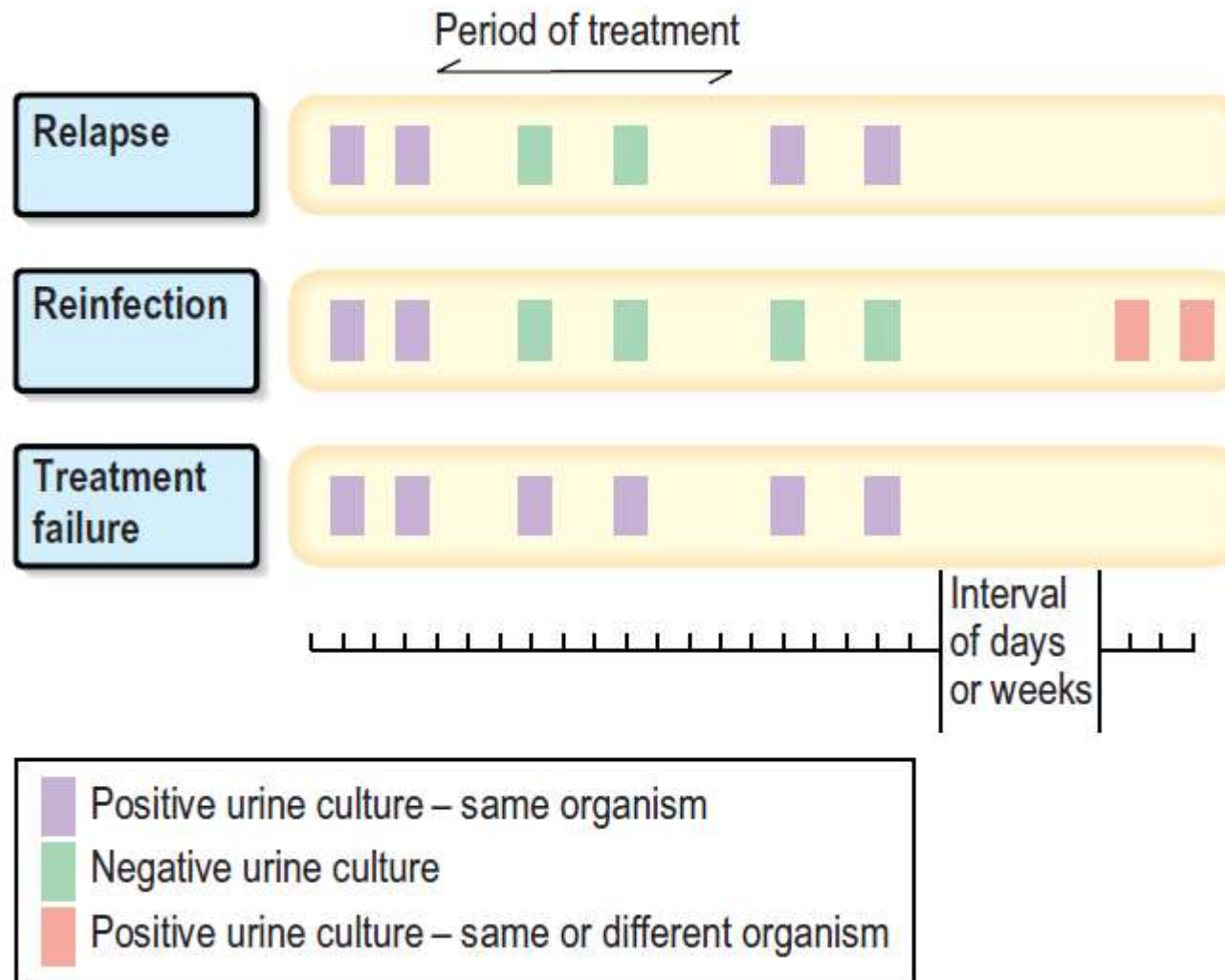
The burden of disease



- 11M office visits
- 1.7M ER visits
- \$3.5 BN cost
- 1:28 ratio pyelonephritis to cystitis
- 25 cases/10000

- 50% of the women
- 2.4% have very frequent UTIs

12% of men



Ιστορικό (I)

- Γυναίκα, 23 ετών, φοιτήτρια
- Δυσουρία, συχνουρία, έπειξη προς ούρηση, επεισόδιο μακροσκοπικής αιματουρίας
- Δύο προηγούμενες ουρολοιμώξεις τον τελευταίο χρόνο που είχαν θεραπευθεί με τριήμερα σχήματα κοτριμοξαζόλης. Τελευταίο επεισόδιο πριν 4 μήνες.
- Προηγούμενος U/S έλεγχος ουροποιητικού φυσιολογικός

Πώς γίνεται η σωστή λήψη των ούρων;

- Τοπική απολύμανση με σαπούνι και νερό Σκούπισμα με αποστειρωμένη γάζα για να αποφευχθεί ανάμιξη του αντισηπτικού με τα ούρα.
- Η λήψη από το μέσο της ούρησης
- Τα ούρα έξω από το ψυγείο διατηρούνται μόνο μία ώρα. Μέσα στο ψυγείο 24 ώρες.

Πότε μια καλλιέργεια είναι θετική;

Table 53.6 Value of quantitative urine culture in diagnosis of urinary tract infection with Gram-negative bacilli in women

	Number of specimens	Organisms/ml of urine	Sensitivity (%)	Specificity (%)
Asymptomatic women	Two	$>10^5$	>95	>80
Symptomatic women with pyuria	One	$>10^5$	51	99
	One	$>10^3$	80	90
	One	$>10^2$	95	85

Table 1. Differential Diagnosis of Acute Cystitis in Women

Condition	Pathogens	History	Symptoms
Vaginitis	<i>Candida</i> , <i>Trichomonas vaginalis</i> , <i>Bacteroides</i> species, <i>Gardnerella vaginalis</i>	Possibly new sex partner or unprotected sexual activity; history of vaginitis	Vaginal discharge, odor, or itching; "external" dysuria (from urine coming into contact with inflamed and irritated vulvar epithelial surfaces)
Urethritis	<i>Chlamydia trachomatis</i> , <i>Neisseria gonorrhoeae</i> , or herpes simplex virus	New sex partner, unprotected sexual activity, history of sexually transmitted disease or recurrent genital herpes simplex virus	Gradual onset of symptoms (<i>Chlamydia</i>) ± vaginal discharge; ± urinary frequency or urgency
Irritation	None	No unusual sexual exposure; possible chemical or allergen exposures (e.g., douches, bath products, feminine hygiene products, spermicides)	Vaginal itching or discharge; usually a diagnosis of exclusion, unless withdrawal of a suspected offending substance leads to resolution of symptoms
<u>Pyelonephritis</u>	Same as acute cystitis	Previous urinary tract infection (pyelonephritis or cystitis)	Constitutional symptoms (fever, malaise, sweats, headache), gastrointestinal symptoms (anorexia, nausea, vomiting, abdominal pain), local renal symptoms (back, flank, or loin pain), ± voiding symptoms (as in cystitis)

Δυσουρία

■ Κυστίτιδα

- *E.coli*
- *Proteus* spp.
- *Klebsiella* spp.
- *Staphylococcus saprophyticus*

■ Ουρηθρίτιδα

- *Chlamydia trachomatis*
- *Neisseria gonorrhoeae*
- *Herpes simplex virus*

■ Κολπίτιδα

- *Candida* spp.
- *Trichomonas vaginalis*

Acute uncomplicated cystitis: from surveillance data to a rationale for empirical treatment

Uropathogen distribution per type of infection, age group and gender.

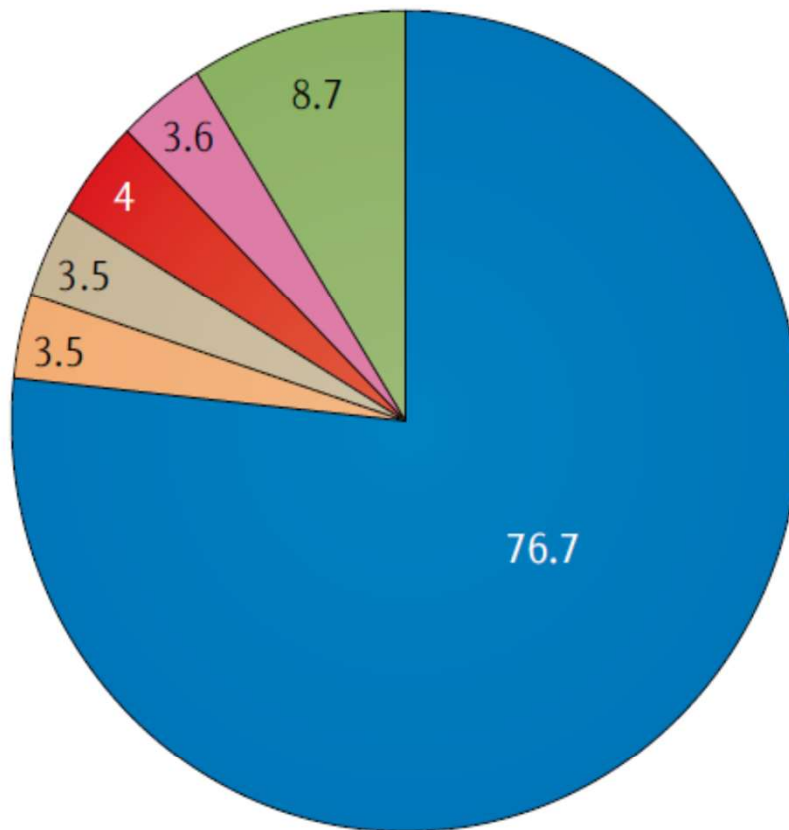
Uropathogen	Uropathogen distribution (%)						Total (%)
	Age		Gender		Type of infection		
	15-65 years	>65 years	Male	Female	AUC	Complicated UTI	
<i>Escherichia coli</i>	85.7	74.0	75.0	84.3	85.4 [*]	79.9 [*]	83.0
Non- <i>E. coli</i>	14.3 ^{**}	26.0 ^{**}	25.0 ^{**}	15.7 ^{**}	14.6	20.1	17.0
<i>Proteus</i> spp.	6.5	9.7	7.3	7.5	7.4	8.0	7.4
<i>Klebsiella</i> spp.	3.1	5.3	3.1	3.6	3.0	2.9	3.6
<i>Enterococcus</i> spp.	1.6	3.3	5.9	1.3	1.2	3.1	2.0
<i>Pseudomonas</i> spp.	0.9	4.0	6.3	0.8	0.3	3.1	1.7
<i>Staphylococcus</i> spp.	0.9	1.3	1.0	1.0	1.1	1.3	1.0
<i>Citrobacter</i> spp.	0.5	0.9	0.7	0.5	0.6	0.8	0.6
<i>Enterobacter</i> spp.	0.4	1.1	—	0.7	0.7	0.4	0.6
Other	0.3	0.4	0.7	0.2	0.2	0.4	0.3

AUC, acute uncomplicated cystitis; UTI, urinary tract infection.

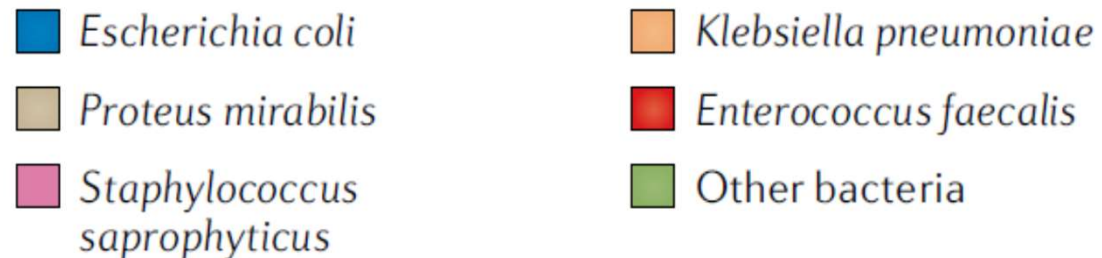
^{*} $P=0.042$.

^{**} $P<0.001$.

Uncomplicated cystitis



- *S saprophyticus* is a common cause of cystitis in young women
- In non-pregnant women other Gram (+) represent contamination
- Resistance to *E.coli* is a major issue
- Even in acute uncomplicated cystitis there is a risk for MDR pathogens



Risk factors for multidrug-resistant gram-negative urinary tract infections

Suspect multidrug-resistant gram-negative urinary tract infection in patients with a history of any of the following in the prior three months:

- A multidrug-resistant gram-negative urinary isolate or a fluoroquinolone-resistant *Pseudomonas aeruginosa* isolate
- Inpatient stay at a health care facility (eg, hospital, nursing home, long-term acute care facility)
- Use of a fluoroquinolone, trimethoprim-sulfamethoxazole, or broad-spectrum beta-lactam (eg, third or later generation cephalosporin)*
- Travel to parts of the world with high rates of multidrug-resistant organisms[¶]

NOTE: The predictive value of these risk factors for multidrug-resistant gram-negative urinary tract infections has not been systematically evaluated. In particular, the time interval since these exposures is not well validated. The threshold for empirically covering a multidrug-resistant infection varies with the severity of infection, with a lower threshold warranted for more severe disease.

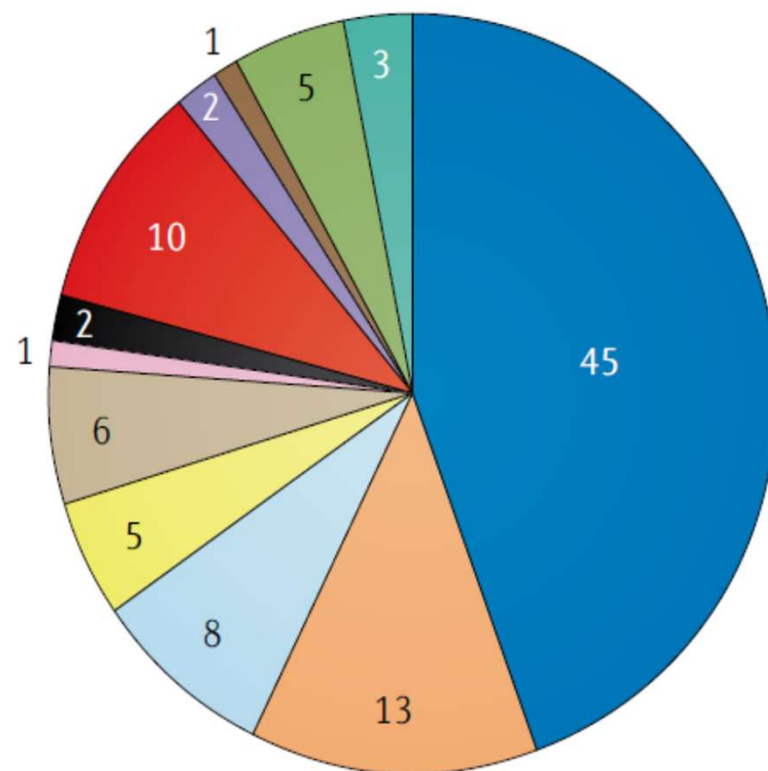
Multidrug resistance refers to nonsusceptibility to at least one agent in three or more antibiotic classes. This includes isolates that produce an extended-spectrum beta-lactamase (ESBL).


Συμπτώματα UTI


Table 1 | Classical symptoms of different UTI entities


Acronym	Clinical diagnosis	Clinical symptoms	Severity grade
CY-1	Cystitis	Dysuria, frequency, urgency, suprapubic pain; sometimes unspecific symptoms	1
PN-2	Mild to moderate pyelonephritis	Fever, flank pain ^a , CVA tenderness ^a ; sometimes unspecific symptoms with or without symptoms of cystitis	2
PN-3	Severe pyelonephritis	As for PN-2, but, in addition, nausea and vomiting with or without symptoms of cystitis	3
US-4 ^b	SIRS	Temperature >38 °C or <36 °C, heart rate >90 beats/min, respiratory rate >20 breaths/min or PaCO ₂ <32 mm Hg (<4.3 kPa), WBCs >12,000 cells/mm ³ or <4,000 cells/mm ³ or ≤10% immature (band) forms with or without symptoms of cystitis or pyelonephritis (>2 SIRS criteria must be met for US-4 diagnosis)	4
US-5 ^b	Severe urosepsis	As for US-4, as well as organ dysfunction, hypoperfusion or hypotension; hypoperfusion and perfusion abnormalities may include but are not limited to lactic acidosis, oliguria or an acute change in mental status	5
US-6 ^b	Uroseptic shock	As for US-4 or US-5, as well as hypotension despite adequate fluid resuscitation and the presence of perfusion abnormalities that may include, but are not limited to, lactic acidosis, oliguria or an acute change in mental status; patients who are on inotropic or vasopressor agents may not be hypotensive when perfusion abnormalities are measured	6


Pyelonephritis





 *Escherichia coli*


 *Pseudomonas aeruginosa*


 *Proteus* spp.


 *Citrobacter* spp.


 *Staphylococcus aureus*

 Other bacteria

 *Klebsiella* spp.

 *Enterobacter* spp.

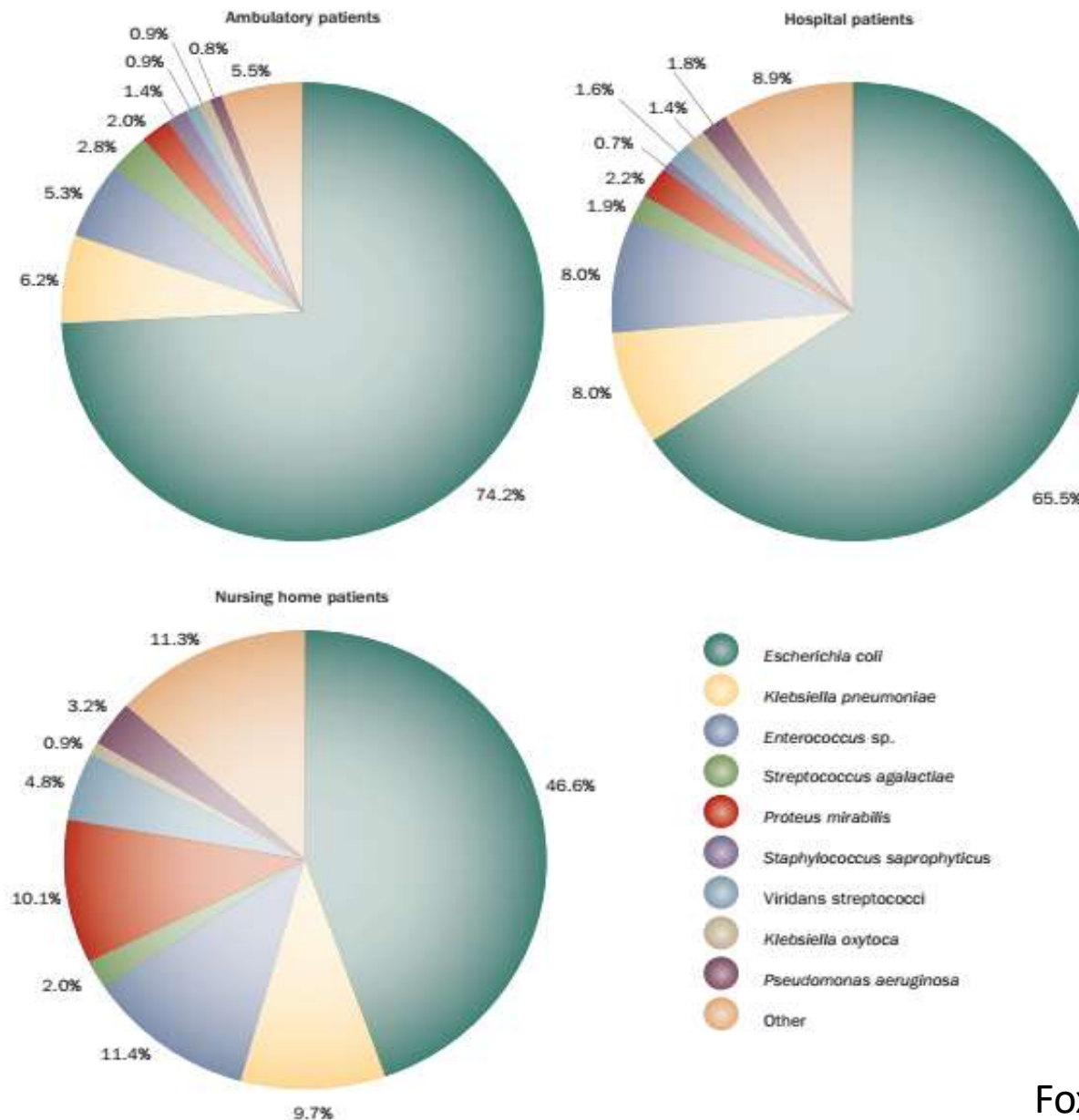
 *Acinetobacter* spp.

 *Enterococcus* spp.

 CoNS

 Fungi

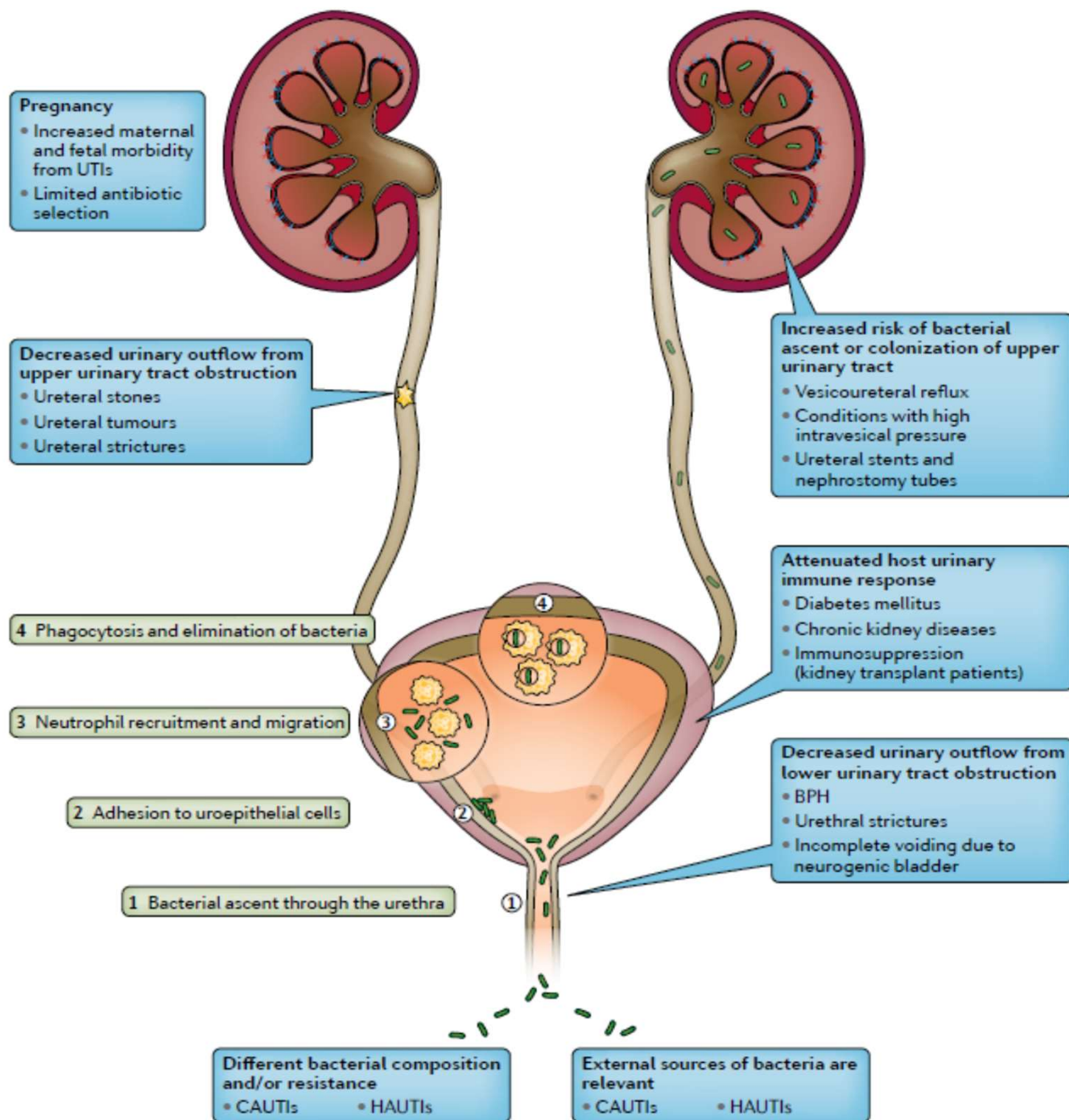
Bacteriology according to the population

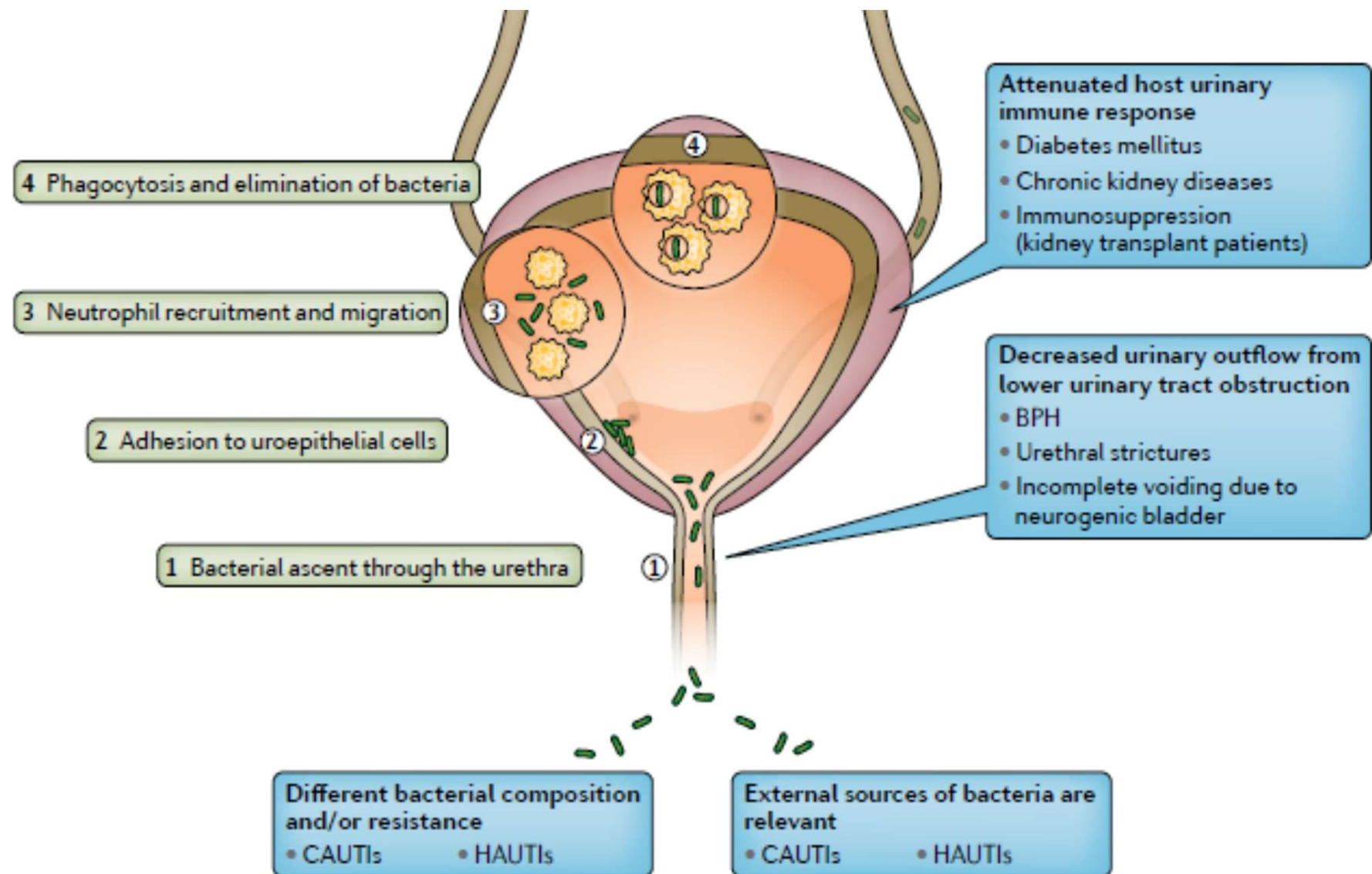


Think of the setting!

		<ul style="list-style-type: none"> Pyuria and bacteriuria are typically absent on urine studies of a properly collected specimen
	Pelvic inflammatory disease	<ul style="list-style-type: none"> Can be associated with dysuria Predominant features include lower abdominal or pelvic pain Suggested by cervical motion, uterine, and/or adnexal tenderness on pelvic examination; mucopurulent endocervical discharge may be present Bacteriuria is typically absent on urinalysis or urine culture
	Bacterial prostatitis	<ul style="list-style-type: none"> Presents with same symptoms as cystitis Acute prostatitis is associated with fevers and signs of systemic illness Also associated with pelvic or perineal pain Digital rectal examination demonstrates tender prostate Pyuria and bacteriuria are commonly present in urine studies
	Benign prostatic hyperplasia	<ul style="list-style-type: none"> Can be associated with lower urinary tract storage symptoms (frequency, urgency, nocturia, incontinence) and voiding symptoms (slow stream, hesitancy, terminal dribbling) Digital rectal examination demonstrates non-tender, enlarged prostate Pyuria and bacteriuria are typically absent on urine studies
Pyelonephritis symptoms: <ul style="list-style-type: none"> Flank pain Fever Nausea/vomiting Costovertebral angle tenderness 	Nephrolithiasis	<ul style="list-style-type: none"> Kidney and upper ureteral stones can cause flank pain and associated nausea/vomiting Can occur concomitantly with UTI Fever is uncommon without superimposed infection Pyuria can be present on urinalysis Bacteriuria is typically absent on urinalysis or urine culture without superimposed infection
	Renal infarct	<ul style="list-style-type: none"> Can present with acute flank or abdominal pain and associated nausea/vomiting Fever is less common A history of atrial fibrillation increases likelihood of renal infarct Costovertebral angle tenderness is uncommon Pyuria and bacteriuria are typically absent on urine studies
	Herpes zoster	<ul style="list-style-type: none"> If affecting lower thoracic/upper lumbar dermatomes, can present with flank pain that precedes typical vesicular lesions by a few days, although lesions are not always seen Pyuria and bacteriuria are typically absent on urine studies
	Intraabdominal processes: <ul style="list-style-type: none"> Appendicitis Cholecystitis/biliary colic Pancreatitis 	<ul style="list-style-type: none"> Can occasionally be associated with flank pain in addition to generalized abdominal pain, nausea, and vomiting, with or without fevers Pyuria and bacteriuria are typically absent on urine studies
Signs of systemic infection (eg, fever) in the setting of pyuria and bacteriuria	Other common infection with coincident bacteriuria: <ul style="list-style-type: none"> Upper or lower respiratory tract infection (including influenza) Skin/soft tissue infection Intraabdominal infection Primary bloodstream or intravascular-catheter-associated infection 	<ul style="list-style-type: none"> In the absence of symptoms localized to the urinary tract, the possibility of other infections should be considered before attributing pyuria and bacteriuria to UTI

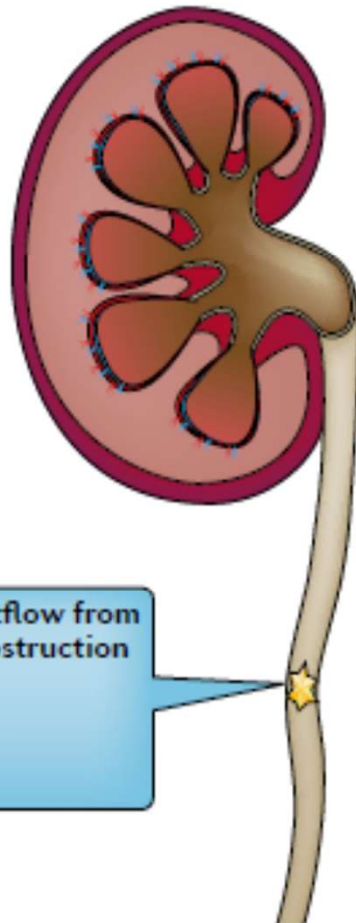
Copyrights Patients with urinary tract infection almost always have pyuria and bacteriuria on urine studies. Their absence should raise suspicion for other conditions.





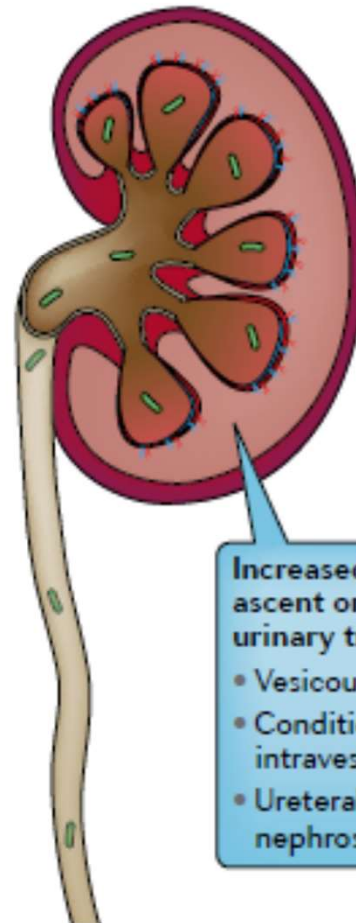
Pregnancy

- Increased maternal and fetal morbidity from UTIs
- Limited antibiotic selection



Decreased urinary outflow from upper urinary tract obstruction

- Ureteral stones
- Ureteral tumours
- Ureteral strictures



Increased risk of bacterial ascent or colonization of upper urinary tract

- Vesicoureteral reflux
- Conditions with high intravesical pressure
- Ureteral stents and nephrostomy tubes

Lungs
Bronchopneumonia
Smoking
Acute exacerbations of chronic bronchitis
Intrinsic airway disorders:
Bronchiectasis, foreign body, bronchial stenosis, bronchomalacia, tracheobronchial fistula
Recurrent aspiration (alcohol/drug use, seizure disorder)
Esophageal disease (gastroesophageal reflux, Zenker's diverticulum, achalasia)
Bronchial obstruction (extrinsic versus intrinsic obstruction)
Unrecognized cystic fibrosis
Unrecognized ciliary dyskinesia
Genitourinary tract
Cystitis
Urinary stasis
Incomplete bladder emptying (bladder outlet obstruction, bladder atony/denervation)
Compromised perineal hygiene (overactive bladder/urinary incontinence)
Diaphragm use
Prostatic infection
Instrumentation (especially chronic urinary catheter)
Pyelonephritis
All of the conditions that predispose to cystitis plus:
Renal calculi
Ureteral obstruction (stone, stricture, malignancy)
Ureteral reflux
Skin
Cellulitis
Recurrent trauma (eg, shaving legs, sports-related abrasions)
Dermatophyte infection
Lymphedema
Postoperative lymphatic dysfunction (groin/axillary exploration, lymphadenectomy)
Venous insufficiency/vein harvesting for coronary artery bypass grafting (CABG)
Chronic edema (congestive heart failure, hepatic insufficiency, nephrotic syndrome)
Prior cellulitis (lymphatic scarring)
Obesity
Filariasis
Poor hygiene
Abscess
<i>Staphylococcus aureus</i> carriage (methicillin-sensitive or methicillin-resistant), especially with recurrent trauma
Autoinoculation (subcutaneous drug injection or "skin popping," factitious)
Crohn disease
Hidradenitis suppurative (axillary, groin, perianal)
Retained foreign body
Central nervous system
Meningitis

- Stasis
- Hygiene
- Contraception
- Instrumentation
- Obstruction
- Reflux

Risk Factors Associated with Acute Pyelonephritis in Healthy Women

Delia Scholes, PhD, Thomas M. Hooton, MD, Pacita L. Roberts, MS, Kalpana Gupta, MD, MPH, Ann E. Stapleton, MD, and Walter E. Stamm, MD

From Group Health Cooperative and University of Washington, Seattle, Washington

Context

Little information is available about risk factors for pyelonephritis among healthy, community-dwelling women.

Contribution

In a population-based case-control study of women with pyelonephritis 18 to 49 years of age, intercourse history variables, including frequency, new sexual partners, and spermicide use, were strongly associated with pyelonephritis. Personal and family histories of urinary tract infection, presence of diabetes, and stress incontinence were also associated with pyelonephritis on multivariable analysis. *Escherichia coli* was the predominant infecting organism.

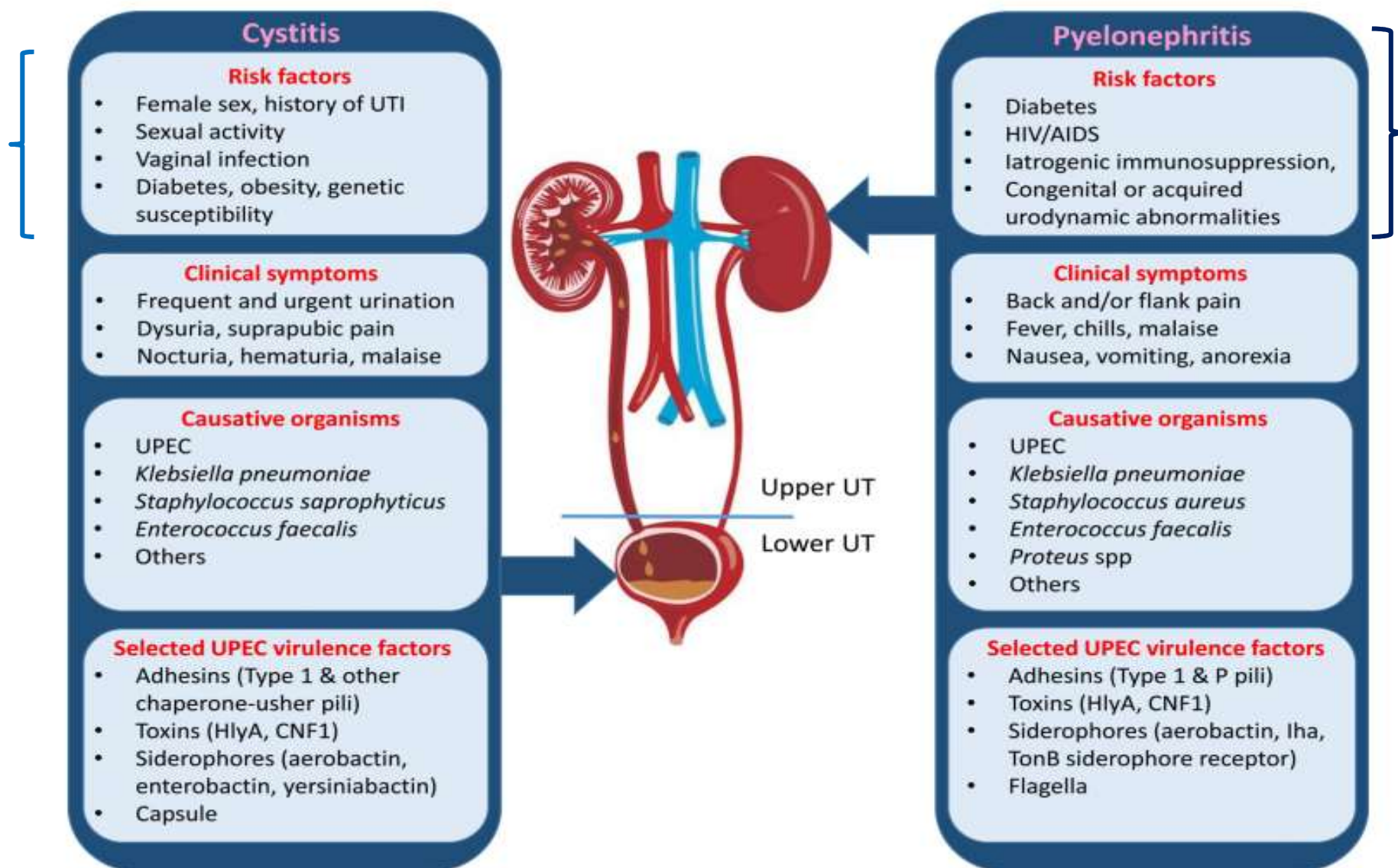
Implications

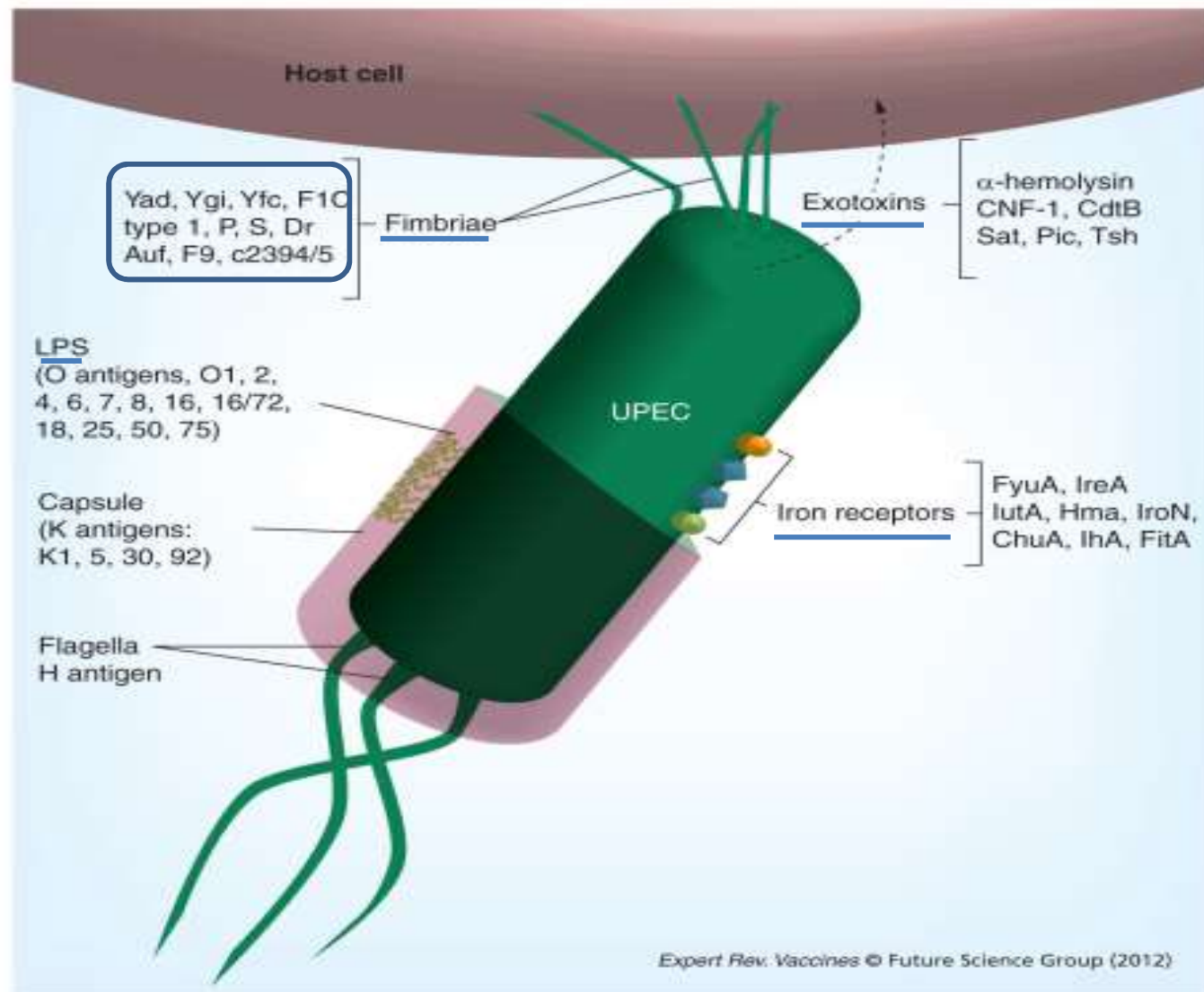
Risk factors for pyelonephritis were similar to those for acute and recurrent cystitis and asymptomatic bacteriuria, supporting the concept that pyelonephritis is usually caused by the ascent of organisms from the bladder.

KEY CLINICAL POINTS

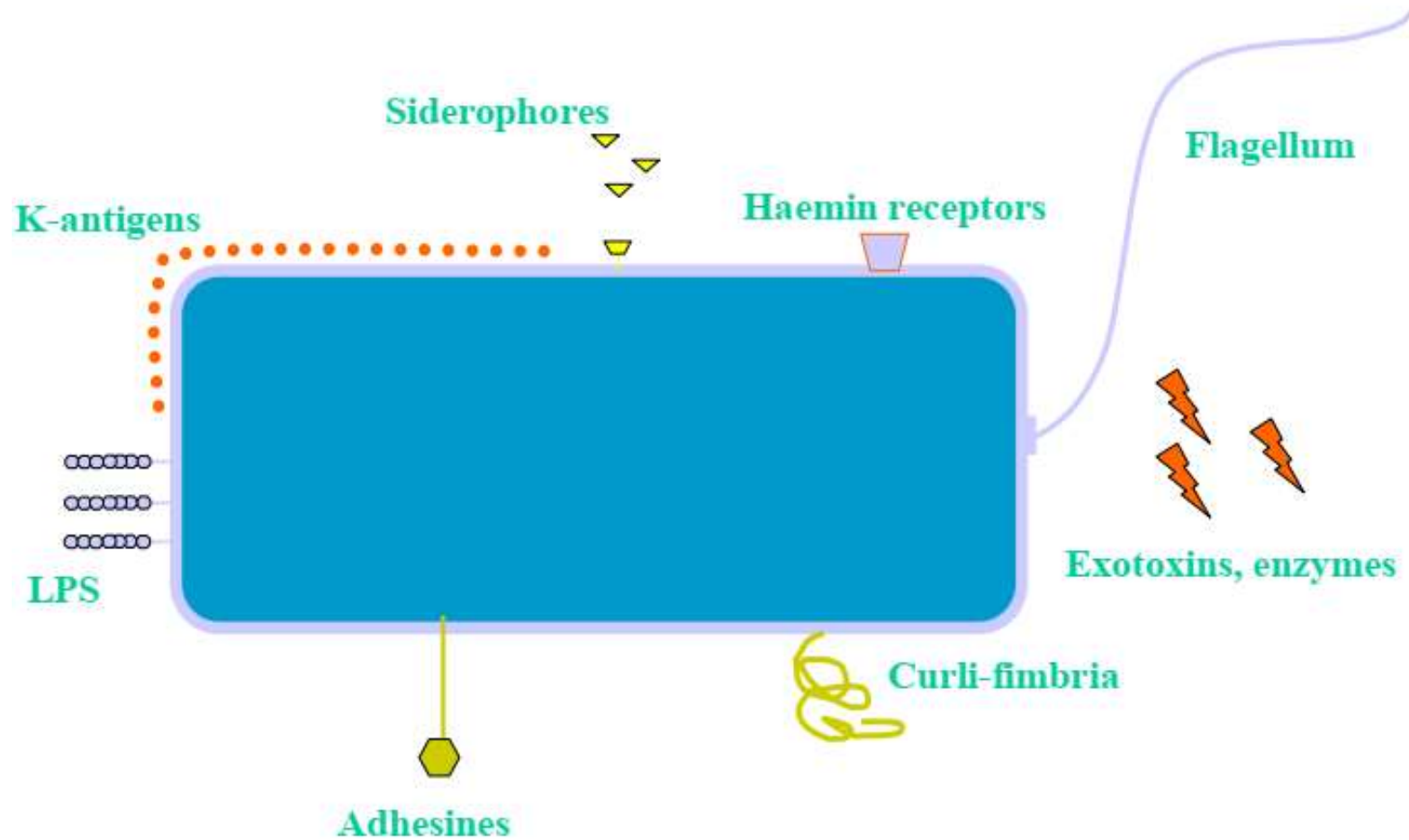
ACUTE UNCOMPLICATED CYSTITIS AND PYELONEPHRITIS

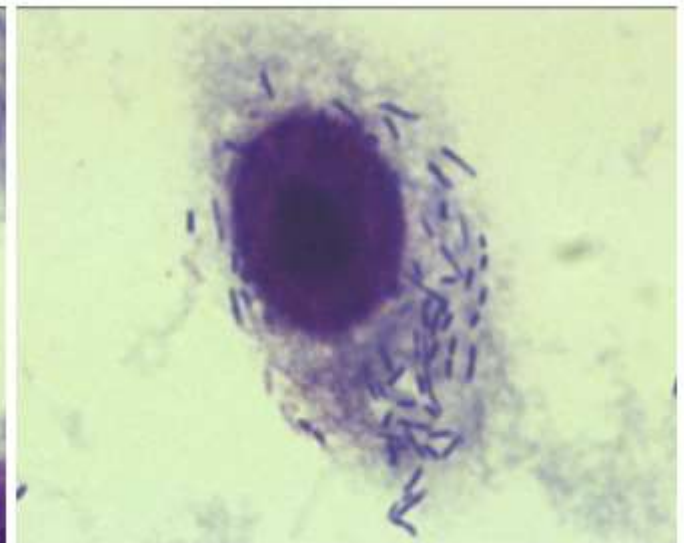
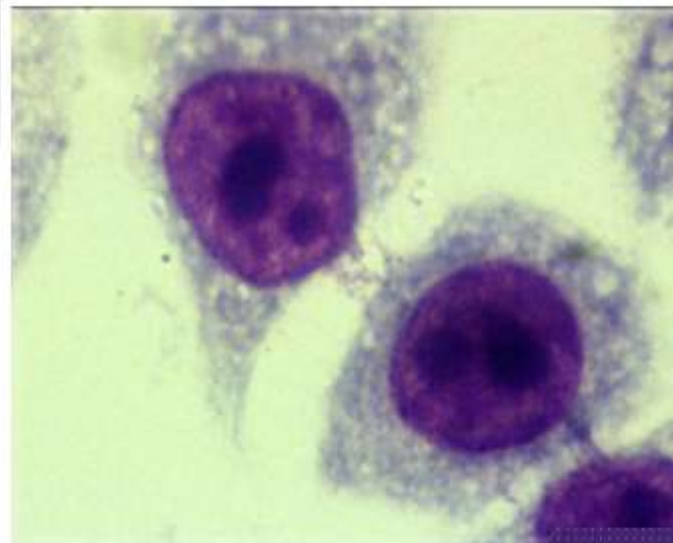
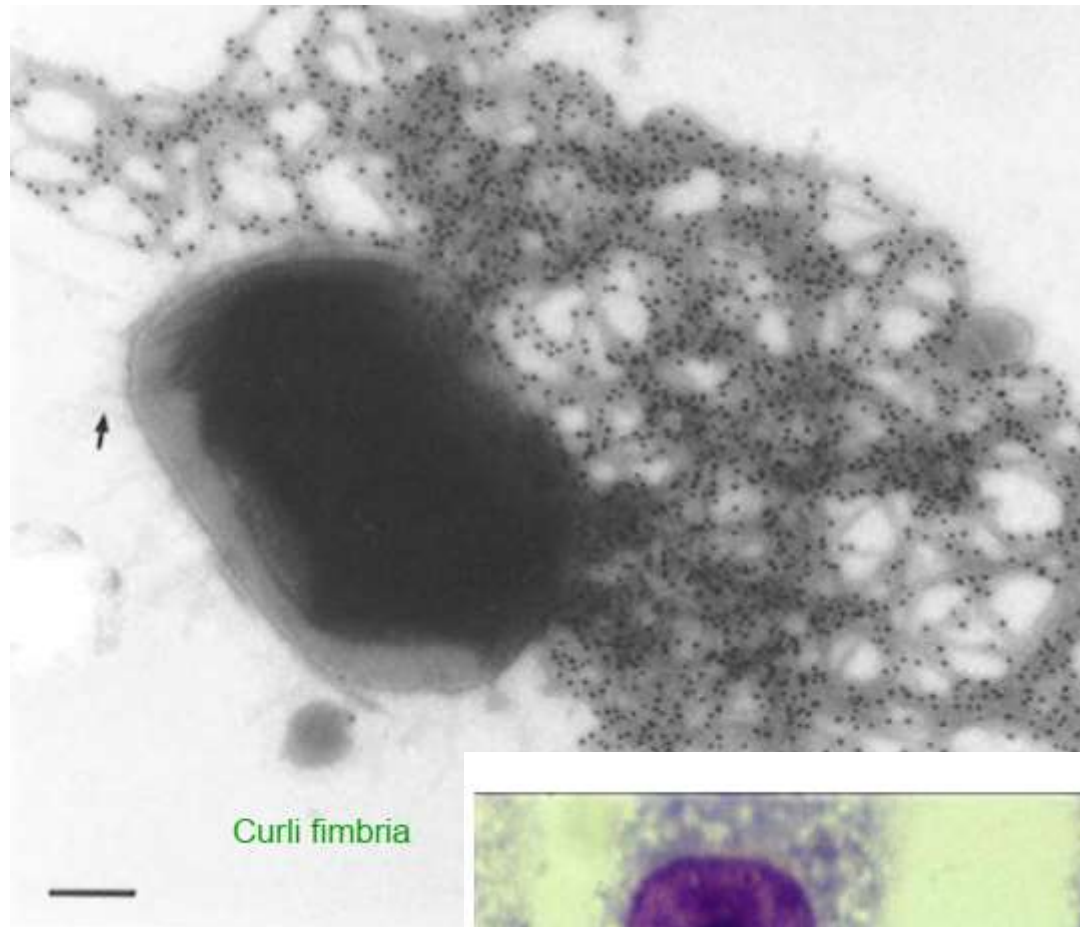
- Acute uncomplicated cystitis rarely progresses to severe disease, even if untreated; thus, the primary goal of treatment is to ameliorate symptoms.
- New treatment guidelines for cystitis from the Infectious Diseases Society of America recommend that ecologic adverse effects of an antimicrobial agent (selection for antimicrobial-resistant organisms) be considered along with efficacy in selecting antimicrobial therapy.
- With respect to both ecologic adverse effects and efficacy, nitrofurantoin, trimethoprim–sulfamethoxazole, fosfomycin, and pivmecillinam (not approved in the United States) are considered first-line agents for cystitis, even though there are concerns about increasing resistance (to trimethoprim–sulfamethoxazole) and suboptimal efficacy (of fosfomycin and pivmecillinam).
- Recurrent cystitis should be managed with prophylactic antimicrobial therapy only when nonantimicrobial preventive strategies are not effective.
- Fluoroquinolones have other important indications and thus should be considered second-line agents for cystitis, but they are the drugs of choice for empirical treatment of pyelonephritis.





BACTERIAL VIRULENCE FACTORS

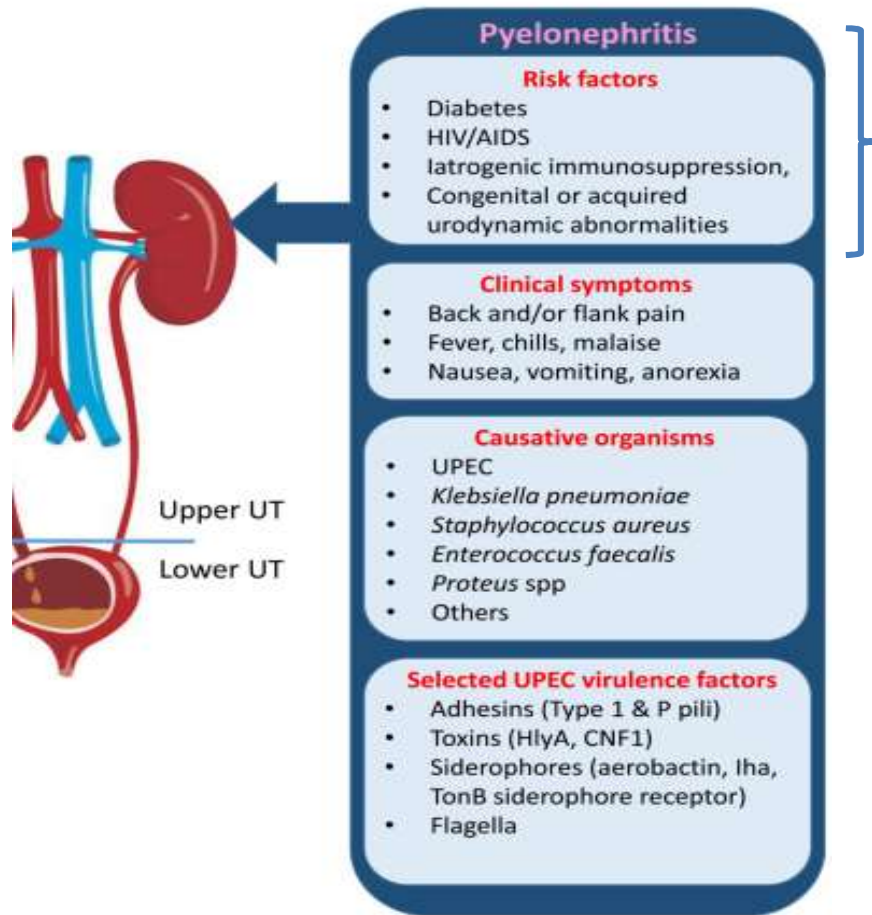




Applicability of research

1. Investigation of clonal relations between pathogens
2. Gaining new knowledge on regulation and expression of virulence genes
3. Exploitation of the new knowledge in diagnosis, therapy and prevention

Acute pyelonephritis



- Global emergence of E.coli ST131 (harbors NDM)
- **LTCF** strongest risk factor for ST131
- Independent risk factor for FQ R and ESBL pathogens
- Complications- sepsis
- Imaging? Culture?
- Hospitalization?

Ιστορικό (II)

- Άνδρας, 40 ετών, προσέρχεται διότι παρουσιάζει πυρετό (39°C) με ρίγος από δώρου
- Από διημέρου: δυσουρία, συχνουρία, έπειξη προς ούρηση και έντονο περινεϊκό άλγος
- Ατομικό αναμνηστικό ελεύθερο. Είναι η πρώτη φορά που παρουσιάζει αυτά τα συμπτώματα

Ποια η πιθανότερη διάγνωση;

- Οξεία πυελονεφρίτιδα
- Οξεία προστατίτιδα
- Έξαρση χρόνιας προστατίτιδας
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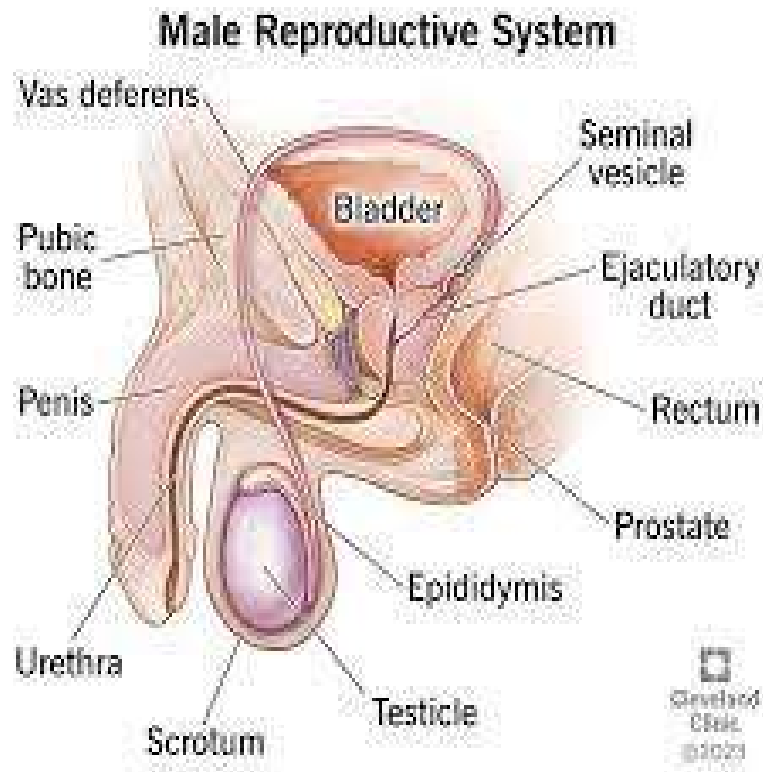
Πώς θα τεθεί η διάγνωση;

- Με γενική και καλλιέργεια ούρων
- Με καλλιέργεια προστατικού ύστερα από μάλαξη του προστάτη
- Με καλλιέργεια σπέρματος
- Με καλλιέργεια προστατικού ύστερα από μάλαξη του προστάτη + υπερηχογράφημα

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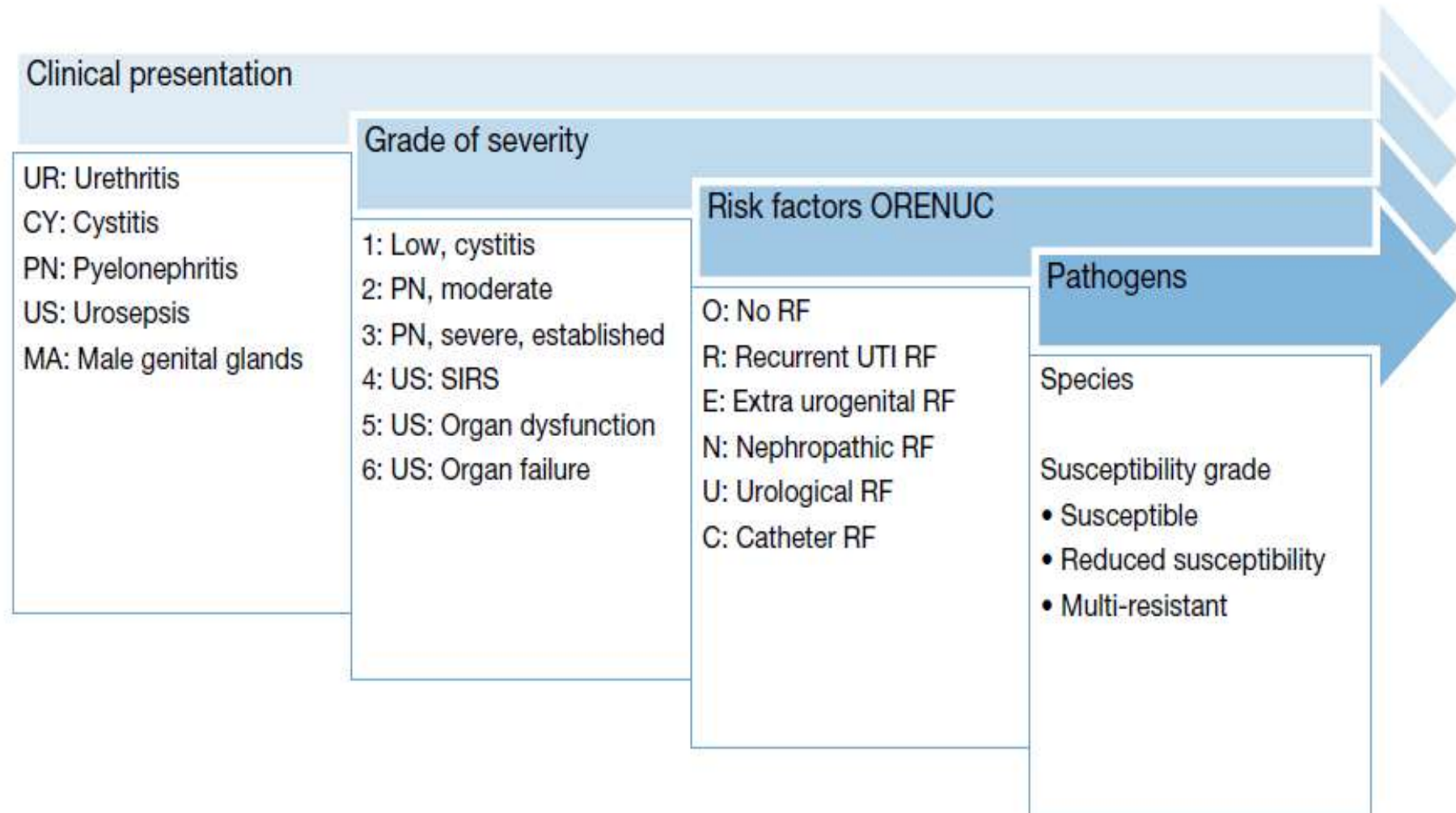
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What happens with males?



- Approach to treatment based on the extent of infection and the severity of illness
- It is not always possible to rule out prostate infection
- 5-8 UTI/year/10.000 young-middle aged men
- Prostatic fluid: antibacterial
- Lack of circumcision
- *E.coli*

EAU: UTI classification and severity assessment

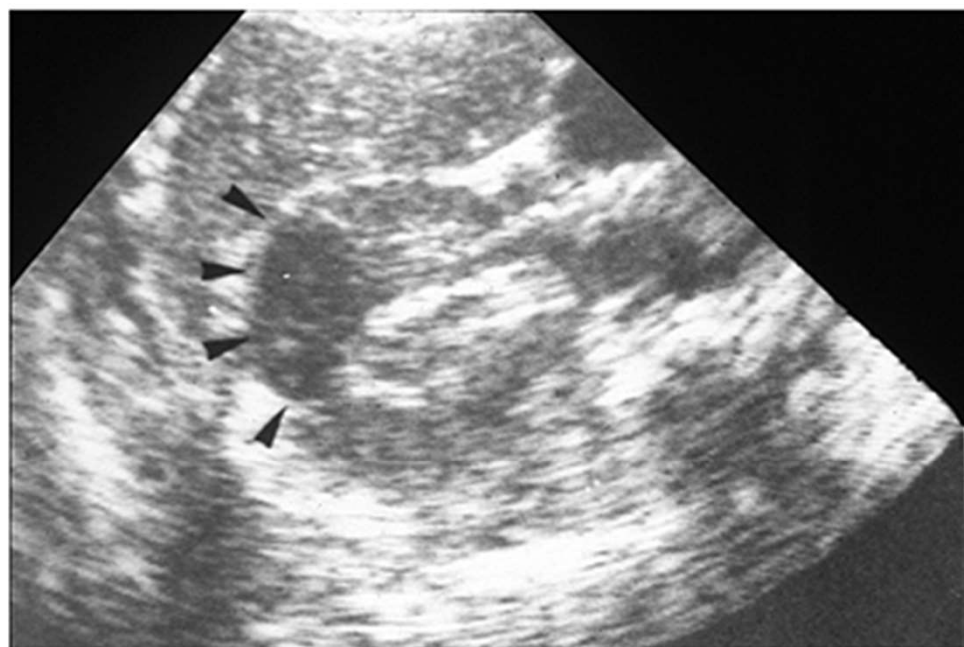




Imaging needed?



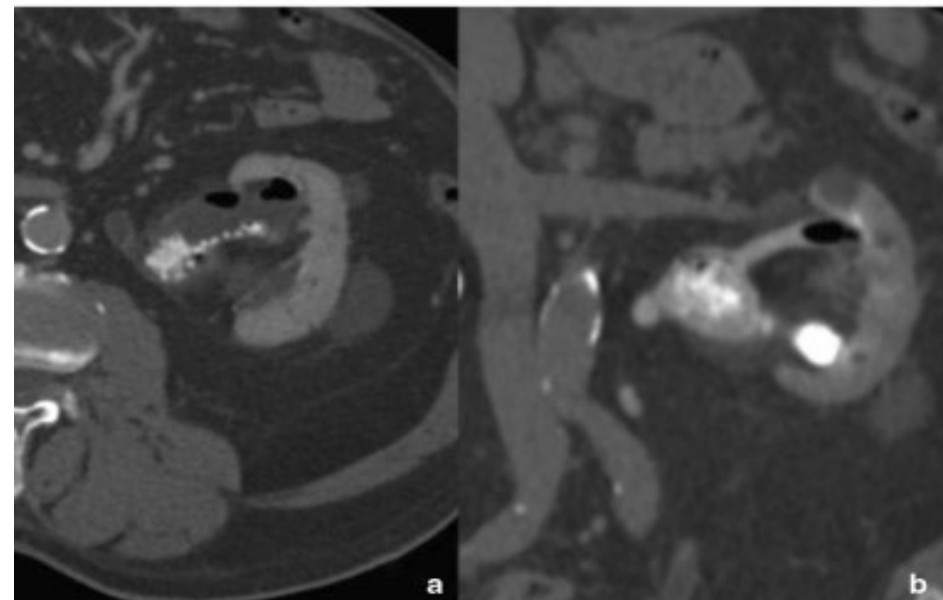
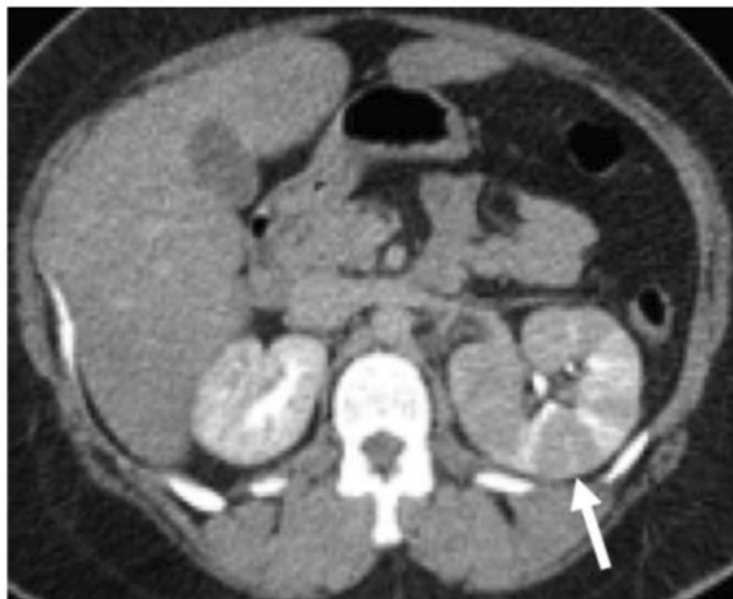
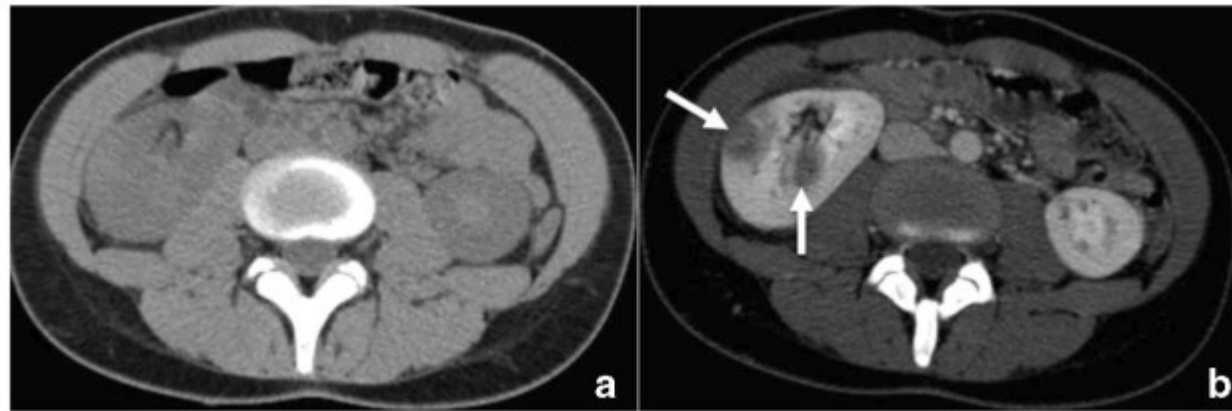
Ultrasonography of acute pyelonephritis



Renal ultrasonography in a patient with acute pyelonephritis showing a hypodense mass with internal echoes (outlined by the arrows).

Courtesy of Alain Meyrier, MD.

UpToDate®





Imaging (U/S, CT)

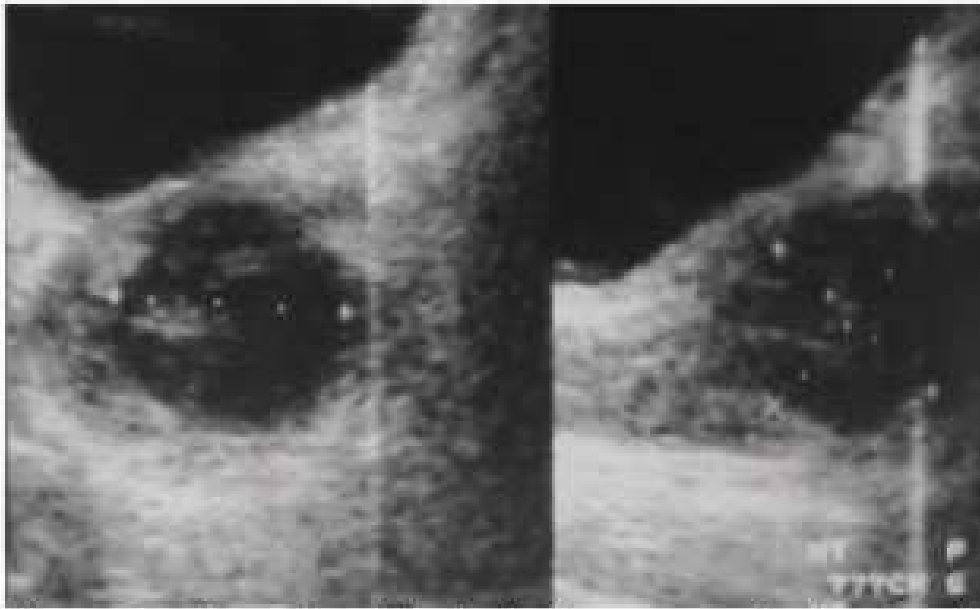


Figure 3 – Prostatic abdominal ultrasonography showing the prostatic abscess.

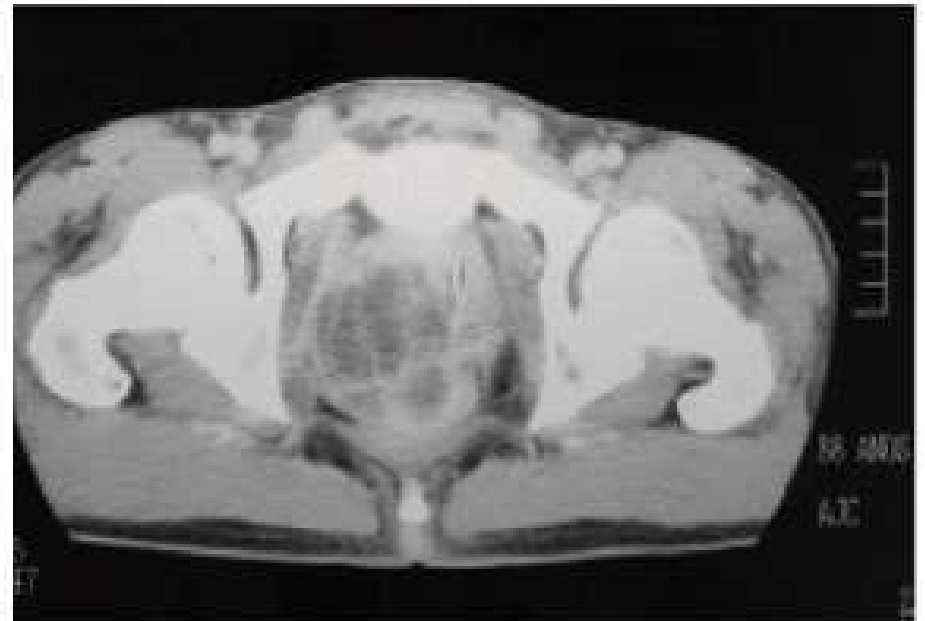
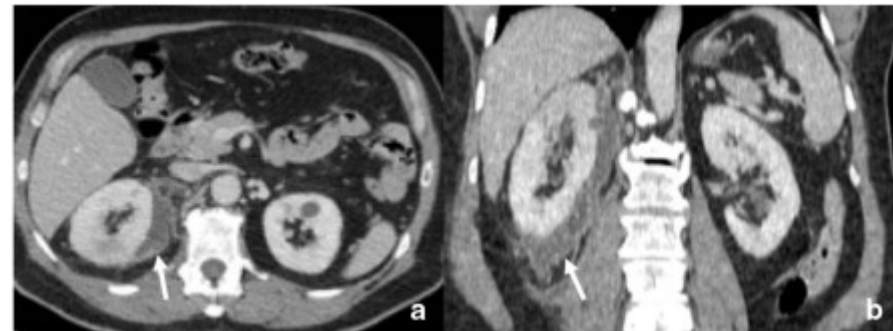
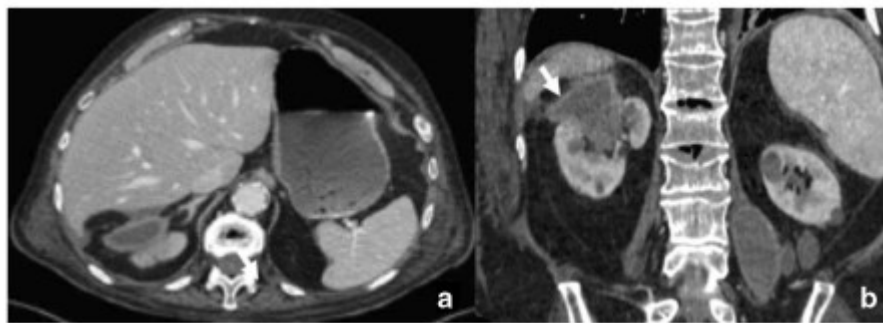
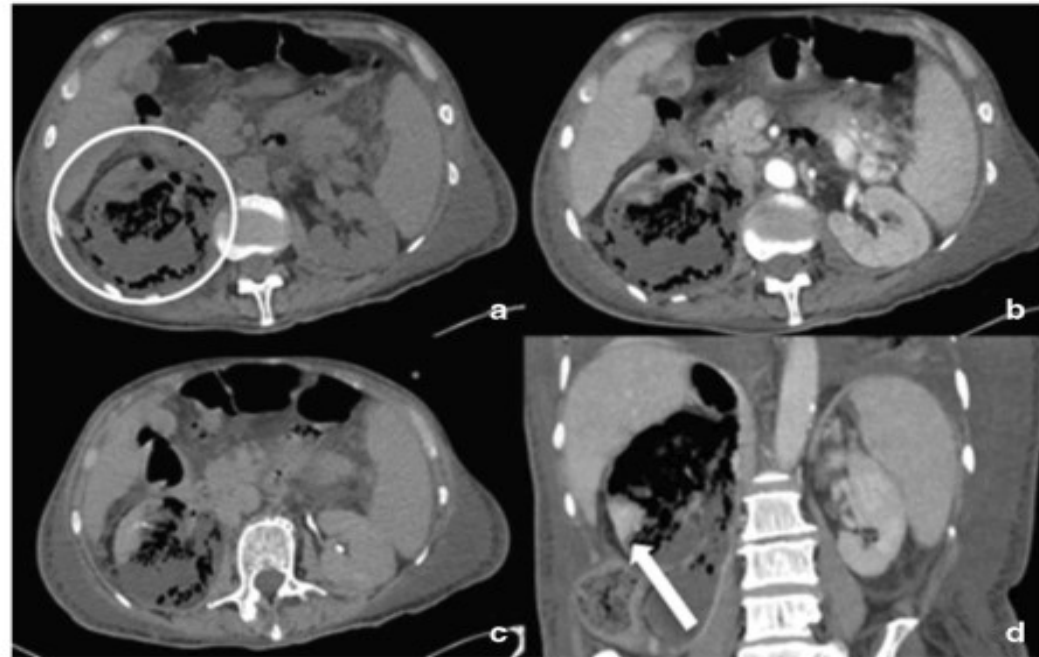
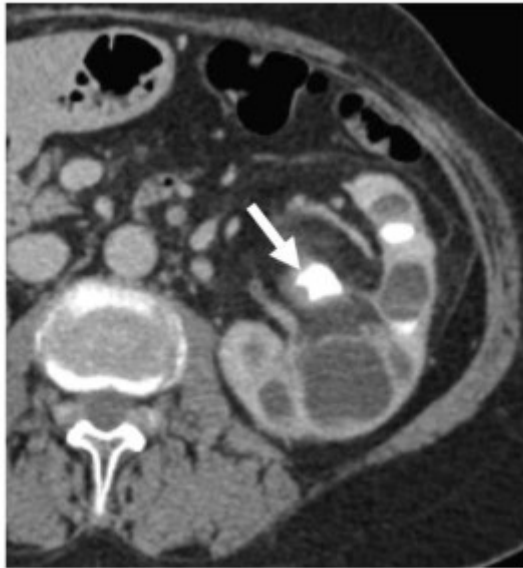


Figure 2 – Pelvic computed tomography showing an abscess in the prostate.

Xanthogranulomatous pyelonephritis



Επιπτώσεις της ασυμπτωματικής βακτηριουρίας

- Η ASB δεν συσχετίζεται με υπέρταση, χρόνια νεφρική νόσο ή μειωμένη επιβίωση
- Η ASB είναι δείκτης κακής συνολικής κατάστασης σε διαβητικούς ασθενείς, ηλικιωμένους σε μονάδες φροντίδας, ασθενείς με ουροκαθετήρες αλλά δεν είναι ανεξάρτητος παράγοντας κινδύνου για θνητότητα
- Σε έγκυες γυναίκες η ASB σχετίζεται με υψηλή πιθανότητα (20-40%) εξέλιξης σε πυελονεφρίτιδα και με ελλειποβαρή νεογνά ή πρόωρο τοκετό

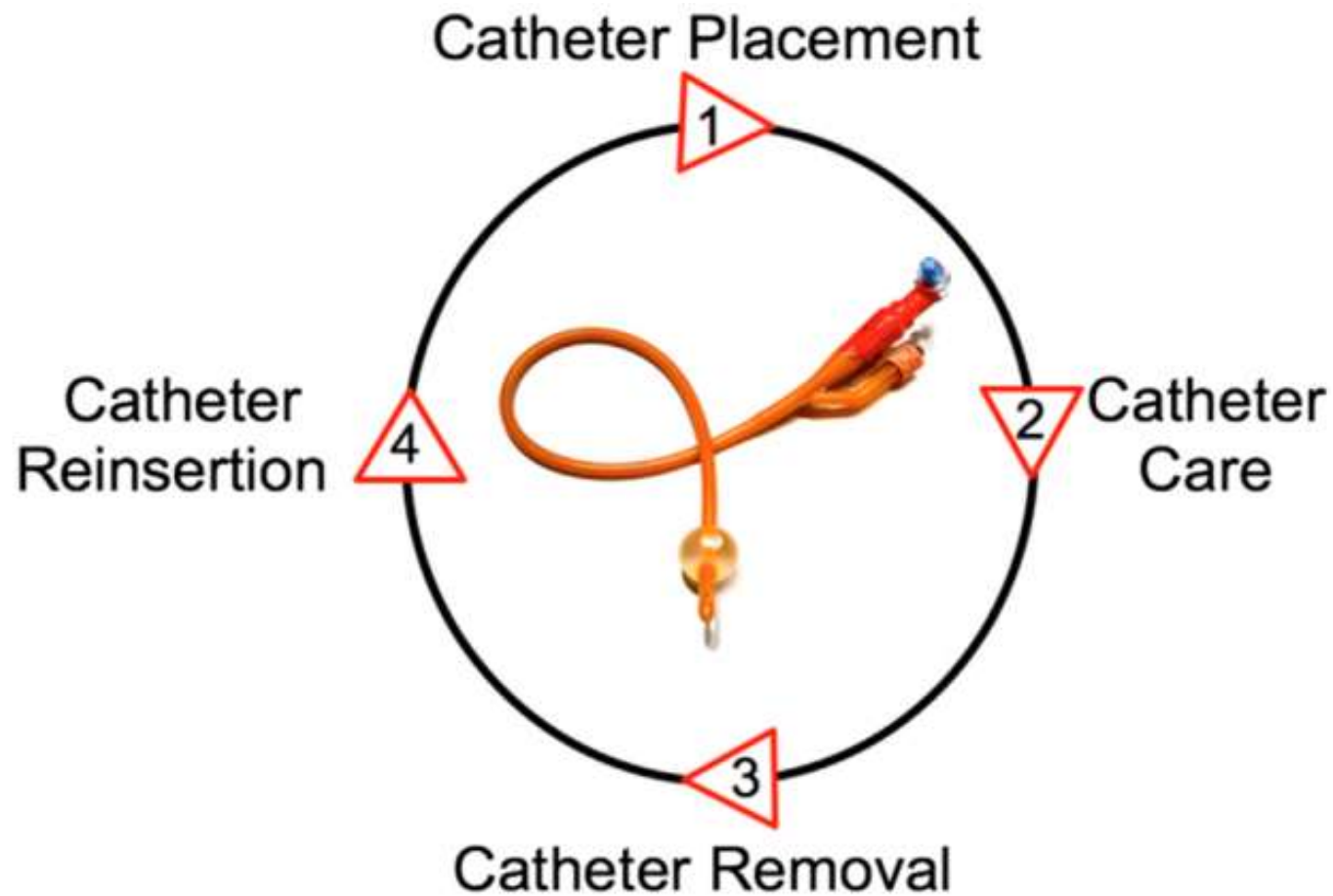
Asymptomatic bacteriuria

Table 56.8 Indications for the treatment of asymptomatic bacteriuria

Definite	Before an invasive genitourinary procedure Pregnancy
Not indicated	In the elderly For schoolgirls or healthy women Intermittent catheterization Indwelling urinary catheter Diabetic women

Data from Nicolle *et al.*²⁵

Catheter Life Cycle



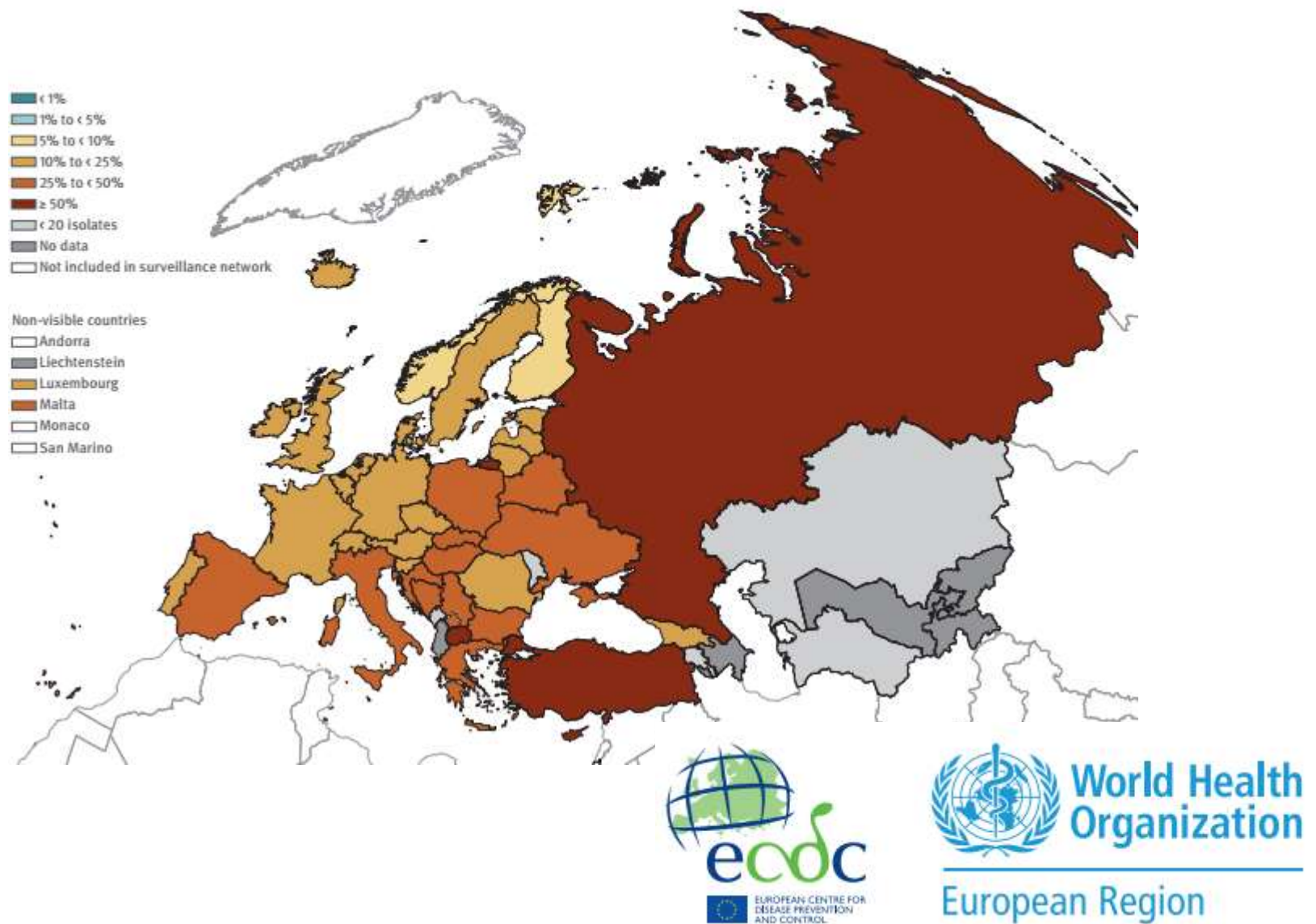
Catheter-associated UTI

- Common HCAI- 3-10%/ day
- Among bacteriuria- 25% will develop infection
- Duration is the most important risk factor
- In change of mental or functioning status, do not check urine
- Do not treat asymptomatic bacteriuria
- Avoidance of unnecessary catheterization
- “Catheter-out”

WHY catheters out?

ID specialists	Urologists
<ul style="list-style-type: none">• Reduce UTI• Reduce antibiotic use• Reduce R and C difficile	<ul style="list-style-type: none">• Reduce trauma• Meatal and urethral injury• Hematuria
Hospitalists	Geriatricians
<ul style="list-style-type: none">• Infectious and mechanical complications• Length of stay	<ul style="list-style-type: none">• Frail elderly• Inappropriate catheter placement• Increase immobility and deconditioning

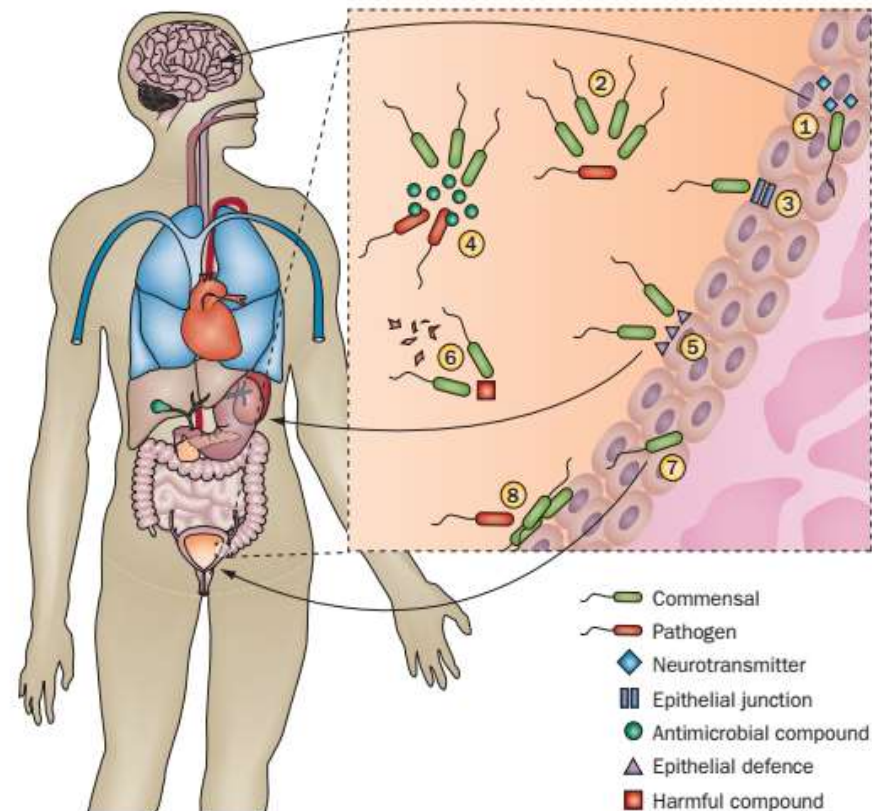
Fig. 1 *Escherichia coli*. Percentage of invasive isolates resistant to fluoroquinolones (ciprofloxacin/levofloxacin/ofloxacin), by country, WHO European Region, 2021





Old dogma: Urinary tract is a sterile site

- Microbiomes exist in many body compartments once considered sterile
- The urinary tract harbors a resident microbial community
- >100 species
- Role of urobiome in health and disease?



Clinician's corner

- The bladder hosts a “urinary microbiome” that may influence UTI
- Public health impact of UTI
- Know when to admit a patient
- Know when treatment is indicated