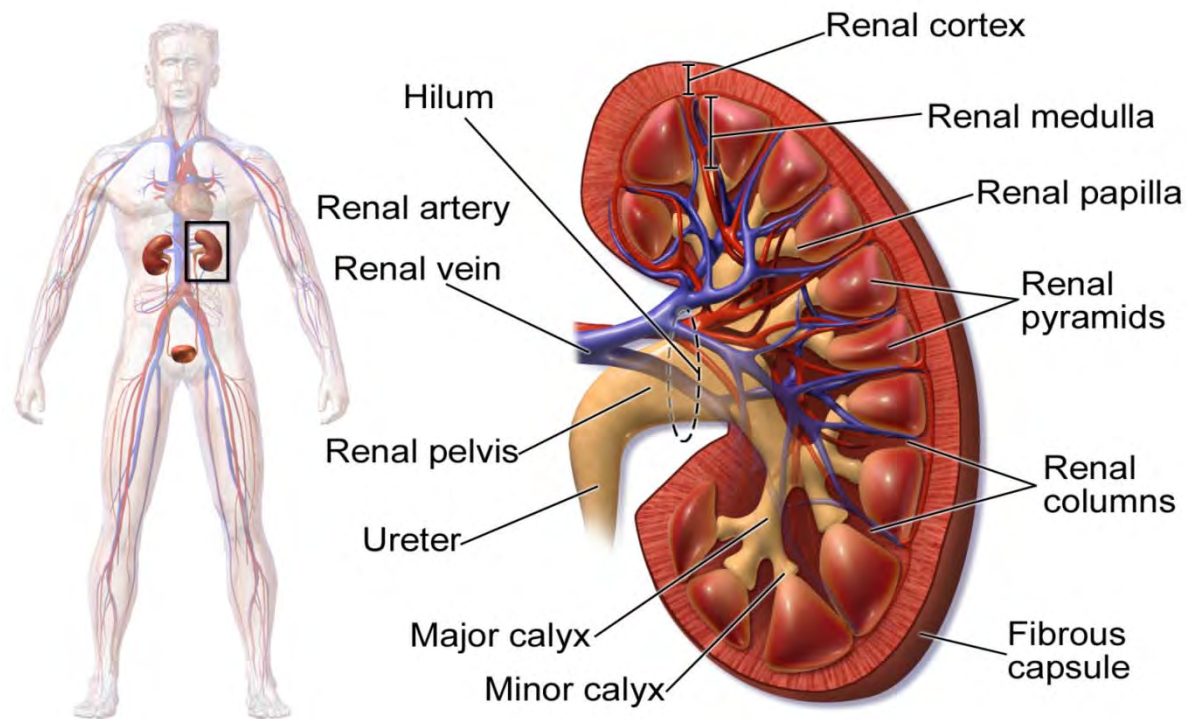


Urinary tract infection



ประสิทธิ์ อุพาพรรณ

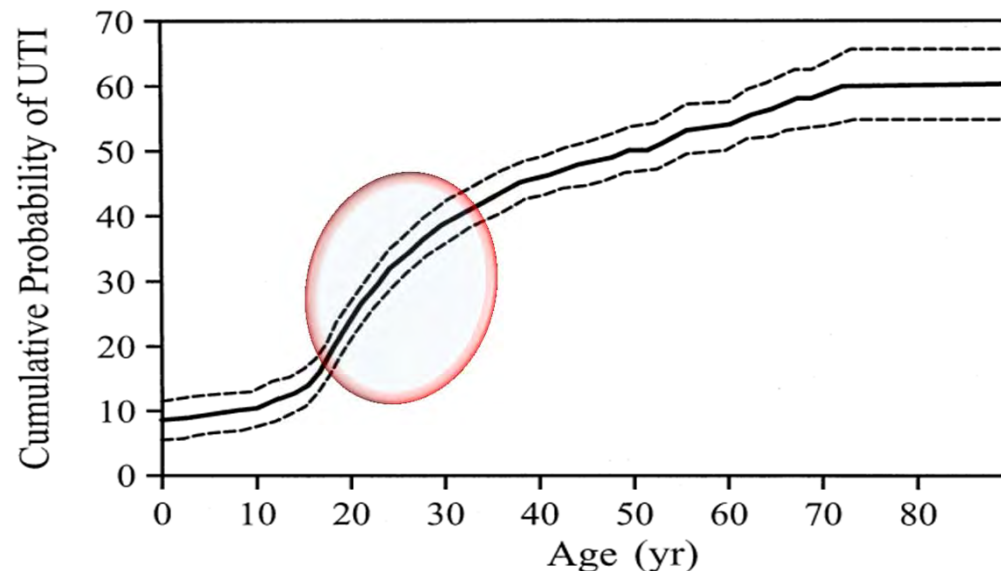
สาขาวิชาโรคติดเชื้อ ภาควิชาอายุรศาสตร์

คณะแพทยศาสตร์มหาวิทยาลัยศรีนครินทรวิโรฒ



Introduction

- Urinary tract infections (UTIs) are extremely common.
- Most frequent in infants, young women, and the elderly.
- UTIs are around twice as common in women as in men (except age < 1 yr ; vesicoureteral reflux and age > 50 yr ; BPH, calculi).
- 50 % of women having had an episode of UTI in their lifetime.



-Am J Med 2002;113(1A):5S-13S.

-Abhay Rané RD. Urinary Tract Infection: New York Dordrecht; 2013.

-Foxman B, UTI; self-reported incidence and associated costs. *Ann Epidemiol* 2000;10:509-15.

-Hooton TM, A prospective study of risk factors for symptomatic UTI in young women. *N Engl J Med* 1996;335:468-74.



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Epidemiology

Risk Factors for Urinary-tract Infections by Age Group

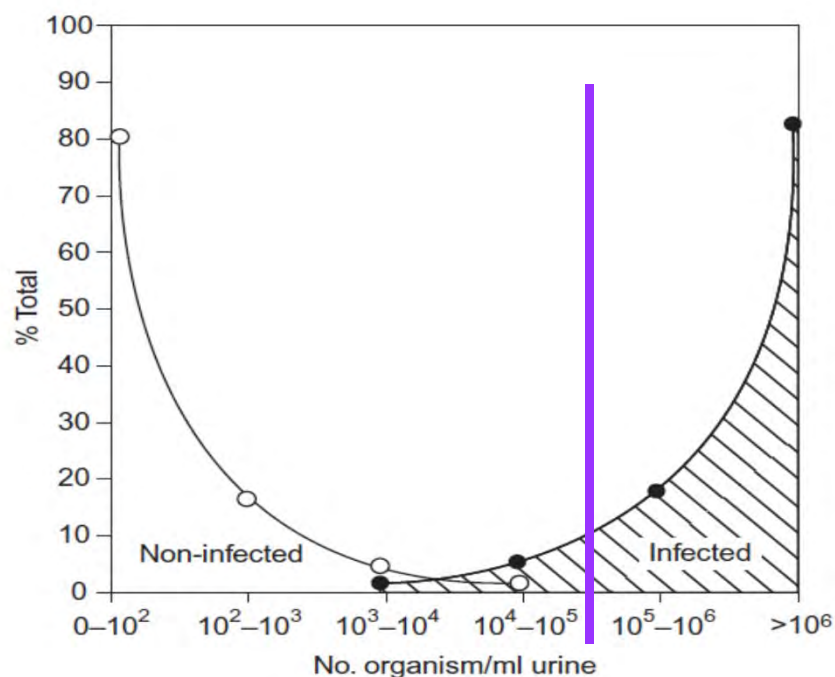
Age in yrs.	Females (% prevalence)	Males (% prevalence)
<1	Anatomic or functional urologic abn. (1%)	Anatomic or functional urologic abn. (1%)
1-5	Congenital abn. ; vesicoureteral reflux (4.5%)	Congenital abn., uncircumcised penis (0.5%)
6-15	Vesicoureteral reflux (4.4%)	Vesicoureteral reflux (0.5%)
16-35	Sexual intercourse, diaphragm use, spermicidal jelly, previous urinary tract infection (20%)	Anatomic urologic abnormality. Insertive rectal intercourse. (0.5%)
36-65	Gynecologic surgery, bladder prolapse (35%)	Prostate hypertrophy, obstruction (20%)
>65	Estrogen deficiency (40%)	All of the above, incontinence, long-term catherization, condom catheters (35%)



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Common definitions

Bacteriuria	Bacteria in urine, demonstrated by microscopy or quantitative culture
Pyuria	UA ; WBC > 5 cells/HPF in unspin urine If pyuria but not found the bacteriuria = sterile pyuria
Significant bacteriuria	- Specified quantitative count of bacteria (> 10^5 CFU/ml) - 10^2 - 10^4 CFU/ml (with symptoms and signs/ Male)



Clin Infect Dis 2005;40(5):643-54.

Abhay Rané RD. Urinary Tract Infection: New York ; 2013.



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Common definitions

Symptomatic bacteriuria	Bacteria in urine in the context of typical symptoms of UTI
Asymptomatic bacteriuria	<p>Bacteria in urine in the absence of symptoms of UTI</p> <p>-Women: 2 consecutive voided urine specimens (isolation of the same bacterial strain in quantitative counts $> 10^5$ cfu/mL)</p> <p>- Men: A single, clean-catch voided urine specimen (1 bacterial species isolated in a quantitative count $> 10^5$ cfu/mL)</p>
Urosepsis	UTI with accompanying sepsis syndrome

Clin Infect Dis 2005;40(5):643-54.

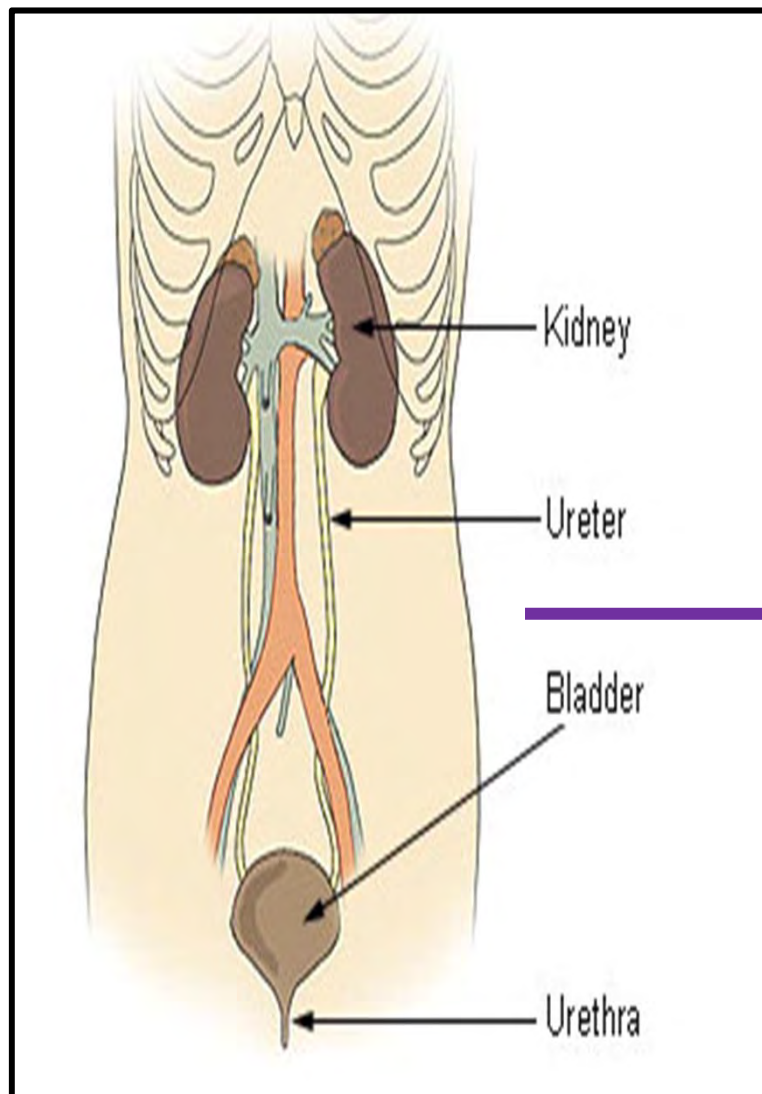
Abhay Rané RD, Urinary Tract Infection: New York ; 2013.



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Classifications



Upper urinary tract infection (pyelonephritis)

- Classically presenting
(Fever, N/V, CVA tenderness)
- Lower UTI symptoms may or may not be present.
- Frequently cause urosepsis , and complications.
- Most cases ; admission and IV ATB

Lower urinary tract infection (cystitis/urethritis)

- Rare; Systemic manifestations (fever)
And long-term sequelae.
- Usually treated with oral antibiotics
(high levels in the urine, but not necessarily achieving
high systemic or tissue levels)



Classifications

Uncomplicated UTIs	Complicated UTIs
<ul style="list-style-type: none">-Lower UTI, pyelonephritis (no complicate)-Young women with healthy-Treat; narrower spectrum, oral antibiotics for short courses.	<ul style="list-style-type: none">DiabetesPregnancySymptoms for seven or more days before seeking careRenal failureUrinary tract obstructionPresence of indwelling urethral catheter stent or nephrostomy tubeRecent urinary tract procedure or instrumentationFunctional or anatomic abnormalities of the urinary tractRenal transplantImmunosuppression

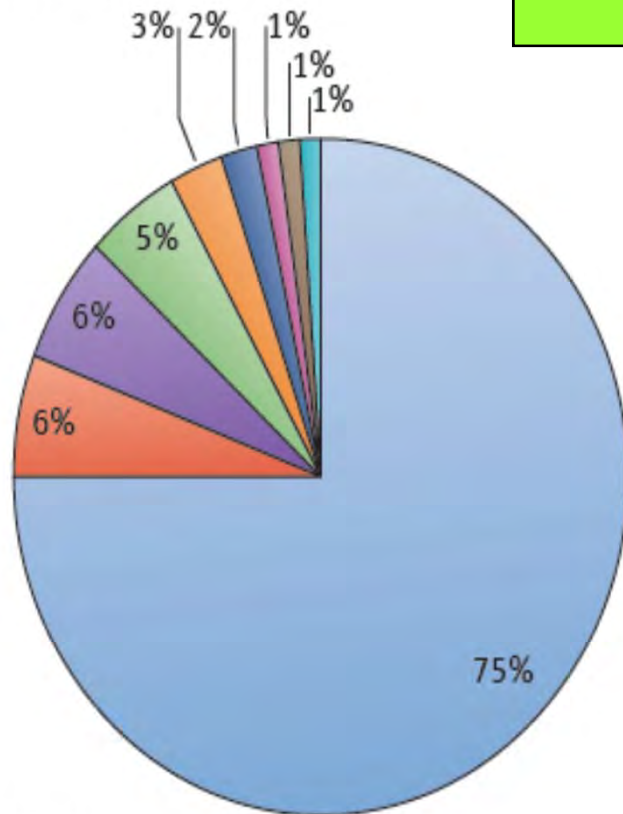
Recurrent UTIs ; > 25% of women (UTI) will experience a recurrence.

- Relapses ; recur on cessation of treatment (**same organism**)
- Reinfection ; a **new causative organism**.

Important to explore non-pharmacological methods to reduce recurrences

Etiology

Uncomplicated UTI

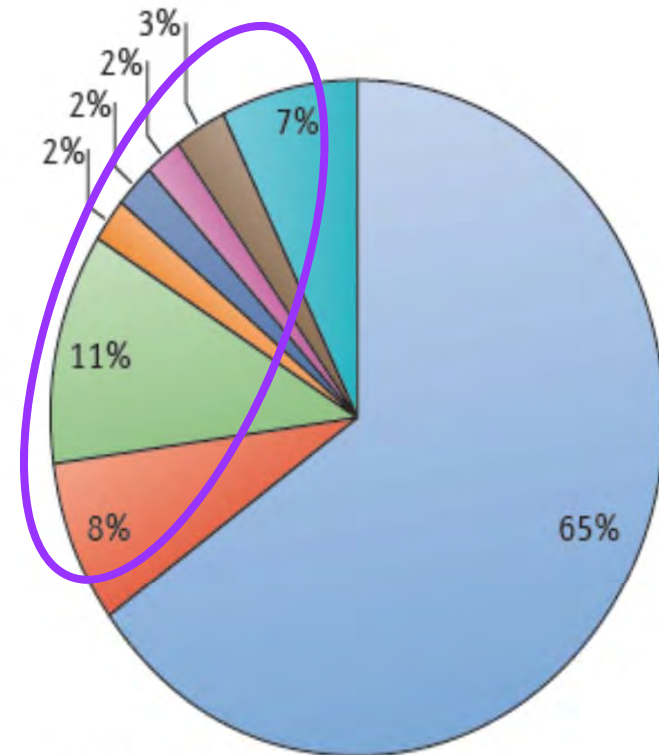


Risk factors

- Female gender
- Older age
- Younger age

Virus ; Adenovirus type 11
(hemorrhagic cystitis, transplant pt.) and type 21

Complicated UTI



Risk factors

- Indwelling catheters
- Immunosuppression
- Urinary tract abnormalities
- Antibiotic exposure

Flores-Mireles AL, Urinary tract infections: epidemiology, mechanisms of infection and treatment options. Nat Rev Microbiol 2015;13:269-84.



Most common route: 95%

Enterobacteriaceae: *E. Coli*

Entry of pathogen

- Instruments
- Sexual intercourse
- Vesicoureteral reflux

Pathogenesis

Ascending route

Uncommon ;

Staphylococcus aureus and *Candida*

*Originate from oral sources in immunosuppressed patients.

Rare ;

- Bacteria from adjacent organs.

- Conditions ; retroperitoneal abscesses and severe bowel infections.

Haematogenous route

Lymphatic route

Urinary Tract Infection

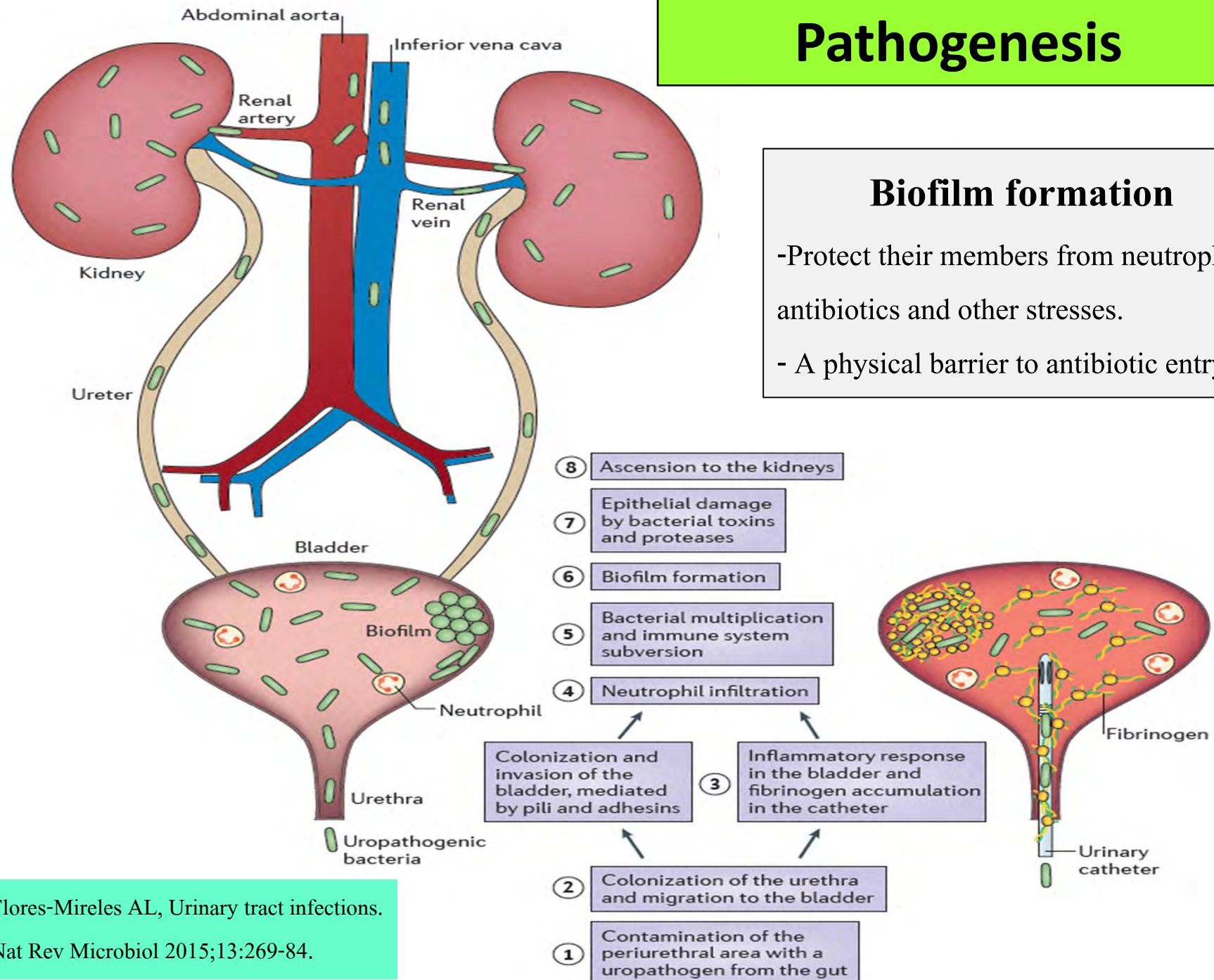
Brenner & Rector's The kidney, 8th edition 2008.

Niall F. Davis and Hugh D., The Pathogenesis of Urinary Tract Infections, september 2011.

Pathogenesis

Biofilm formation

- Protect their members from neutrophils, antibiotics and other stresses.
- A physical barrier to antibiotic entry



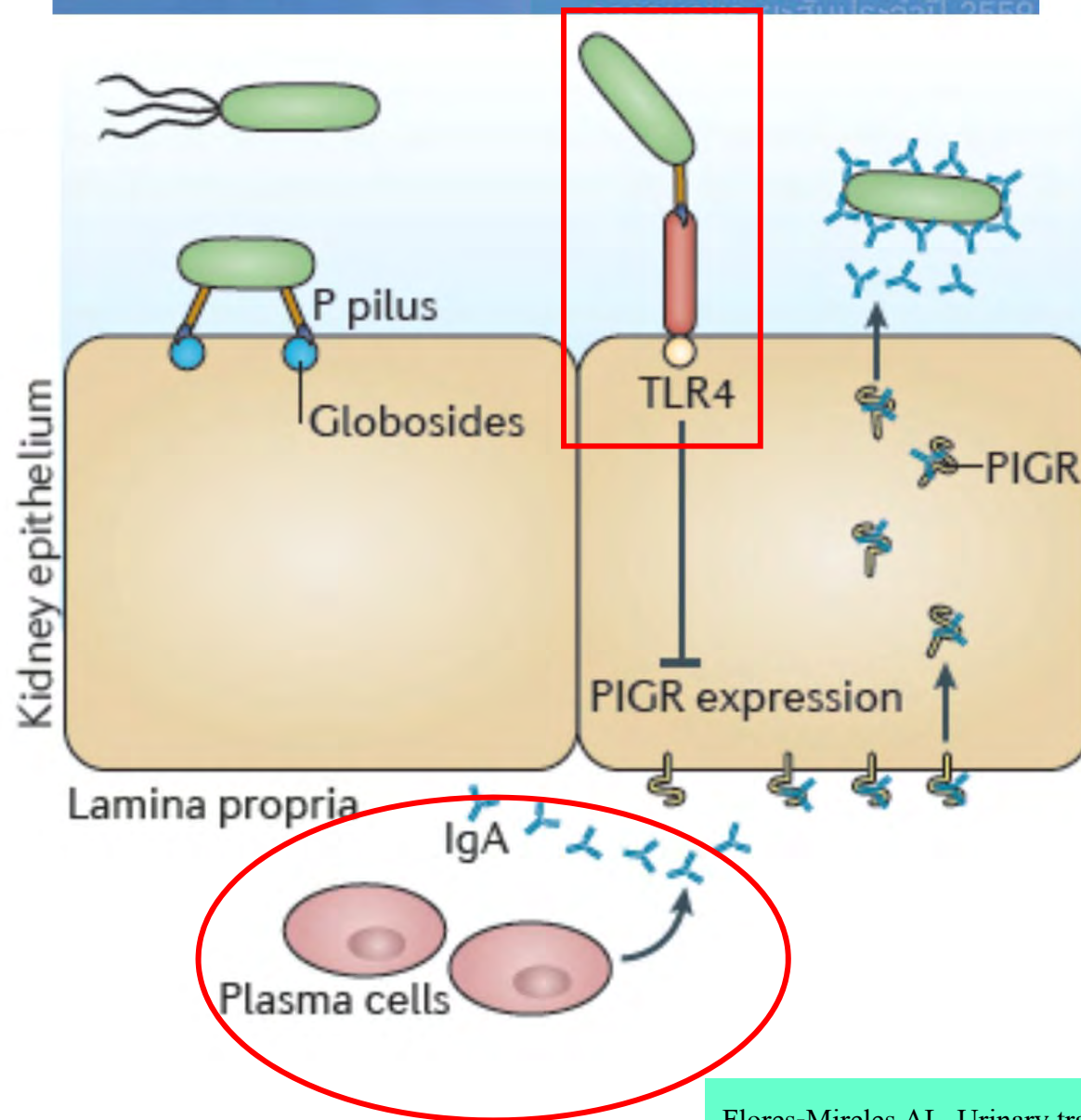
Flores-Mireles AL, Urinary tract infections.
Nat Rev Microbiol 2015;13:269-84.

Symptoms of cystitis

Flores-Mireles AL, Urinary tract infections. Nat Rev Microbiol 2015;13:269-84.



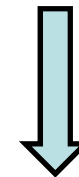
Pathogenesis



Colonization of the kidneys



Host tissue damage by
bacterial toxins ; **Symptoms**



Bacteraemia ; Urosepsis

Host factors

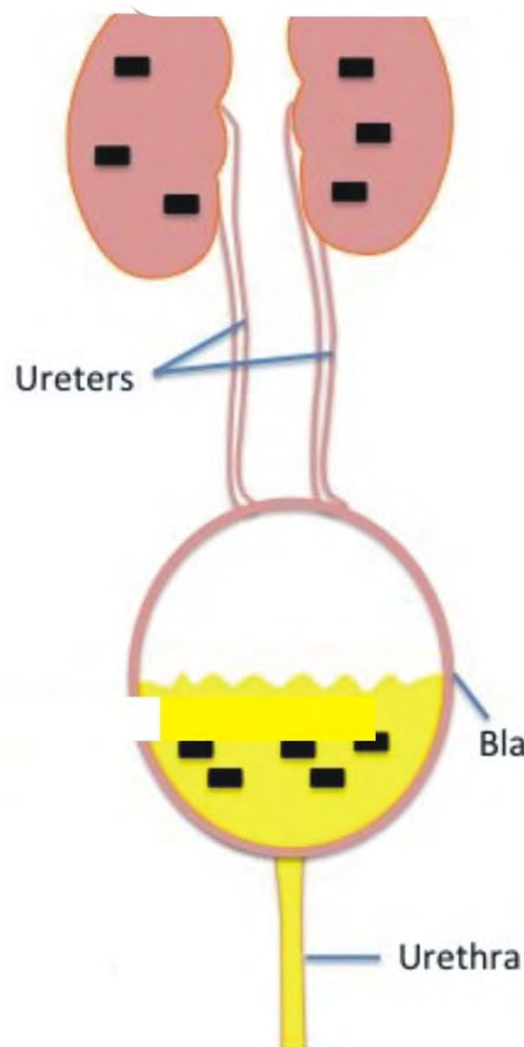
- **Female sex**: short urethra
- **DM** (increase risk)
- **Smoking** :
associated with lower UTI in male.
- **Presence of a catheter** :
disrupt glycosaminoglycan (bladder)

Environmental factors

- **Blockages in the urinary tract**
 - Urinary stone or BPH
- **Pregnancy**
 - Uterus compress the ureter
 - High progesterone level
(decrease muscle tone of ureter and bladder...induced vesicoureteral reflux)
- **Increase vaginal pH** (decrease acidity)
or change of normal floras
 - sexual activity
(increase *E. coli* colonization)
 - cervical diaphragms or spermicides
(toxic to normal flora)
 - Menopause : estrogen deficiency
(decrease vaginal acidity)
(Lactobacilli ลดลง และ *E. coli* มาแทนที่)



Clinical manifestations



Pyelonephritis

(Kidney infection)

- **flank pain**
- **high fever**
- malaise
- WBCs & bacteria in urine
- urinary symptoms similar to cystitis

Cystitis

(Bladder infection)

- increased urinary frequency
- urgency
- dysuria (painful urination)
- pain above the pubic region
- WBCs & bacteria in urine
- more common in women



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Laboratory findings

- Pyuria : **high sensitivity**, low specificity
- **Bacteriuria (microscopic exam or urine strip test)**
 - Gram stain of uncentrifuged urine ≥ 1 cell/oil field : **low sensitivity** ($< 10^5$ cfu/ml)
 - Nitrate test: **poor sensitivity**, high specificity
 - Enterobacteriaceae*: limit to others organism
 - nitrate-reductase enzyme Nitrates \rightarrow nitrite (need time 4 hr)
 - Leukocyte esterase test : **high sensitivity** and specificity
 - Detect leukocyte esterase enzyme : the host's PMN leukocytes in the urine (cell intact or lysed)

Clin Infect Dis 2004;38(8)1150-8 // Clinical practice, acute uncomplicated UTI in women, 2012
S.guido, Asystematic review, The diagnosis of urinary tract infection, Dtsch Arztebl int 2010.



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Diagnosis

- Clinical syndrome and significant bacteriuria
- Urine culture : gold standard : Results not available until 24-48 hr.

Test, colony count	Performance characteristics			
	Sensitivity	Specificity	Predictive values	
			Positive	Negative
Leukocyte esterase				
≥10 ⁵ cfu/mL	68-98	59-96	19-86	91-97
≥10 ⁴ cfu/mL	64-77	59-83	16-52	89-96
≥10 ³ cfu/mL	62-79	55-84	3-81	51-99
Nitrite				
≥10 ⁵ cfu/mL	19-45	95-98	50-78	82-89
≥10 ⁴ cfu/mL	8-39	97-98	27-81	85-87
≥10 ³ cfu/mL	0-50	48-98	0-82	37-99
<u>Leukocyte esterase and nitrite</u>				
≥10 ⁵ cfu/mL	35-84	98-100	84	98
≥10 ³ cfu/mL	0-45	62-98	0-66	42-99
<u>Leukocyte esterase and/or nitrite</u>				
≥10 ⁵ cfu/mL	67-100	67-98	40-95	84-96
≥10 ⁴ cfu/mL	74-79	66-82	42-54	91-92
≥10 ³ cfu/mL	71-84	41-83	49-81	46-90

Dipstick method

- cheaper, faster
- more convenient.
- most accurate



Radiologic and urologic evaluation

Men and women with persistent hematuria, recurrences pyelonephritis (same strain), persistent fever after proper Tx, complications or anatomy abnormality.

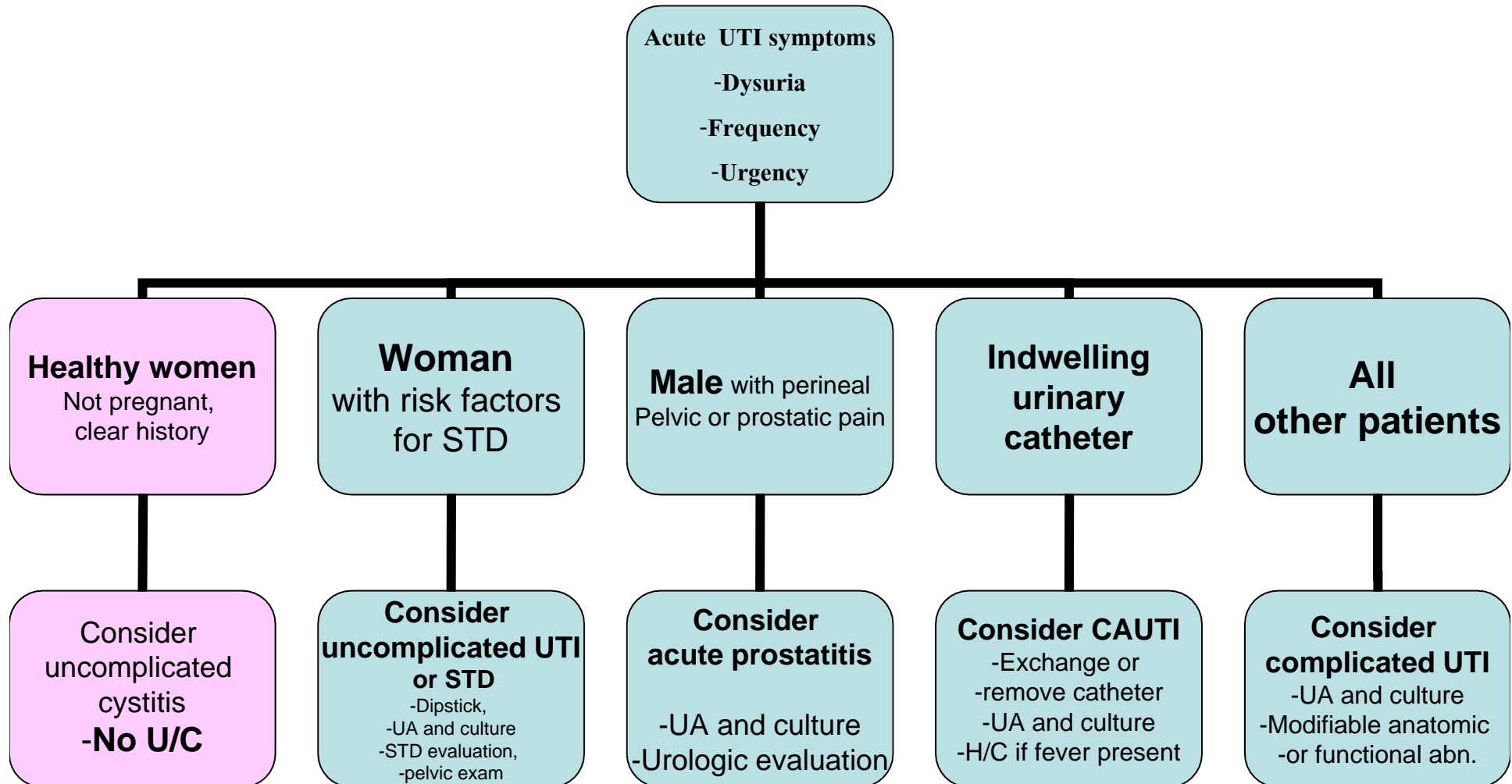
- **Plain KUB:** Urinary calcium stone, screen for abnormal anatomy.
- **Ultrasound KUB :** kidneys (hydronephrosis), bladder, and prostate (Operator dependent)
- **Intravenous pyelogram (IVP) :** Obstructions : cautions for GFR < 30, pregnancy
- **CT scan :** Stone (non-contrast), High sensitivity compare to ultrasound.
- **Voiding cystourethrography (VCU) :** detect vesicoureteral reflux
- **Cystoscope :** Stricture of urethra or hemorrhagic cystitis.



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Management

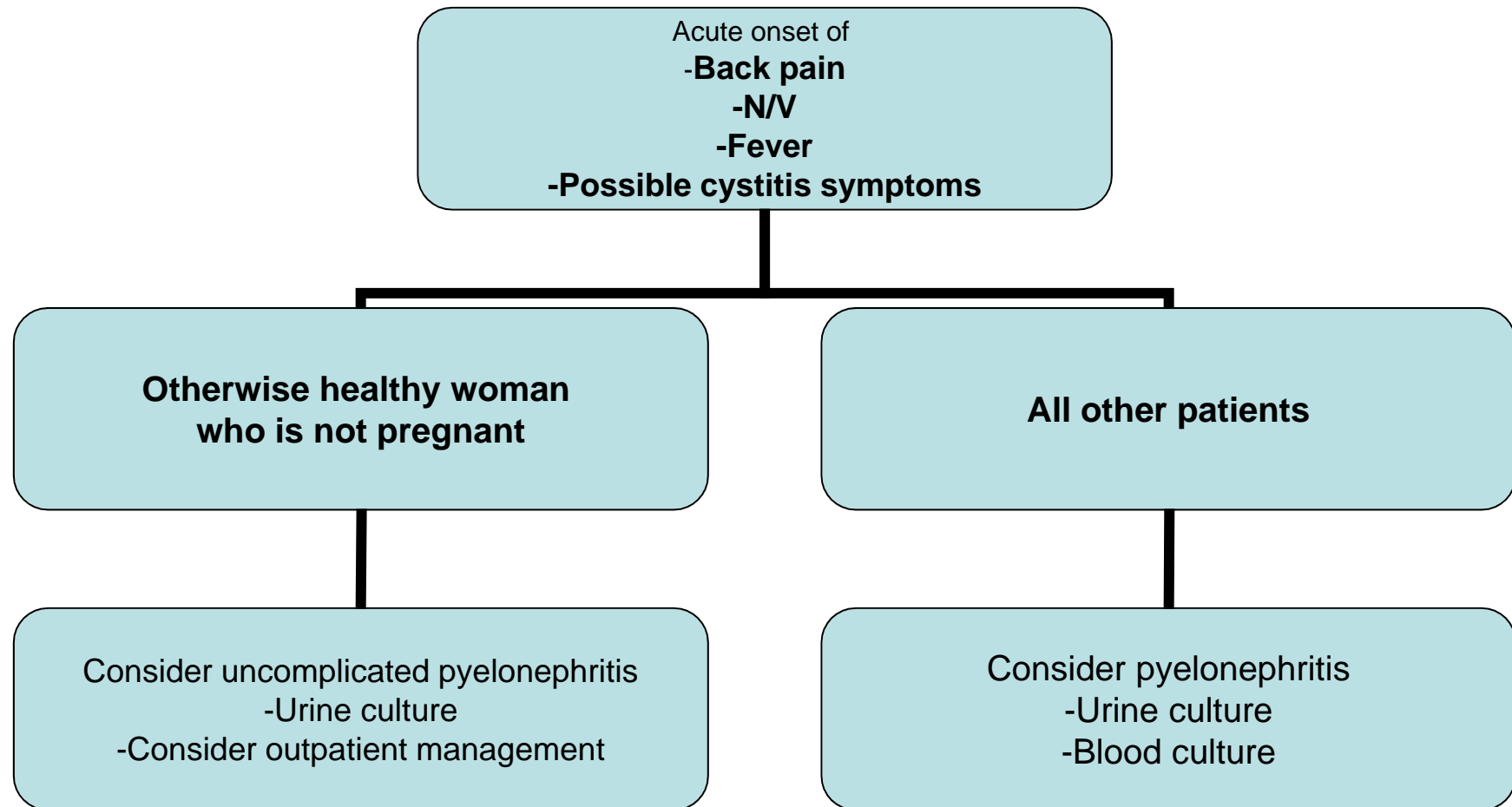




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Management





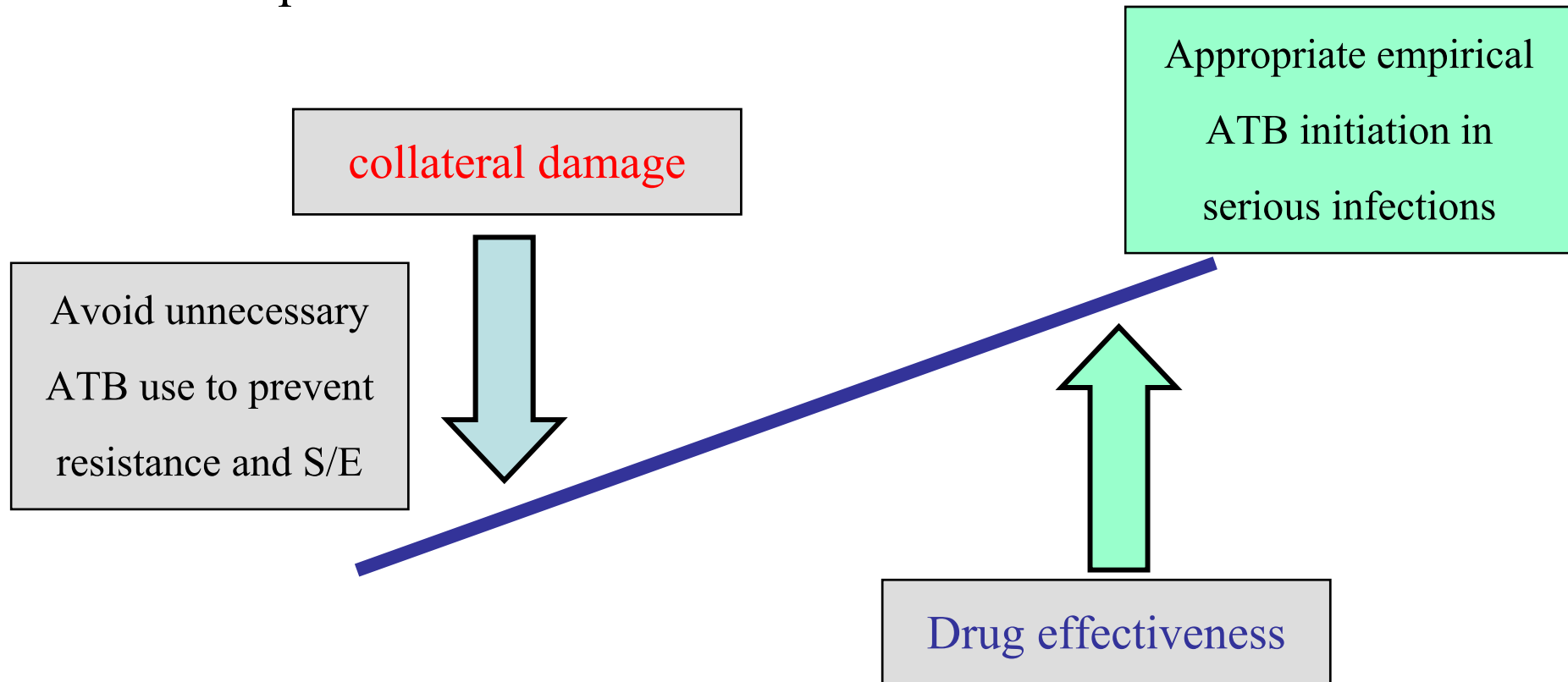
สมาคมเภสัชกร
แห่งประเทศไทย

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อบรมเภสัชกรด้านเภสัชวิทยา

Treatment

- Acute uncomplicated cystitis and pyelonephritis
- Complicated UTI



Choice of regimen : antimicrobial resistance (uropathogenic strains of *E. coli*)



Acute uncomplicated cystitis: empirical treatment

First-line therapy

Nitrofurantoin monohydrate macrocrystals, 100 mg twice daily for 5 days (with meals)†

TMP-SMX, 160 mg and 800 mg twice daily for 3 days‡

Fosfomycin trometamol (Monurol), 3-g sachet in a single dose†

Second-line therapy

Fluoroquinolones: ciprofloxacin, 250 mg twice daily for 3 days‡; levofloxacin, 250 mg or 500 mg once daily for 3 days‡

Beta-lactams (e.g., amoxicillin–clavulanate, cefdinir, cefaclor, and cefpodoxime–proxetil) for 3 to 7 days†

Goal ; rapid resolution of symptoms

Not recommended if resistant > 20%

Not recommended if resistant > 10%

National Antimicrobial Resistance Surveillance Center : 2015 Susceptibility report of UA specimen, Thailand

Organism	Total specimen	AMPICILLIN	CEFTRIAXONE	MEROPENEM	CIPROFLOXACIN	LEVOFLOXACIN	OFLOXACIN	AMIKACIN	GENTAMICIN	Fosfomycin	NITROFURANTOIN	CO-TRIMOXAZOLE
<i>E. coli</i>	1 7,137	13 (12641)	52.8 (11200)	99.2 (12336)	37.6 (12320)	38.8 (4874)	39.4 (2917)	97.1 (14821)	63.1 (16055)	98.3 (2592)	94.3 (1227)	39.3 (14568)

**Main pharmacokinetic parameters of quinolones (mean values)**

Quinolones	Dose (mg)	C_{\max} (mg/L)	$t_{1/2\beta}$ (h)	Bioavailability (%)	PB (%)	Metabolism (%)	Fu (%)	Urinary C_{\max} (mg/L)
First generation								
Nalidixic acid	1000	20–35	1.5	95	90	70	90	150–400
Pipemidic acid	400	3–4	3.5	70	15	<5	50–70	600–900
Second generation								
Norfloxacin	400	1–2	3.5–5	40	15	20	30	30
Ofloxacin	300	5–7	6–8	90	25	<10	80	85–95
Ciprofloxacin	250	0.8–1.9	5–6	70–80	30	35	40–50	200
	500	2–3						
Prulifloxacin	600	≈ 2	10		50	<20	20	110
Third generation								
Levofloxacin	500 ^a	5–7	7–8	99	24–38		85	521–771

$t_{1/2\beta}$ elimination half-life; PB, protein binding; Fu, fraction recovered in urine; C_{\max} , peak concentration.

^a 250 mg dose is recommended for UTI.

Lower UTI : OK // Upper UTI ; sense to this drug, Low MIC



Acute uncomplicated pyelonephritis : empirical treatment

Antimicrobial Regimen†

Fluoroquinolones
given orally twice
(extended-release)
7 days†; levofloxacin
orally once daily

Not recommended

TMP-SMX, 160 mg
daily for 14 days

Not recommended

Oral beta-lactams
in IDSA guideline

Outpatients

- Not complicated infection
- No signs of systemic toxicity
- Take oral medications, closely followed
- Initial treatment : 1 g of ceftriaxone or 24-hr dose of an aminoglycoside is recommended (Thailand).

Admit

- Severe cases
- Treated with a parenteral antimicrobials
- Improvement 24-48h
changed to an oral antimicrobials

efficacy

7 days; 96%

7 days; 86%

efficacy

ceftriaxone

is susceptible

is susceptible

is inferior to that
of quinolones^{28,32};
not recommended agents

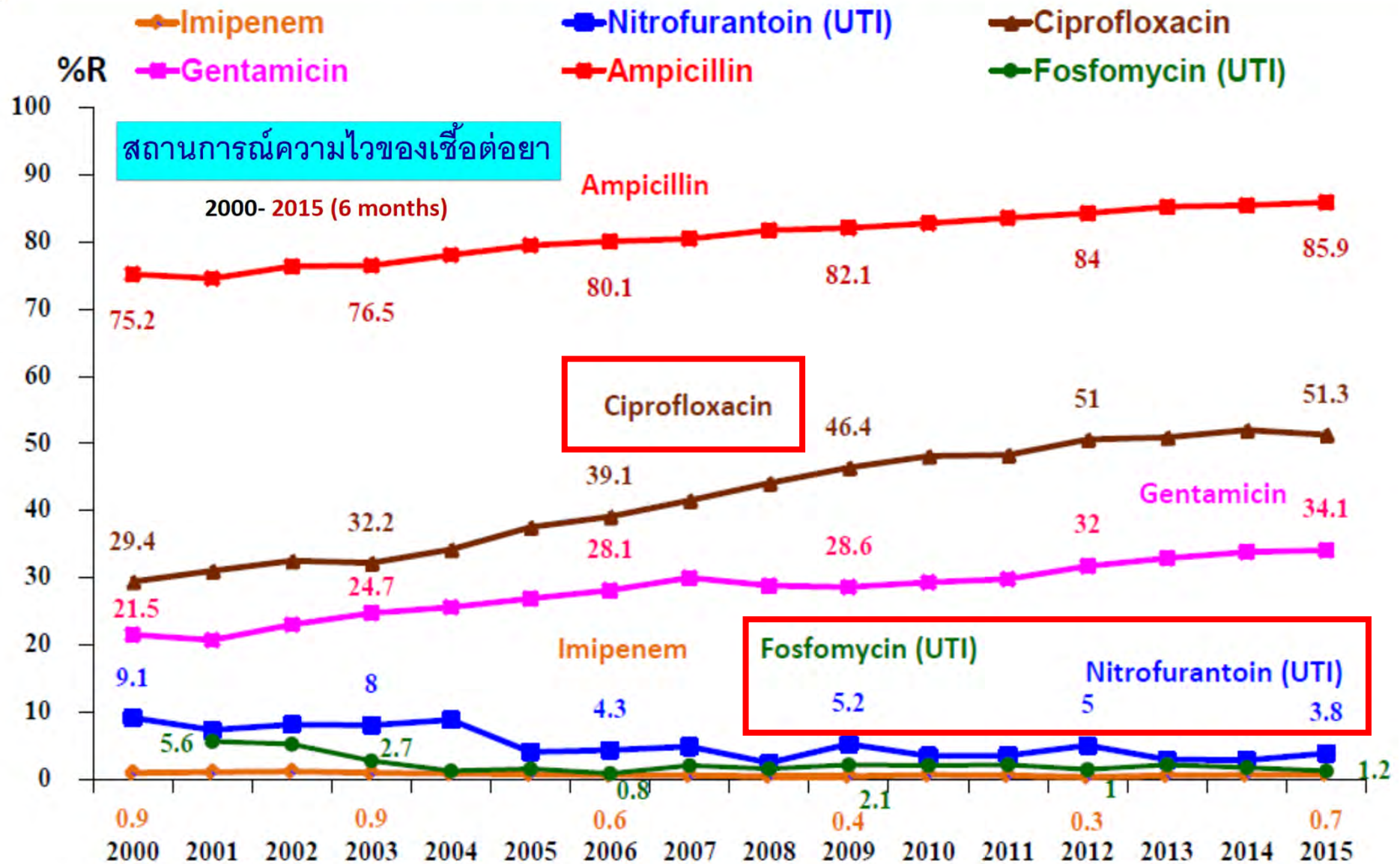
cannot be used



Complicated UTI treatment

- Individualized patient care; previous urine culture.
- Minimize the effects of obstruction / anatomic abnormality
- Aggressive use of antibiotics
 - Appropriate use and dosages of broad-spectrum drugs (the antibiogram)
 - Adjust antibiotics after the cultures and sensitivities have returned
- Clinical not improved, urologic evaluation

Antimicrobial Resistance rates of *E. coli* by year (NARST-50 hospitals, 2000-2015)





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Prevention

Behavioral counseling

Reduction in frequency of intercourse

-The strongest risk factor

Spermicide (condoms), diaphragm contraceptive
recommend changing to another method

-Strong risk factor

Recommend

- urinate soon after intercourse
- drink fluids liberally
- not routinely delay urination
- wipe front to back after defecation
- avoid tight-fitting underwear
- avoid douching

-In case-control studies

*None of these : shown to be associated with
a reduced risk of recurrent UTIs

**Suggest; low risk and might be effective



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Prevention

Biologic mediators

Cranberry juice, capsules or tablets

-**Inhibition of uropathogen adherence.**

-**Cochrane review** 2008: significantly reduced the incidence of UTIs at 12 months (RR 0.65, 95%CI 0.46-0.90)

-Cranberry juice **fails to prevent recurrent UTI**
(RCT, Clin Infect Dis 2011)

Topical estrogen

-Postmenopausal women: **topical estrogen** normalizes the vaginal flora and reduces the risk of recurrent UTIs.

-**Oral estrogens are not effective**

Adhesion blockers (D-mannose)

-Mannosides ; block adhesion;

-D-mannose has not been evaluated in clinical trials

Management : Recurrent Acute Uncomplicated Cystitis

Strategy

Self-diagnosis and self-treatment

- Not a preventive strategy.
- U/C ; periodically before treatment to confirm presence of UTI and drug susceptibilities

Antimicrobial prophylaxis†

Postcoital antimicrobial prophylaxis: single dose of antimicrobial agent as soon as feasible after intercourse

Nitrofurantoin, 50–100 mg†

TMP-SMX, 40 mg and 200 mg or 80 mg and 400 mg§

TMP, 100 mg§

Cephalexin, 250 mg†

Fluoroquinolones; Pregnancy category C

Continuous antimicrobial prophylaxis: daily bedtime dose (except fosfomycin; see below)

Nitrofurantoin, 50–100 mg†

TMP-SMX, 40 mg and 200 mg (3 times weekly is also effective)

TMP, 100 mg§

Cephalexin, 125–250 mg†

Fosfomycin, 3-g sachet every 10 days†⁴⁵

Quality of life



Drug resistance

- If UTIs are temporally related to coitus

- First ; confirmed U/C negative 1-2 wk
- Recommend ; 6-month trial
- Discontinue ; 50% recurrences of cystitis.



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UTI in pregnancy

- **Asymptomatic bacteriuria** : occur in 2-10%.
- If untreated mothers : 30% acute cystitis, 50% acute pyelonephritis
(low birthweight and preterm birth).
- Dipstick testing: not sufficiently. (**U/C should be the investigation of choice**)
- ATB treatment is effective : 7 days course
- Ampicillin, and the cephalosporins : relatively safe.
- **Avoid** : Sulfonamides 1st trimester (possible teratogenic effect) and near term (kernicterus), Fluoroquinolones (cartilage development)



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UTI in special conditions

- Post-coital UTI
- Pregnancy
- Men
- Catheter-associated UTI
- Infected stone
- Transplant kidney
- Cystic kidney
- Renal tuberculosis
- Candiduria
- Xanthogranulomatous pyelonephritis

Vaccines

ATB prophylaxis for UTI after removal of urinary catheter: meta-analysis, 2013



Conclusions

- Urinary tract infections (UTIs) ; common diseases.
- Frequently affect ; women (due to a shorter urethra)
- Diagnosis ; clinical symptoms + significant bacteriuria (urine culture).
- Antibiotics are often effective therapy, antibiotic resistance is increasing.

Pyuria, Bacteriuria \neq Antibiotic use

~~Colonization~~



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THANK

YOU



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Thank you
for your attention

เชื้อก่อโรค	สิ่งส่งตรวจทั้งหมด	PENICILLIN	AMPICILLIN	CEFTRIAXONE	MEROPENEM	CIPROFLOXACIN	LEVOFLOXACIN	OFLOXACIN	AMIKACIN	GENTAMICIN	FOSFOMYCIN	NITROFURANTOIN	CO-TRIMOXAZOLE
<i>E. coli</i>	1 7,137	-	13 (12641)	52.8 (11200)	99.2 (12336)	37.6 (12320)	38.8 (4874)	39.4 (2917)	97.1 (14821)	63.1 (16055)	98.3 (2592)	94.3 (1227)	39.3 (14568)
<i>Enterobacter spp.</i>	1 97	-	3.5 (142)	39 (82)	88.6 (123)	57.9 (164)	31.2 (32)	76.9 (52)	86.1 (180)	64.9 (191)	-	-	52.8 (163)
<i>Klebsiella spp.</i>	2 70	-	2.3 (177)	21.4 (140)	61.5 (205)	26.5 (200)	20 (70)	40.8 (49)	68.4 (263)	50.2 (261)	-	23.3 (30)	27.3 (245)
<i>Proteus mirabilis</i>	1 ,404	-	50.6 (1058)	86.6 (830)	98.1 (855)	73.5 (1066)	73.5 (344)	75.7 (263)	98.9 (1230)	77.6 (1312)	-	3 (99)	51.9 (1223)
<i>P. aeruginosa</i>	2 ,058	-	-	-	62.9 (1577)	58.9 (1525)	54.1 (518)	56.9 (102)	69.6 (1820)	61.1 (1747)	-	-	-
<i>Enterococcus spp.</i>	1 ,793	42.1 (1219)	56.5 (1737)	-	-	14 (229)	15.2 (198)	-	-	-	-	-	-
<i>S. aureus</i>	4 70	8.9 (192)	-	-	-	71.9 (96)	63.2 (57)	58.7 (46)	-	77.2 (302)	84.8 (164)	-	92.8 (400)
<i>S. saprophyticus</i>	9 6	18.9 (37)	-	-	-	65.5 (29)	-	-	-	97 (66)	78.2 (55)	-	91 (89)

Susceptibility report : UA specimen, Thailand, 2015

NARST report website, 2015