



Dr Richard Everts

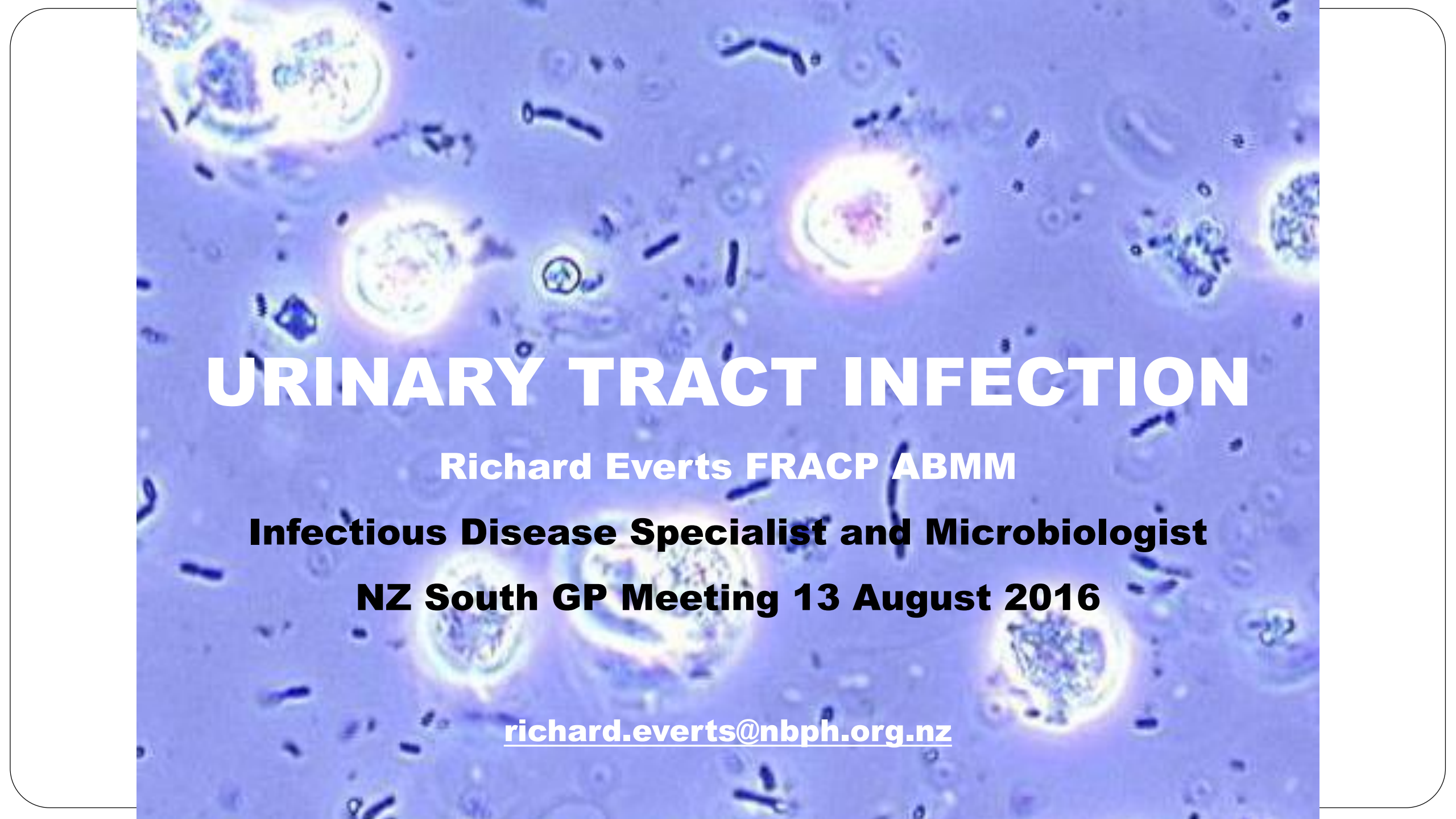
Infectious Disease Specialist

Microbiologist and General Physician, Nelson

Saturday, August 13, 2016

(Room 6)

16:30 - 17:30 WS #133: What's New Treating UTI's?

A microscopic image of a urine sample, likely a Gram stain, showing numerous white blood cells (leukocytes) and various types of bacteria. The bacteria appear as small, dark, rod-shaped structures, some of which are clustered together. The white blood cells are larger, with prominent nuclei and surrounding cytoplasm. The background is a light blue/purple color.

URINARY TRACT INFECTION

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Infectious Disease Specialist and Microbiologist

NZ South GP Meeting 13 August 2016

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Introduction

Young women

- Half by 32 years
- Challenges:
 - Screening in pregnancy
 - Antibiotic resistance.

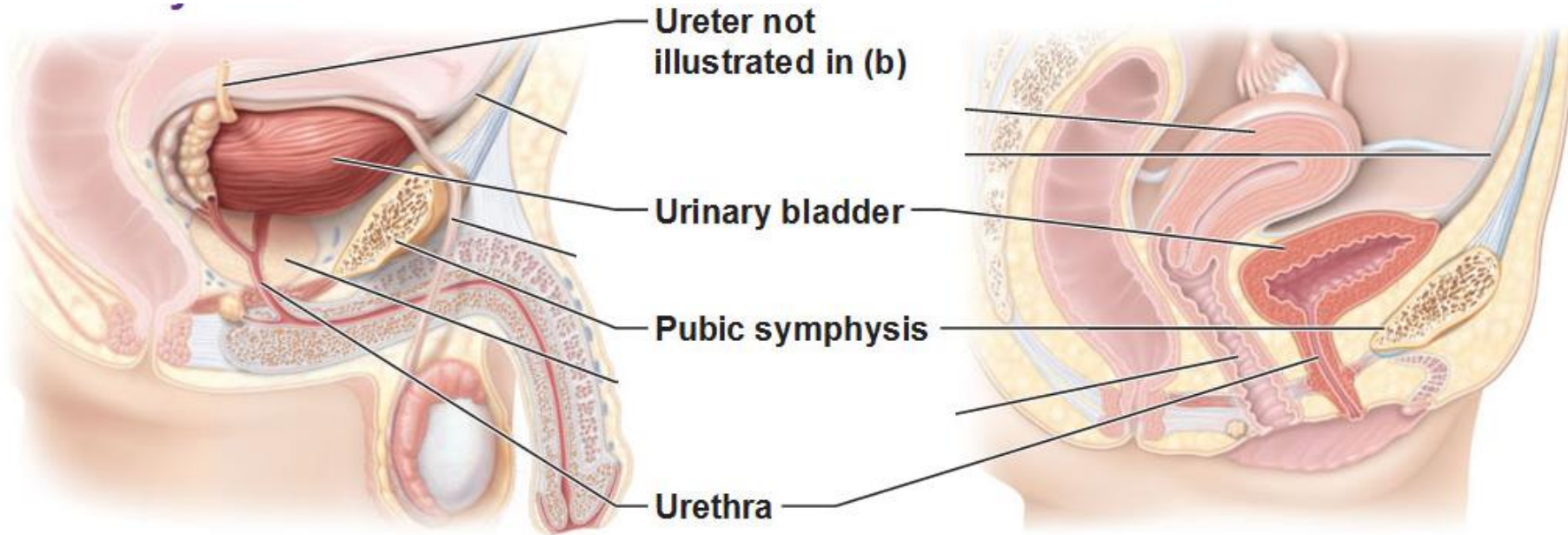


Later in life.....

- Urinary tract anatomical or functional abnormalities, indwelling catheters
- Challenges:
 - Asymptomatic bacteriuria
 - Non-specific symptoms and signs
 - Getting a good urine sample
 - Antibiotic resistance (e.g. ESBLs)
 - High incidence of recurrence.



Origin of UTI micro-organisms

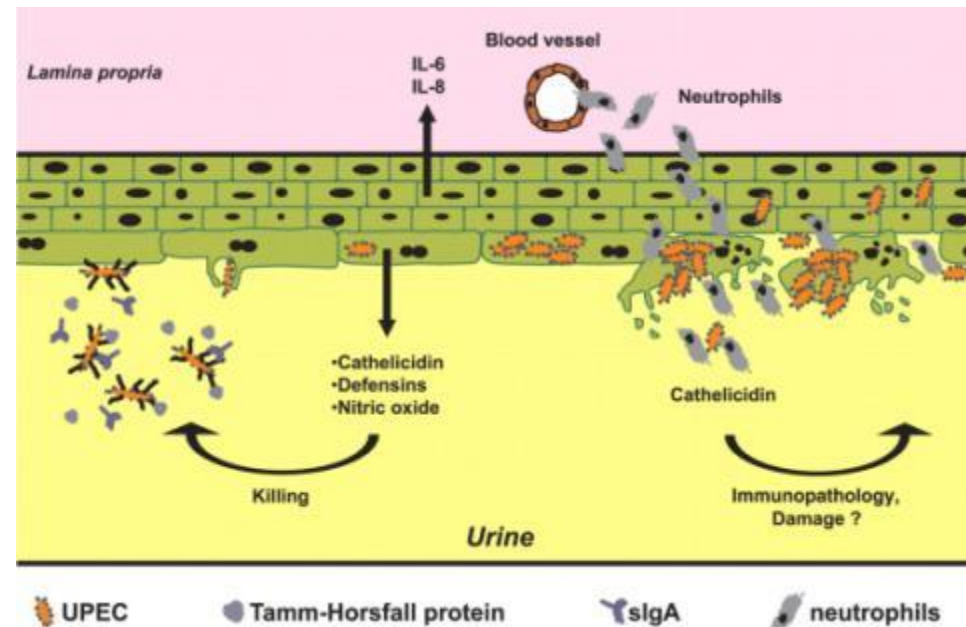


- Ascend urethra – women $>$ men
- (Bloodstream – only *Staphylococcus aureus*)

Urinary tract defences

- Vagina – acid pH, normal vaginal flora
- Urethra – flow, PSA in men
- Bladder – normal emptying, mucopolysaccharide, antibacterial secretions (iron-sequestering proteins, defensins, cathelicidin, Tamm-Horsfall protein)

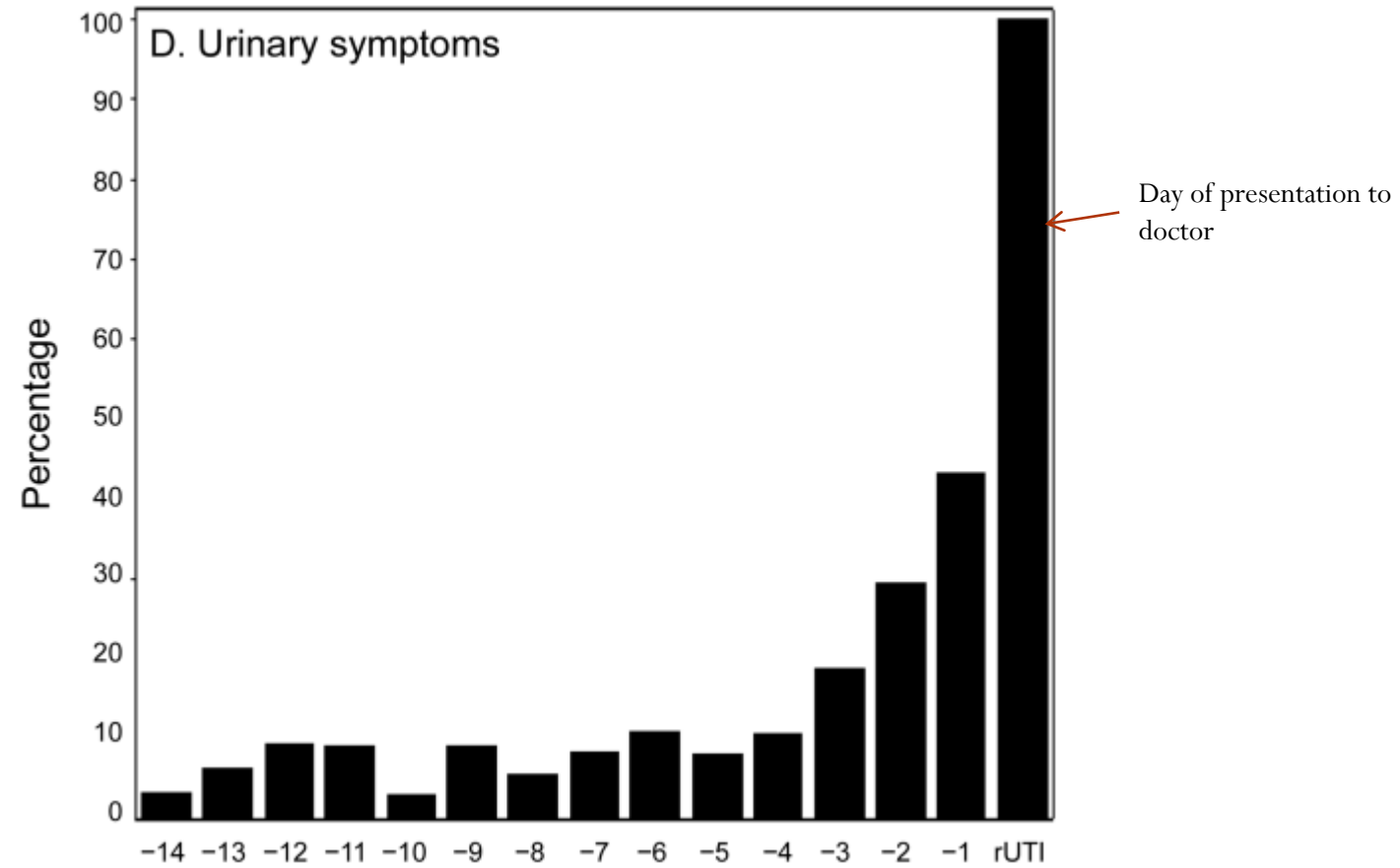
Bladder mucosal defences
minimal compared with
bowel



Pathogenesis – ‘uncomplicated’

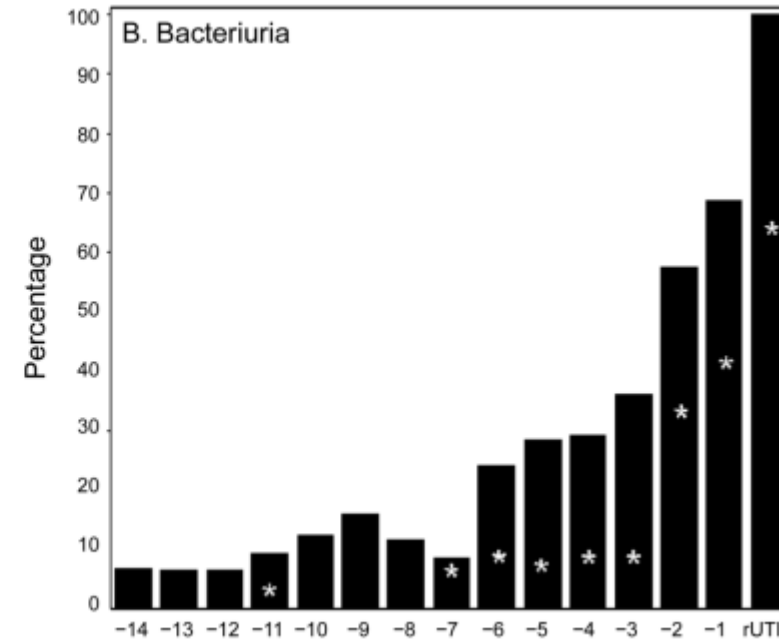
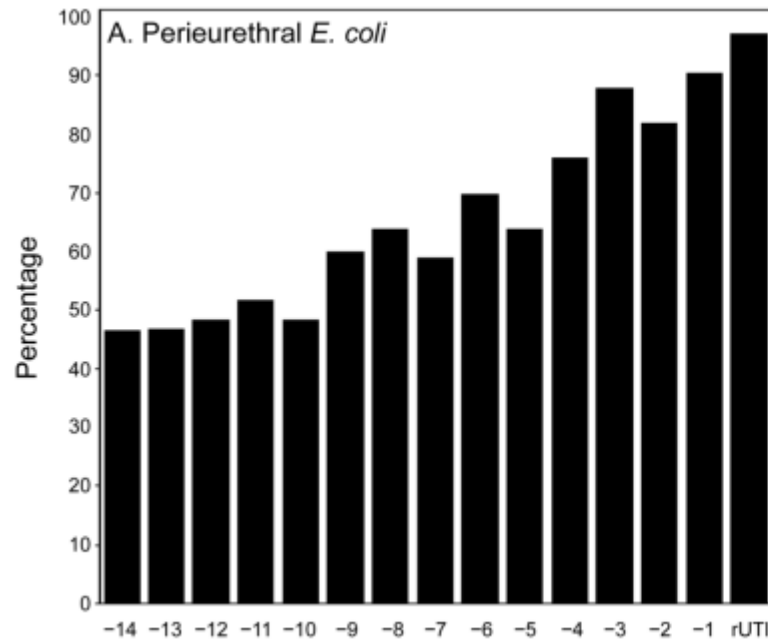
- Young, otherwise healthy females
- Risk factors
 - Genetics, family clustering
 - Sexual intercourse and spermicide.
- Only the most uro-pathogenic bacteria
 - fimbriated strains of *E. coli* (75-95%)
 - *Staphylococcus saprophyticus* (10-20%)





104 women with recurrent UTI; mean age 22 yr
Daily peri-urethral swab, MSU, symptom diary for 3 months
Studied 38 UTIs.

J Infect Dis 2009; 200(4): 528-36

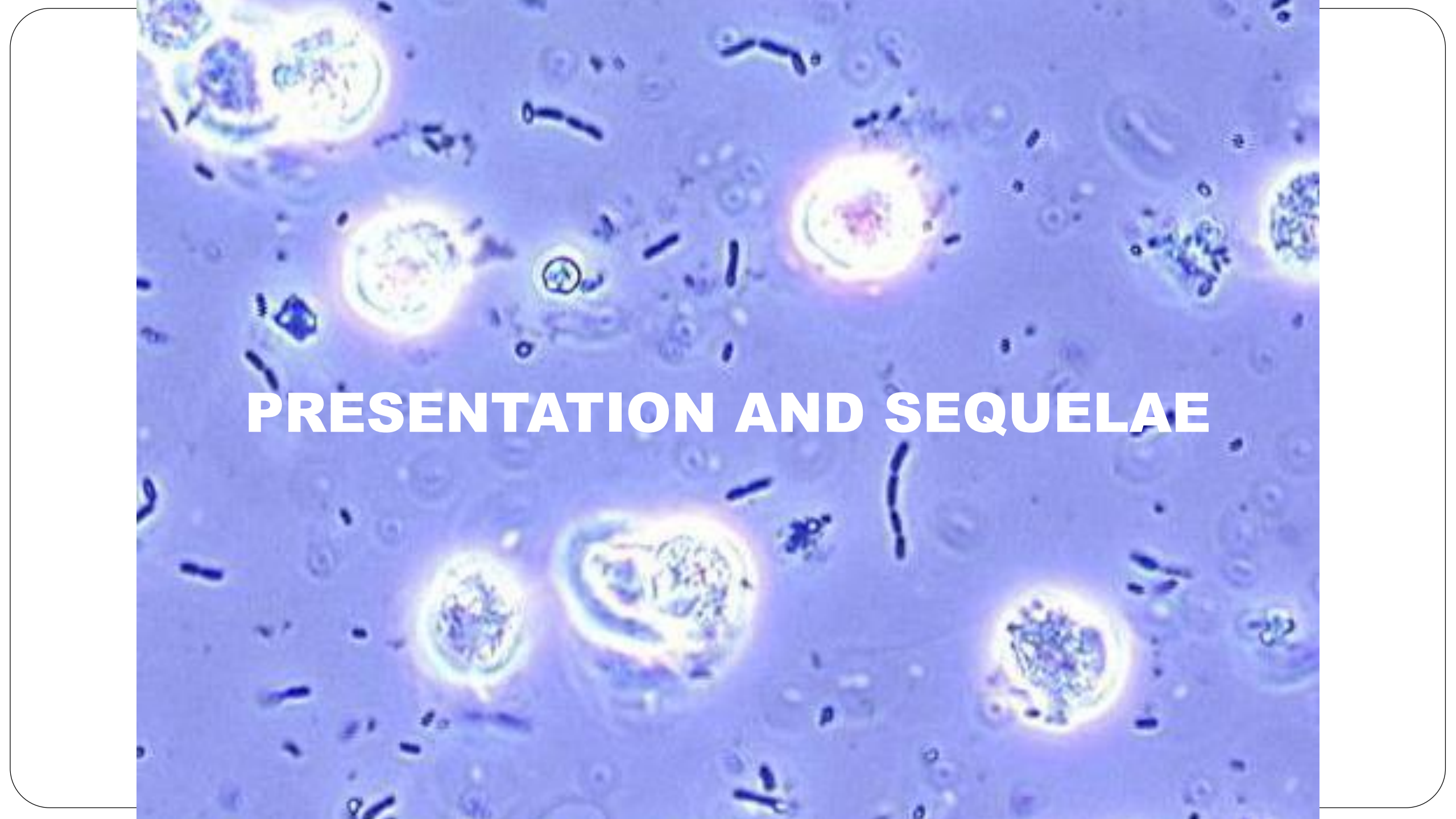


Frequently triggered by sexual intercourse
 Illustrates value of prophylactic twice-weekly antibiotic
 (? Value of vaginal antiseptic or probiotic)

Pathogenesis – ‘complicated’

- Anyone other than young, otherwise-healthy women
- Risk factors
 - Old age (e.g. loss of vaginal oestrogenisation)
 - Pregnancy
 - Diabetes; immune-compromise
 - Urinary obstruction (e.g., congenital, strictures, prostatic)
 - Urinary tract catheterisation or surgical instrumentation; condom catheters in men
 - Incomplete bladder emptying (for any reason)
 - Urinary tract stones.
- A wide range of micro-organisms
 - Fimbriated and non-fimbriated *E. coli* (27%)
 - *Proteus mirabilis*, *Klebsiella* spp., *Enterobacter* spp.
 - *Pseudomonas aeruginosa*
 - *Candida* spp.
 - Enterococci, *Staphylococcus aureus*
 - Polymicrobial?





PRESENTATION AND SEQUELAE

Presentation

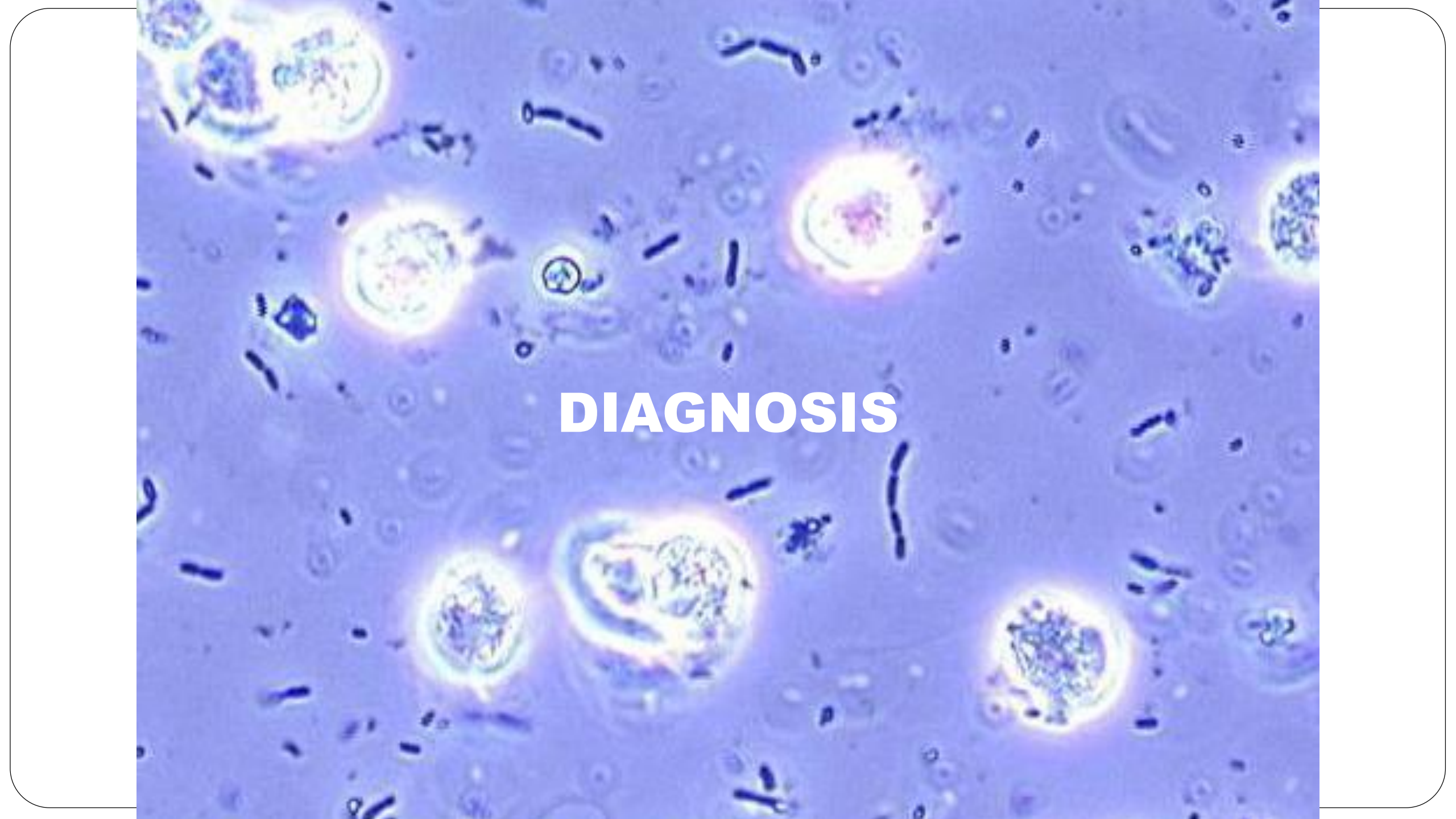
	Cystitis	Pyelonephritis
Symptoms and signs	Dysuria, frequency, urgency, suprapubic discomfort, haematuria, turbid urine <u>Elderly</u>: as above but may be more subtle or absent, new or worse incontinence, epididymo-orchitis in males, change in mental status	May or may not include same symptoms as cystitis, plus: nausea or vomiting, fever or chills, malaise, costo-vertebral angle pain and tenderness, rapid pulse If severe: shock; multi-organ system dysfunction
Laboratory findings	Bacteriuria +/- pyuria	Bacteriuria +/- pyuria, raised inflammatory markers (CRP) If severe: renal impairment

Pneumaturia

- “Frothy urine” or “flatus-like sound” when passing urine
- Consider:
 - Post-cystoscopy
 - Vesicovaginal or vesicoenteric fistula (Crohn’s disease, malignancy, diverticular disease, surgery)
 - Diabetic with yeast or enteric gram-negative bacilliary infection (emphysematous pyelonephritis.)

Sequelae

- Symptomatic cystitis:
 - Does not often progress to pyelonephritis
 - Rare serious sequel
 - Resolves without antibiotics in 25 to 40% of cases within a week or two.
- Bacteriuria (even asymptomatic) in pregnancy:
 - Pyelonephritis in 15% and 40% (mostly 2nd or 3rd trimester)
 - 2- to 3-fold increased risk of pre-term birth, low birth weight and perinatal mortality
 - ↑ risk pre-eclampsia.
- Pyelonephritis:
 - Occasionally sepsis, acute kidney injury, renal abscess or metastatic infection
 - Renal scarring and impairment, especially diabetes, ureteric reflux or obstruction.



DIAGNOSIS

Who to test – no symptoms

- Pregnant
- Before a urological procedure (as directed by the Urologist to reduce the risk of post-operative infection)
- Institutional outbreak (as directed by Infection Prevention and Control or Public Health staff).



Who to test - symptoms

No



Yes

‘Complicated’ infection (**wider range of causative micro-organisms**):

- Old age
- Pregnancy
- Diabetes; immune-compromise
- Urinary obstruction (e.g., congenital, strictures, prostatic)
- Urinary tract catheterisation or surgical instrumentation; condom catheters in men
- Incomplete bladder emptying (for any reason)
- Urinary tract stones.



Yes

Those with increased of **antibiotic resistance**:

- Recurrent infection
- Recent antibiotic treatment
- Recent hospital inpatient?
- Overseas travel within the last 6 months (especially to Asia, Middle East or Africa)
- Previous infection or carriage of a multi-drug-resistant gram-negative rod (e.g. an ESBL-producing *E. coli* or *Klebsiella* spp.)



Yes



Who to test – elderly, no IDUC

- Acute dysuria, or
- 2 or more of:
 - Fever
 - Mental status change without other explanation
 - New or worsening urinary urgency
 - Urinary frequency
 - Suprapubic pain or tenderness
 - Gross haematuria
 - Costovertebral angle tenderness
 - New or worsening urinary incontinence
 - *(NOT smelly or cloudy urine).*

→ Stop AB if culture negative.

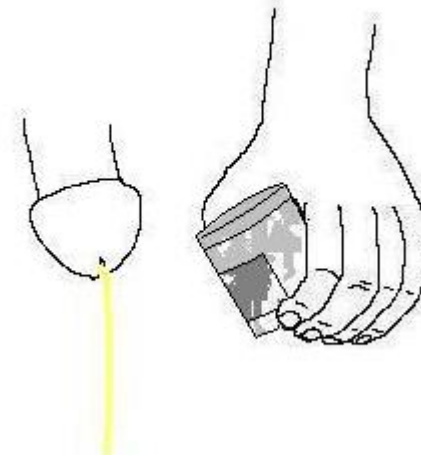
Who to test – elderly, IDUC

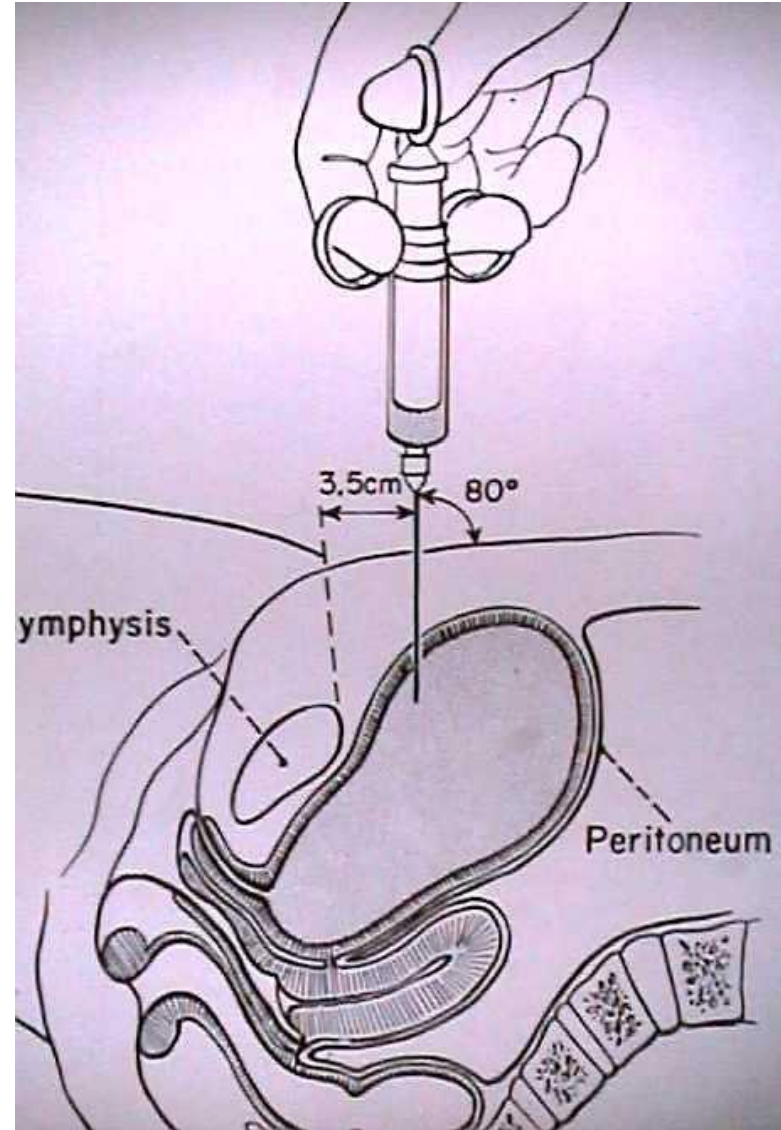
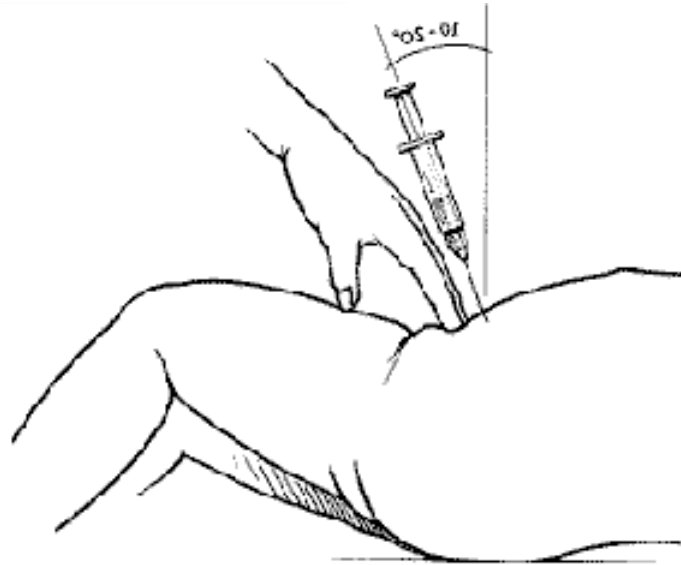
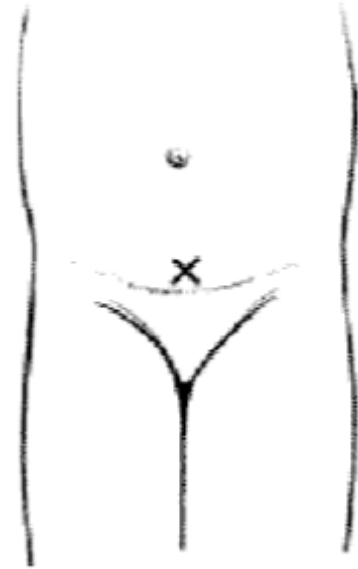
- 1 or more of:
 - Fever
 - Rigors (with or without an identified cause)
 - Mental status change without other explanation
 - Costovertebral angle tenderness
 - *(NOT smelly or cloudy urine).*

→ Stop AB if culture negative.

How to test urine

- Goal = avoid contamination (occurs in 30%)
- MSU
 - Give instructions to patient
 - Void first part
 - Female – cleanse vulva with apart
 - Uncircumcised male – retract
- In/out catheter if can't do MSU or critical result
- Gold standard = supra-pubic aspirate

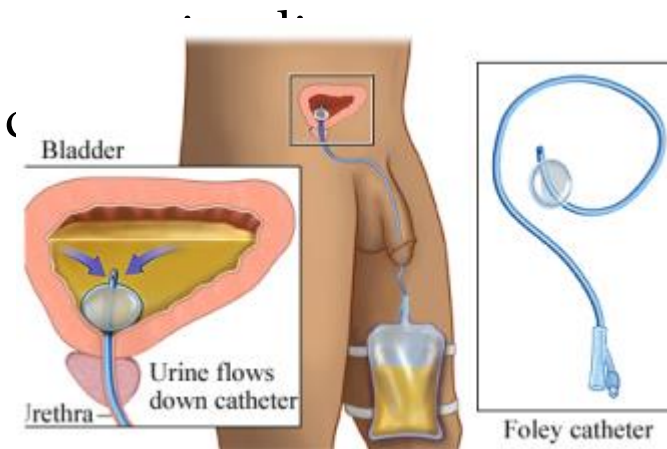




Sampling from an IDUC

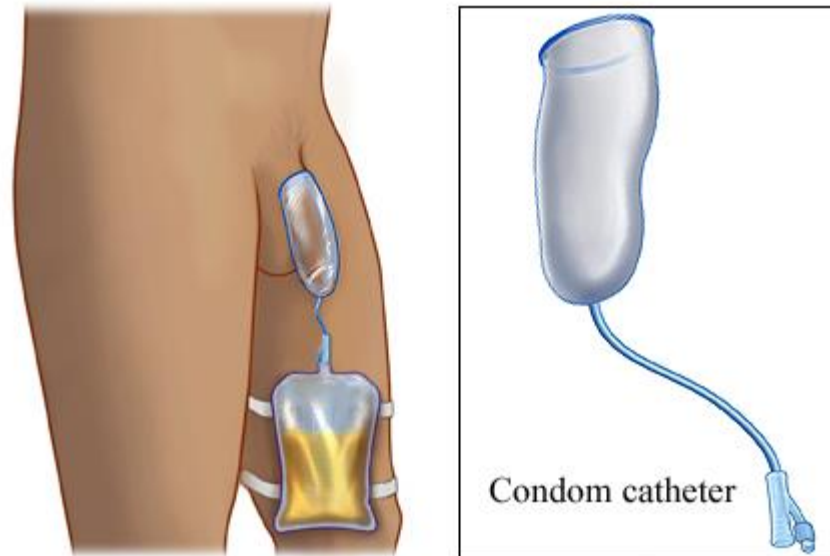
- Invariably contaminated, esp. drainage bag.
- Ideal = remove IDUC, get MSU
- Second best = remove IDUC, replace with fresh sterile IDUC and catch urine
- Third best = leave IDUC in, sample urine through collection port (cleanse first)
- Fourth best = leave IDUC drainage port, collect urine

bag from c



Sampling from a condom catheter

- Ideal = remove condom, cleanse peri-urethral area then collect MSU
- Second best = remove condom and drainage bag, cleanse peri-urethral area then apply sterile fresh condom catheter and collect the first urine.



To dipstick or not?



- How does the test work?
 - Neutrophils produce leukocyte esterase (LE)
 - *Enterobacteriaceae* convert nitrates to nitrite
- Potential benefits
 - Aid to diagnosis (UTI vs other)
 - Avoid unnecessary urine culture (Labtest Auckland 1300 urine cultures/day, most are negative)
 - Avoid inappropriate antibiotic use and resistance
 - Screen for diabetes (glycosuria)
 - Patient perception of being thorough.

To dipstick or not?



- Sensitivity - marginal
 - LE 59-87% - false negatives partly due to degeneration of WC in transit
 - Nitrite 10-50% - false negatives due to infection by *S. saprophyticus* or other non-enteric microbes, insufficient nitrates from lack of vegetables in diet, short bladder incubation time
 - Combined LE or Nitrite 90%
- Specificity – poor, esp. LE
 - LE – also positive in urethritis, other infections (esp. gynae), nephritis, contamination
 - Nitrite – also positive if air exposed (2 weeks → 75% positive).

To dipstick or not?



- Positive predictive value (PPV)
 - Proportion of positive tests that have the disease
 - 'rule in'
- Negative predictive value (NPV)
 - Proportion of negative tests that do not have the disease
 - 'rule out'

DEPEND ON SENSITIVITY/SPECIFICITY (e.g. TB) AND PREVALENCE
(e.g. Antenatal HIV)

To dipstick or not?



- 90% of young women with dysuria and frequency (but no vaginal discharge) have a urinary tract infection
- What is dipstick NPV?
- Should negative dipstick change management?

RCT in dipstick-negatives

- Symptomatic women with suspected UTI in Christchurch
- Dipstick positive → Rx
- 59 dipstick negative → randomised to trimethoprim versus placebo
 - Trimethoprim – 3 days to resolution
 - Placebo – 5 days to resolution.

BMJ 2005; 331(7509): 143-

To dipstick or not?



Elderly with classic UTI symptoms

- 917 women > 70 yr (mean 80 yr) attending GP
- 88% culture +
- Dipstick sensitivity 52%
- LE NPV 22%
- Nitrite NPV 22%, PPV 99%
- Authors: 'dipstick helped confirm UTI'

Internat J Antimicrob Agents 2006; 27(3): 236-41

To dipstick or not?



Elderly with classic UTI symptoms

- 96 women > 65 (mean 78 yr) at Geriatric Medical Centre in Israel
- 71% culture +
- LE – sens 86%, PPV 81%, NPV 57%
- Nitrite – sens 75%, PPV 79%, NPV 43%
- LE or nitrate NPV 49%
- Authors: ‘dipstick too inaccurate to rule out or rule in UTI’

To dipstick or not?



Men with UTI symptoms

- 422 men (mean 57 yr) attending GP
- 56% culture +
- Nitrite NPV 59%
- LE or nitrate NPV 73%
- Authors: 'negative dipstick can not rule out UTI'

Clin Infect Dis 2007; 45(7): 894-6

To dipstick or not?



General Practice overall

- Meta-analysis of 70 studies of nitrites (N) or leukocyte esterase (LE) by dipstick
- Subset: family physician offices (55% culture +)
 - PPV (LE or Nitrite) 76%
 - NPV – neither LE nor Nitrite 84%
 - (But who tested??)
- Authors: ‘negative dipstick OK to rule out UTI’

BMC Urology 2004; 4: <http://www.biomedcentral.com/1471-2490/4/4>

To dipstick or not?



Urology clinic – symptoms of ?UTI

- > 4000 urine samples from 1223 patients with suspected UTI
- 30% culture +
- Dipstick LE
 - Sensitivity 40%
 - PPV 51%
 - NPV 75%
- Authors: ‘LE dipstick performance poor’

BJU Internat 2013; 112: 231-8

To dipstick or not?



Urology clinic – atypical symptoms

- 508 patients with no dysuria, no acute ↑ frequency and no fever (most overactive bladder)
- 24% culture +
- Sensitivity – LE 56%, Nitrite 10%
- PPV – LE 30%, Nitrite 85%
- NPV – LE 85%, Nitrite 81%
- Authors: ‘Dipstick too inaccurate to rule in or out UTI’

To dipstick or not?



ED – vague symptoms in elderly

- 100 patients with confusion, weakness and fever (no dysuria or frequency) attending ED
- 19% culture +
- Sensitivity – LE or Nitrite 64%
- PPV – 31%
- NPV – 93%
- Authors: ‘Dipstick inaccurate’

To dipstick or not?



ED overall

- Meta-analysis of 70 studies of nitrites (N) or leukocyte esterase (LE) by dipstick
- Subset: ED (15% culture +)
 - PPV (N or LE) 41%
 - NPV (neither) 98%
- Authors: 'negative dipstick OK to rule out UTI'



BMC Urology 2004; 4: <http://www.biomedcentral.com/1471-2490/4/4>

To dipstick or not?



Laboratory in Turkey

- 32,998 urine samples
- 2.3% culture +
- Sensitivity
 - LE 71%
 - Nitrite 18%
- NPV for LE and Nitrite – virtually 100%
- Authors: ‘negative dipstick OK to rule out UTI’

Clin Biochem 2013; 46(13-14): 1285-9

To dipstick or not?



CONCLUSION

- Asymptomatic (e.g. pregnant) – NO (> 3 studies)
- Typical UTI symptoms – NO
 - Too insensitive to deter from urine culture or AB Rx
 - Small value for diabetes screen, ??other diagnosis if negative, patient perception
- Atypical symptoms/low risk – YES
 - Negative dipstick → think alternative causes e.g. vaginitis or urethritis; but ? send MSU anyway
 - Inaccurate if IDUC – few studies
 - Value for diabetes screen, patient perception.

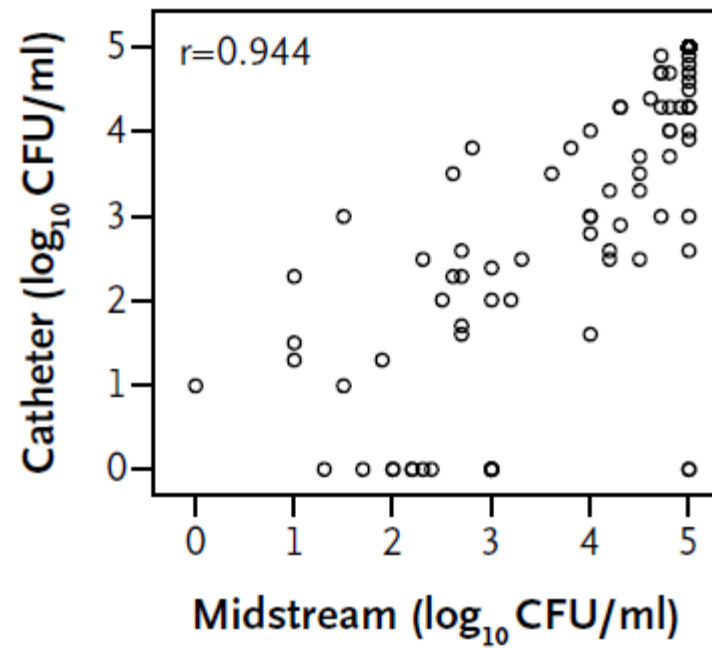
Interpretation of culture result

- Major predictors of true bacteriuria:
 - Number of organisms
 - $> 100 \times 10^6/\text{L}$ usually true bacteriuria
 - $11\text{-}100 \times 10^6/\text{L}$ usually true bacteriuria if uro-pathogen
 - $\leq 10 \times 10^6/\text{L}$ usually not bacteriuria, except *E. coli*
 - Uropathogen
 - *E. coli*, *S. saprophyticus*, other enteric GNR usually true bacteriuria
 - Enterococci, Group B strep, coagulase-negative staphylococci usually contaminants
 - Method of collection
 - In/out catheter more likely to be true bacteriuria than MSU

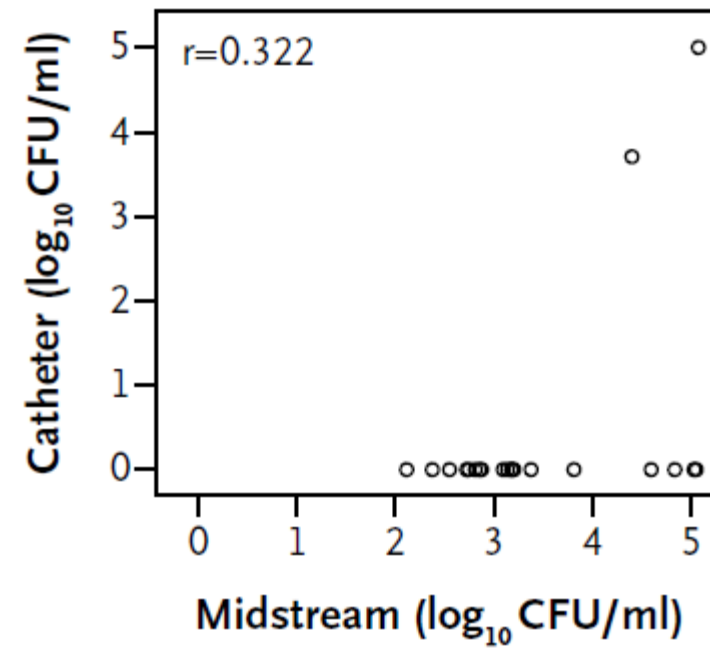




A *Escherichia coli*



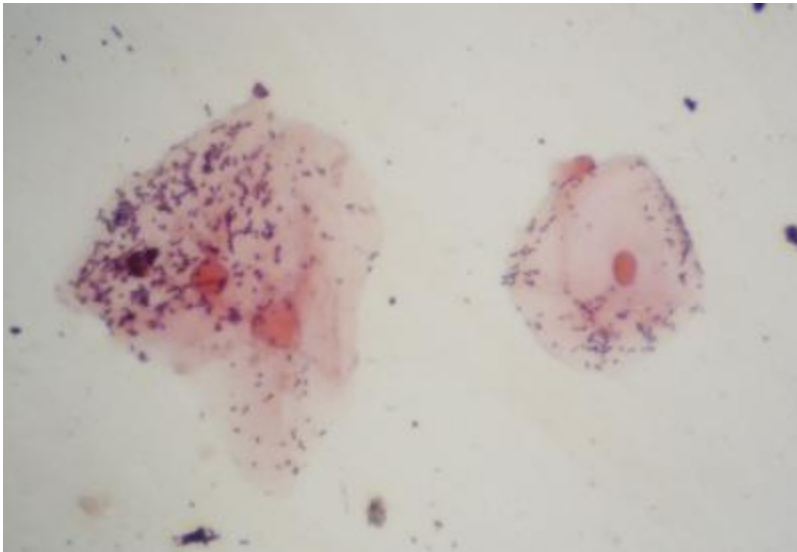
B Enterococci



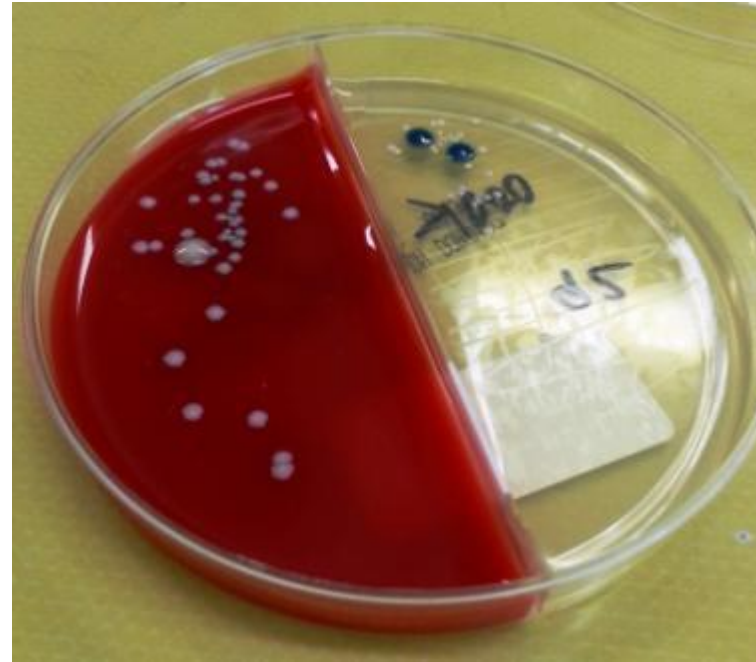
NEJM 2013; 369(20): 1883-91.

Interpretation of the result

- Minor predictors of true bacteriuria:
 - Only one species of micro-organism
 - Absence of squamous epithelial cells (SEC)
 - Typical symptoms.
 - (Pyuria??)



Squamous epithelial cells



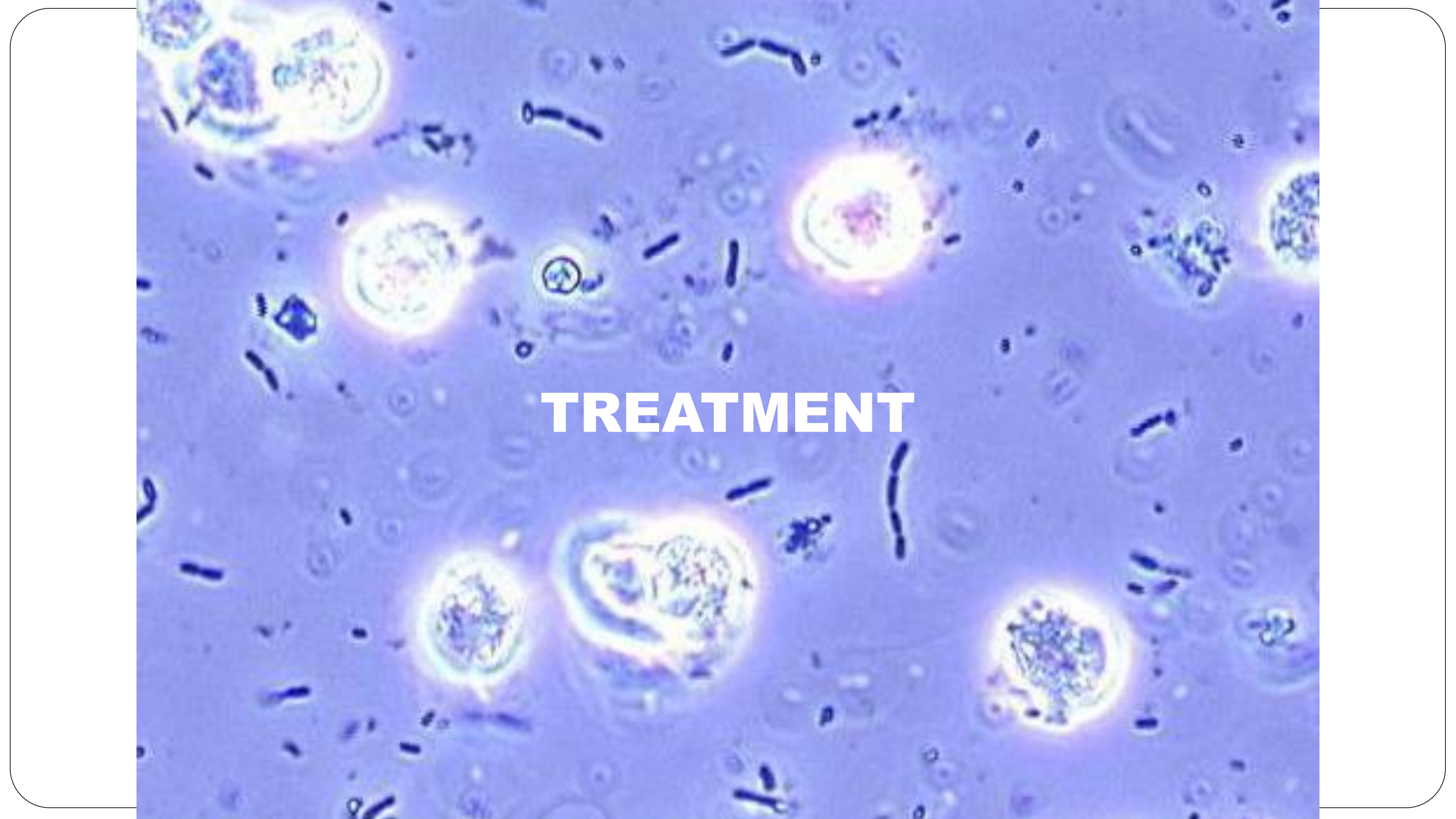
Mixed low-quantity bacteriuria

Interpretation – MSU summary

	$> 100 \times 10^6 / \text{L}$	$11-99 \times 10^6 / \text{L}$	$\leq 10 \times 10^6 / \text{L}$
<i>E. coli</i>	True	True	Often true
<i>S. saprophyticus</i> , enteric GNR	True	Often true	Uncertain*
Enterococci, GBS, other coagulase-negative staphylococci	Often true	Uncertain*	Contaminant

Uncertain

- consider symptoms, SECs, mixed orgs
- consider repeat MSU or in/out catheter sample



TREATMENT

Who needs treatment?

- Symptoms = YES
- Asymptomatic bacteriuria = NO
 - (Except pregnancy (improves multiple outcomes) or before urological procedure.
 - Harmless – less virulent microbes, less bladder inflammation (pyuria does not indicate benefit of Rx)
- If treat:
 - Short-term elimination
 - No change any long-term outcomes
 - ↑ subsequent symptomatic UTI
 - ↑ resistance.

Which antibiotics work?

- NOT macrolides (like erythromycin, roxithromycin or azithromycin), clindamycin or doxycycline
- Similar efficacy in trials:
 - Trimethoprim^C (or trimethoprim/sulfamethoxazole)
 - Augmentin
 - Cefaclor or cefalexin^C
 - Nitrofurantoin^C
 - Ciprofloxacin
 - Fosfomycin^C
 - Pivmecillinam^C

C = cystitis only, not pyelonephritis

Spectrum for 'uncomplicated' cystitis

- *Staphylococcus saprophyticus* – ALL
- Urinary *E. coli* in NZ 2014 – susceptibility:
 - Nitrofurantoin 99%
 - Gentamicin 95%
 - Cefalexin/cefaclor 94% (??)
 - Ciprofloxacin 92%
 - Amox/clavulanate 90%
 - Trimethoprim 74% ← **good enough????**
 - Amoxicillin 51% ← **not good enough**



Community data accurate?

- 374 Christchurch women seen by GP with dysuria and frequency all submitted urine for culture
 - 94 true UTI
 - Trimethoprim resistance 11.5%
 - (Lab community data 19%)

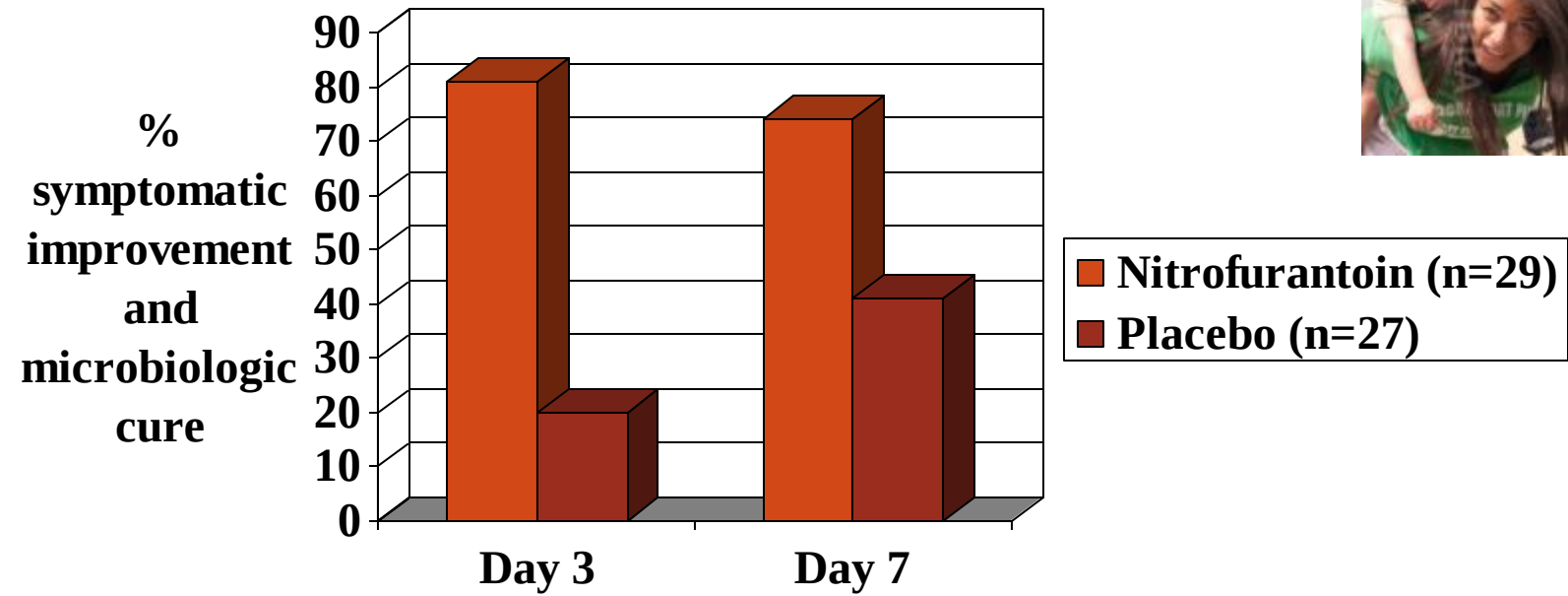
NZMJ 2002; 15(1146): 12-4

- 497 Norwich and Gloucester women with ≥ 2 symptoms of uncomplicated UTI all submitted urine for culture
 - 317 positive cultures
 - Trimethoprim resistance 13.9%
 - (Lab community data 24.5 to 27%)

JAC 2006; 58(5): 1000-8

Uncompl. UTI in non-pregnant ♀

Demonstrated bacteriuria

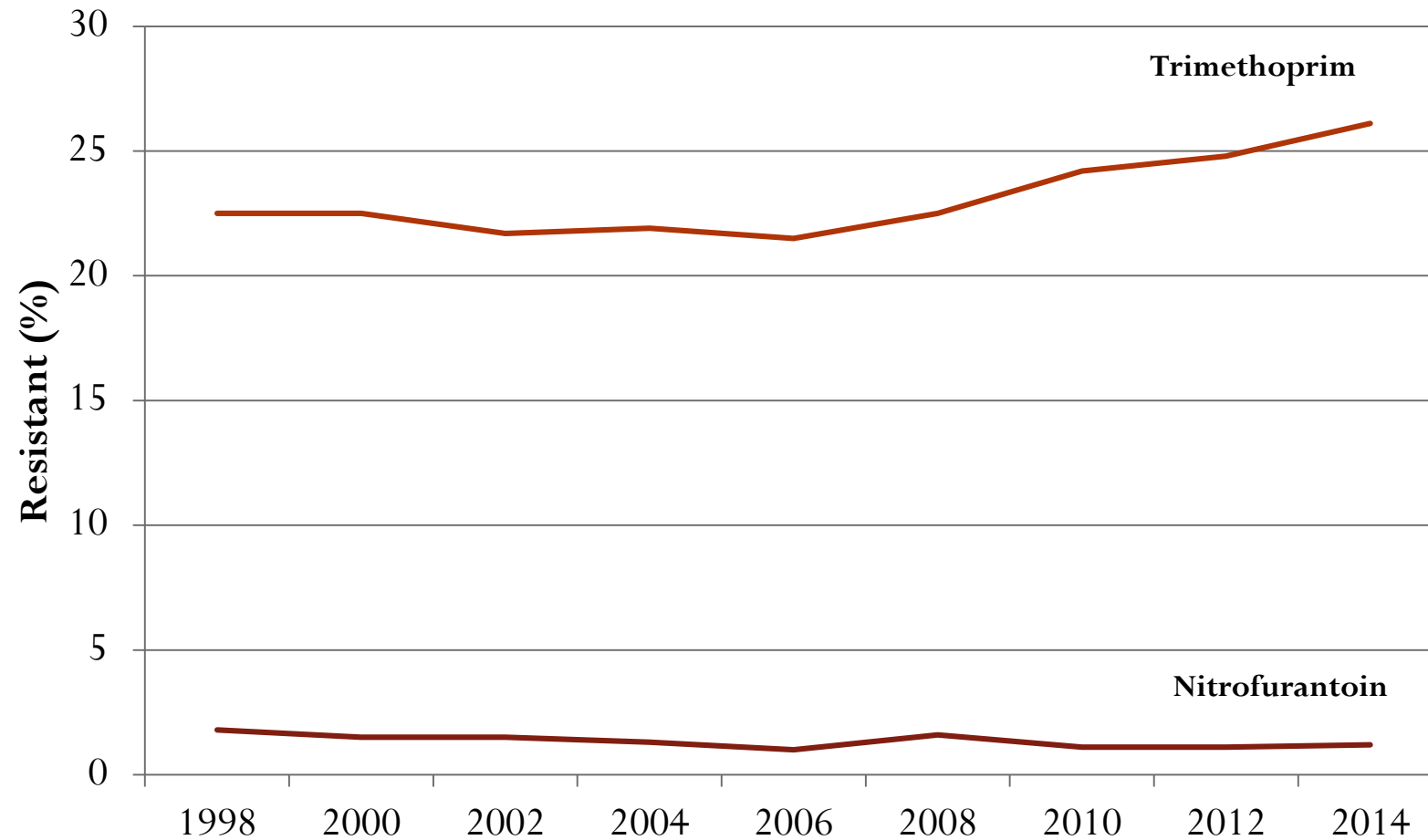


Trimethoprim for uncomplicated cystitis?

- ↑ resistance but community lab data skewed
- Modelling of response to empirical trimethoprim:
 - T resistance 10% → clinical cure 92%
 - T resistance 20% → clinical cure 88%
- Cystitis does not often progress to pyelonephritis
- Avoid trimethoprim if:
 - Recurrent UTI (OR for resistance 2- to 3-fold, unless always trimethoprim-susceptible)
 - Trimethoprim treatment last 3 months (OR for resistance 4- to 14-fold)
 - Overseas travel in last 6 months (especially to Asia, Middle East or Africa)
 - Previous infection with or carriage of a multi-drug-resistant gram-negative rod (e.g. an ESBL-producing *E. coli* or *Klebsiella* spp.)
- Avoid trimethoprim if low doctor or patient threshold for failure.



Urinary *E. coli* resistance in NZ



Spectrum for 'complicated' cystitis

- Wider range of organisms, higher risk of resistance
- All urinary organisms in Nelson/ Marlborough



Antibiotic	Percentage Susceptible – NELSON and MARLBOROUGH 2014 (No. tested)
Amoxicillin-clavulanate	82% (7106)
Cefaclor	81% (7079)
Ciprofloxacin	92% (6816)
Nitrofurantoin	88% (7284)
<u>Trimethoprim</u>	63% (6980)



Lots of infections +
Excessive, unregulated, unguided antibiotic use +
Overcrowding, poor sanitation, poor food standards

Multidrug-resistant GNR



- 40% of travellers to Asia acquire MDR-GNR, especially if use antibiotics during travel
- Carriage detectable for mean 2 months, up to 3 or 4 years
- If carry MDR-GNR and get UTI, > 50% caused by those bacteria, especially if previous UTI caused by those bacteria
- ESBL-producing *E. coli* and *Klebsiella* spp.
 - Usually resistant to trimethoprim, amoxicillin, Augmentin, cefaclor, ciprofloxacin, gentamicin, ceftriaxone
 - Usually susceptible to nitrofurantoin^C, fosfomycin^C, pivmecillinam^C, ertapenem (IV).

Nitrofurantoin

- Now 1st choice for cystitis in many Northern Hemisphere guidelines.
- *E. coli* resistance very uncommon in Western countries despite over 60 years of use; covers *S. saprophyticus*, Enterococci and some other GNR.
- Stewardship: not used outside of the urinary tract.
- NZ formulary: 50 to 100 mg QID, but recent international expert opinion: 100 mg TDS.
- SR formulation (Macrobid®) may become available in NZ: nausea ↓↓ and the dose is 100 mg twice daily.
- SEs: nausea 30%, acute pulmonary reaction 1 / 5000; RCTs show no difference with other urine AB
- Not for GFR < 30; but OK for elderly, pregnancy and men.

Fosfomycin

- Active against most enteric GNR (including almost all ESBL-producers), most *P. aeruginosa*, *S. saprophyticus*, and *E. faecalis*
- 3 g sachet, mix with half cup of cold water
- Dose x1 in uncomplicated women; x2 q3d if complicated; x3 in men; x7 in prostatitis
- \$130/dose
- Hospital Pharmacy – ID/Micro approve only.



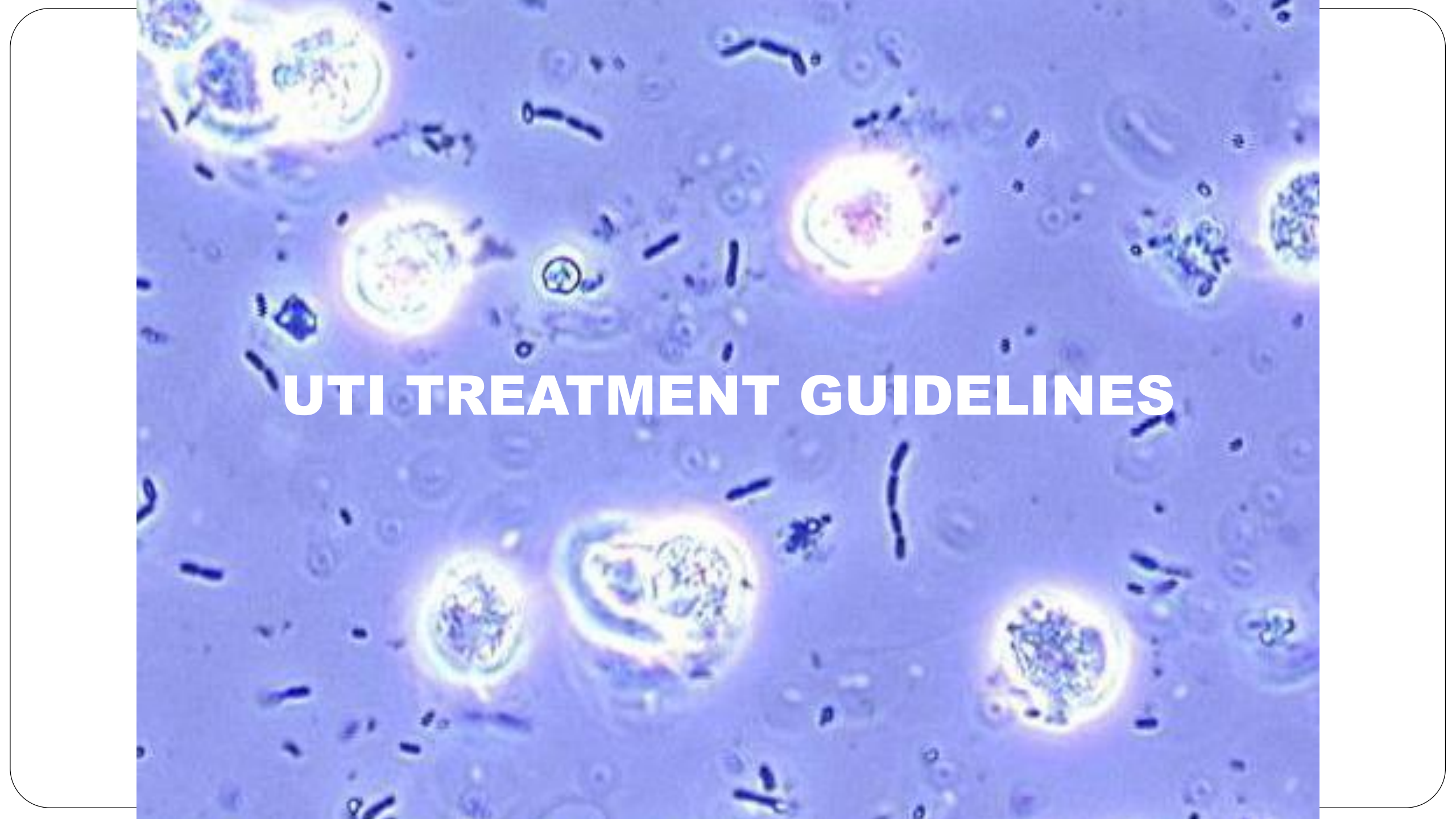
Pivmecillinam

- A beta-lactam active against enteric GNR (including most ESBL-producers) and *Staph. saprophyticus*.
- Not if penicillin allergy
- 2 x 200mg tabs stat then 200mg TDS for 3 days (10 total)
- \$45
- Hospital Pharmacy – ID/Micro approve only.



Why ciprofloxacin not norfloxacin?

- More potent (4- to 8-fold)
- Better penetration of tissue – ?pyelonephritis
- 3 days cipro = 7 days norflox in complicated UTI study
- Toxicity lower
 - Overall 5.8% versus 9.1%
 - Less dizziness
 - Tendonopathy equal
- Less selection of resistant mutants
- Cost 2/3.

A microscopic image of a urine sample, likely a Gram stain, showing numerous white blood cells (leukocytes) and bacteria. The white blood cells are large, round, and have a distinct nucleus. The bacteria are small, rod-shaped, and appear to be clustered together. The background is a light blue/purple color.

UTI TREATMENT GUIDELINES

Cystitis

Note: if early relapse after treatment in women treat as pyelonephritis and in men treat as prostatitis. Assess all men (including PR exam) with urinary tract infection for prostatitis.

Urine testing

- Urine culture not necessary in uncomplicated symptomatic urinary tract infection in young, non-pregnant women except if recurrent infection, recent antibiotic treatment, recent overseas travel (especially Asia, Middle East, Africa), previous infection or carriage of a multi-drug-resistant gram-negative bacillus (e.g. ESBL-producer).
- Culture urine if pregnant, male, indwelling urinary catheter, aged-care facility resident or 'complicated' infection.
- Dipstick urine only if symptoms atypical for urinary tract infection; absence of pyuria increases the likelihood of another diagnosis (e.g. urethritis, vaginitis) but should not preclude sending urine for culture.

Cystitis

- Review recent cultures (recurrent UTI often the same strain)
- If IDUC, wait for cultures.

Empiric choices

Antibiotic	Dose and duration	Comments
Trimethoprim	300 mg once daily for 3 days (7 days in men)	Uncomplicated patients only. Not if recent trimethoprim use. Not 1 st trimester of pregnancy.
Nitrofurantoin	100 mg three times daily for 5 days (7 days in men)	Good option if recurrent infection, recent overseas travel (especially to Asia, Middle East, Africa), or previous known infection or carriage of MDR-GNR. Not in men if febrile or ?prostatitis. Not if GFR < 30.
Amoxicillin/ clavulanate	625 mg twice daily for 5 days (7 days in men)	A good choice for patients with heart conditions that are predisposed to endocarditis.
Cefalexin	500 mg twice daily for 5 days (7 days in men)	

Cystitis

Choices for resistant bacteria

Antibiotic	Dose and duration	Comments
Ciprofloxacin	500 mg twice daily for 3 days	Do not use in pregnancy.
Fosfomycin	3 g every 2 days for 1 to 3 doses	One dose often adequate for uncomplicated cystitis in women. Restricted (2015): Hospital Pharmacy; only with approval from Infectious Diseases or Microbiology Specialist.
Pivmecillinam	200 mg two tabs STAT then one three times daily for 3 days	Restricted (2015): Hospital Pharmacy; only with approval from Infectious Diseases or Microbiology Specialist.

Symptom-based duration

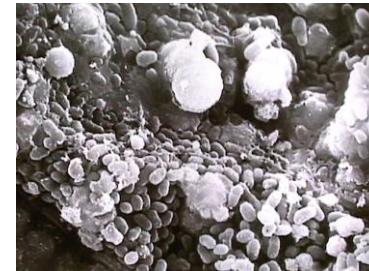
- Small RCT in primary care, Nelson, 2015-16
- Uncomplicated, moderate, community-acquired urine, skin, lung and sinus infections in adults.

	Standard duration (n = 31)	Symptom-based duration (n = 35)
Days of antibiotic treatment (mean (SD))	5.1 (1.7)	4.3 (1.9) $p=0.057$
Defined daily dose (mean (SD))	7.4 (5.6)	5.4 (5.1) $p=0.13$
Treatment-emergent adverse events (TEAE)	7 (23%, none severe)	6 (17%, none severe) ^{NS}
Immediately needed more antibiotic at end of treatment	1 (3%)	- ^{NS}
Relapse within 3 weeks of completing treatment	2 (6%)	2 (6%) ^{NS}

Unpublished as yet

Cystitis

- High fluid intake may help resolution of symptoms
- Complete bladder emptying may help resolution of symptoms
- Alkalinisation of the urine may relieve symptoms and does not adversely affect antibiotic efficacy
- NSAIDS may relieve symptoms – avoid if dehydration
- If IDUC
 - Treat for 7 to 14 days
 - Remove or change catheter during treatment.
- Follow-up testing only in pregnancy.



Pyelonephritis

Note: only treat in the community if mild symptoms (e.g. low fever, not vomiting, not systemically unwell or dehydrated)

Urine testing

- Culture the urine in all patients with suspected pyelonephritis.
- Do not dipstick the urine in these patients as the absence of pyuria should not preclude urine culture or empiric treatment.

Pyelonephritis

- Review recent cultures

Empiric choices – mild, community

Antibiotic	Dose and duration	Comments
Cefaclor	500 mg to 1 g three times daily for 10 to 14 days (up to 21 days if slow response)	Uncomplicated patients only. Consider 1 g dose if obese.
Amoxicillin/ clavulanate	625 mg three times daily for 10 to 14 days (up to 21 days if slow response)	Uncomplicated patients only. A good choice for patients with heart conditions that are predisposed to endocarditis (e.g. prosthetic valves, rheumatic valve disease, congenital valve disease, previous endocarditis).
Ciprofloxacin	500 mg twice daily for 7 days (up to 14 days if indwelling urinary catheter or slow response)	Only for patients who are 'complicated', recurrent infection, recent antibiotic treatment or aged-care facility. Do not use in pregnancy. Give 750 mg twice daily if slow response or obese.

Pyelonephritis

Empiric choices

- For moderate infections, gentamicin 5 mg/kg IV daily or ceftriaxone 1 g IV daily for first 1 to 2 days
- If recent overseas travel (especially to Asia, Middle East or Africa) or previous known infection or carriage of a multi-drug-resistant gram-negative bacillus (e.g. ESBL-producer), give ertapenem 1 g IV or IM daily for first 1 to 2 days

Targeted antibiotic choices

- Oral options also include trimethoprim + sulfamethoxazole (two tablets (160 + 800 mg) twice daily for 14 days; consider increased dose if obese).

Follow up

- Fail to respond (or early relapse)
 - Culture urine
 - Consider alternative diagnosis
 - Pyelonephritis – urgent ultrasound (obstruction or abscess?), probably via hospital
- Routine post-treatment urine cultures (ideally 1 to 2 weeks after completion of treatment) only in pregnant women or before urologic instrumentation
- Recurrent UTI
 - Women – ultrasound if recurrent pyelonephritis, slow response or *Proteus mirabilis* infections
 - Men – evaluate for prostatitis; if negative, ultrasound urinary tract.

A microscopic view of a urine sample stained with Gram stain. The background is a light purple color. Numerous white blood cells (leukocytes) are visible, appearing as large, pale, circular structures with distinct nuclei. Interspersed among the leukocytes are many small, dark purple, rod-shaped bacteria, likely Escherichia coli, which are characteristic of urinary tract infections. The bacteria are scattered throughout the field of view, some appearing in small clusters.

RECURRENT UTI

Recurrences

- DD – interstitial cystitis, lichen sclerosis, others...
- True recurrences:
 - Most women have at least one, usually ≤ 1 year
 - Young women: genetic determinants, sexual intercourse and spermicide use
 - Older women: ? Cause (linked with incontinence, cystocele and post-voiding residual urine)
- If no obstruction, recurrences cause no serious medical sequel.

Prevention

Measures with reasonable supportive evidence	Measures with minimal supportive evidence
Antibiotic prophylaxis (+++)	Ensure the bladder is completely emptied
Topical oestrogen in post-menopausal women (++)	Drink plenty of water, including at night
Cranberry juice and other cranberry products	Void after intercourse
D-mannose	Avoid diaphragms and spermicide
Hiprex® (methenamine hippurate)	Apply a topical antiseptic to the peri-urethral vulva
	Probiotics (oral or intra-vaginal)

Cranberry juice and products

- ↓ adherence of uro-pathogens
- 2012 Cochrane review of 24 studies and including 4471 patients:
 - Non-significant reduction in UTIs (RR 0.86, 95% CI 0.71 to 1.04)
 - Variety of products (juice, concentrate, tablets, capsules) and quantity of active ingredient was often not stated
 - Studies weakened by poor compliance and withdrawal due to palatability of the cranberry products
- Independent 2012 meta-analysis of 10 RCTs and including 1494 patients:
 - Significant reduction in UTIs (RR 0.62 (95% CI 0.49-0.73)
 - Substantial heterogeneity across the trials
- Try juice or products – beware GI side effects and extra calories.

D-mannose

- A sugar that prevents bacteria binding to the urethra
- Two large RCTs – reduced UTI by 70-80%
- Can purchase from Pharmacies - \$220/6 mo

Porru. J Clin Urol 2014; 7(3):208-13

Kranjcec. World J Urol 2014; 32(1):79-84

Hiprex®

- Hiprex® (methenamine hippurate)
- Antibacterial activity in the urine against *E. coli*, enterococci and staphylococci
- ↓ incidence of UTI in patients with anatomically normal renal tracts
- Take 1 g orally twice daily; contra-indicated in renal impairment
- Hiprex® may be purchased over-the-counter or on-line.

Self-Rx (vs prophylactic AB)

- On-hand, self-administered antibiotics
 - Will suffer more infections, but brief
 - Fewer antibiotics - cheaper, less toxicity (thrush, nausea, diarrhoea), less resistance
 - Base choice on previous isolates
 - Contact doctor if symptoms do not respond by 48 to 72 hours.

Prophylaxis

- Average of 3 $\rightarrow$ 0.1 per patient-year
- Nightly = alternate nights = post-intercourse
- Choices
 - Nitrofurantoin 50 to 100 mg at night - resistance rare but occasional interstitial lung disease in elderly
 - Trimethoprim 150 mg at night
 - Cefaclor 250 mg at night
 - Fosfomycin 3 g every 10 days (ID or Microbiology Specialist only; consider for recurrent ESBL-producing *E. coli* infections or intolerant of others).

How to prevent recurrent urine infection

Who gets urine infections?

Most women have at least one recurrence of urinary tract infection, usually within a year.

In young women recurrent urine infections are thought to be caused by certain genetic factors, sexual intercourse and spermicide use. In older women recurrence often occurs in women with urinary incontinence, bulging of the bladder into the vagina and incomplete bladder emptying - but the cause of the recurring infections is usually not clear.

Recurrences often stop occurring eventually and usually do not cause serious medical problems, but they can be very uncomfortable and annoying!

How to prevent urine infections

Many techniques have been proposed for preventing recurrent urinary infection. Some are proven to work and others are suggested but not proven. Check with your pharmacist as the cost of these treatments may vary.

1. Completely empty the bladder each time you pass urine. Some Physiotherapists and Nurses (see below) can teach you how to do this.
2. Drink plenty of water, including at night. This is not proven to make a difference but is commonly recommended.
3. Good hygiene and wiping from front-to-back are commonly recommended.
4. Sexual intercourse is a very common cause of urine infection in women. Try passing urine after intercourse and avoid using a diaphragm or spermicide.
5. Cranberry products may reduce the risk of urine infection by 15 to 40%. Cranberry products are available over-the-counter from community pharmacies; they are not funded on prescription by a doctor. Be aware that cranberry products can cause bowel side effects.
6. Oestrogen cream applied daily to the vulva might help - for post-menopausal women. The best research was done using oestrogen cream nightly for two weeks then twice weekly thereafter. Your doctor or Pharmacist will tell you what products are available and funded in New Zealand for this. Oestrogen cream is not necessary for post-menopausal women taking oral oestrogen tablets (hormone replacement therapy).
7. Dimenzone is a natural sugar available in pharmacies, health food stores and online. It binds to bacteria and prevents them going up the urethra into the bladder. 2 g powder daily, dissolved in water, reduces the risk of urine infections by up to 75%.
8. **Phosphazur** is a tablet that can be purchased over-the-counter from community pharmacies; it is not funded on prescription by a doctor. It has mild antibacterial activity in the urine and reduces the risk of urine infection in patients with normal bladder and kidneys. It is not likely to work in patients with blockages or catheters. The recommended dose of **Phosphazur** is 1 g orally twice daily. Do not take **Phosphazur** if your kidneys are very weak.
9. Applying an antiseptic cream around the urethral opening might reduce urinary tract infections. One option is Microdactyl **Phosphazur** (buy from a pharmacy), applied twice daily or after each time you pass urine.
10. Probiotics seem to work for some women. Ask your Pharmacist about what is available.
11. Ural sachets and other alkalinizing products help with symptoms but do not prevent infections.
12. A small number of women have a surgically correctable problem with the urinary tract (e.g. a blockage, stone, or fistula) that is causing recurrent urine infections and needs to be fixed. This can be checked by your doctor.

13. Men with recurrent urine infections may have a deep infection in the prostate gland - this might need a long course of antibiotics to fix. Some men with recurrent urine infections have a blockage or other anatomical problem in the urinary tract - this can be checked by your doctor.

Antibiotics

Just in case antibiotics

One way to manage recurrent urine infections with antibiotics is to have some available at home (just in case) and to start taking them as soon as you feel the symptoms of a urinary tract infection coming on. This will not reduce the frequency of infections but will clear them up quickly. Taking antibiotics only when needed is cheaper, safer and causes less resistance than taking antibiotics continuously as a preventative (see below). Your GP can help you choose an antibiotic to have on hand for treatment, based on which bacteria have caused your infections in the past. This strategy is best for those women who have clearly documented infections and who are able to communicate easily with their doctor or nurse. If you take antibiotics for a urine infection and are not better within about 48 hours, go and see your doctor.

Antibiotic prevention

Antibiotic prevention is often very effective. It is a last resort because of the risk of developing antibiotic-resistant bacteria and side effects such as thrush or **Phosphazur**. But for some patients the risk of getting an infection falls dramatically when taking preventative antibiotics. Preventative antibiotics can be taken each night, alternate nights or after sexual intercourse - all these different strategies work well.

People who can help you with recurrent urine infections

Your GP, practice nurse or community pharmacist.

Occasionally a medical or urology specialist may be required. These specialist doctors are available privately or by GP referral to the public hospital for more severe problems.

Continence and infection-prevention assessment and advice:

- Yvonne Ferguson, Physiotherapist, Nelson Hospital. Ph 546-1955
- Shirley Little, NSPH at 281 Queen St, Richmond. Ph 545-790
- Erica van der Horst, Physiotherapist, Golden Bay Community Hospital. Ph 525-0105
- Julie Mayrho, Nurse Specialist, Community Nursing, Wairau Hospital. Ph 520-9927 ext 1
- Sharon Wilson, Physiotherapist, Motaro Physiotherapy. 021-209-5514 or www.motaro.physio.co.nz

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Preventing infection with IDUC

Effective measures

1. Remove catheter
(?condom, self-catheter)

Ineffective measures

1. AB prophylaxis (other than first week or so)
2. Antiseptic-impregnated catheters
3. Genital cleansing
4. Routine catheter irrigation or replacement
5. Routine urine surveillance cultures (when asymptomatic)
6. Hiprex[®]
7. Cranberry juice.



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