PRIMARY CARE MANAGEMENT OF RECURRENT UTI

Dr Jon Rees

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PCUS

Primary Care Urology Society

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DECLARATION OF INTERESTS

- Jon Rees has received Consultancy and Speaker fees for Ferring and Astellas and is Chair of PCUS

RECURRENT UTI

- NICE CG 112
- Published October 2018
- www.nice.org.uk/guidance/ng112

WHAT IS THE DEFINITION OF RECURRENT UTI?

- No universally accepted definition
- Most commonly used is "2 in 6 months or 3 in a year"

Schoof and Hill 2005

Hooton and Stamm 2006

- Estimated 20-50% of young women with UTI will have another within a year

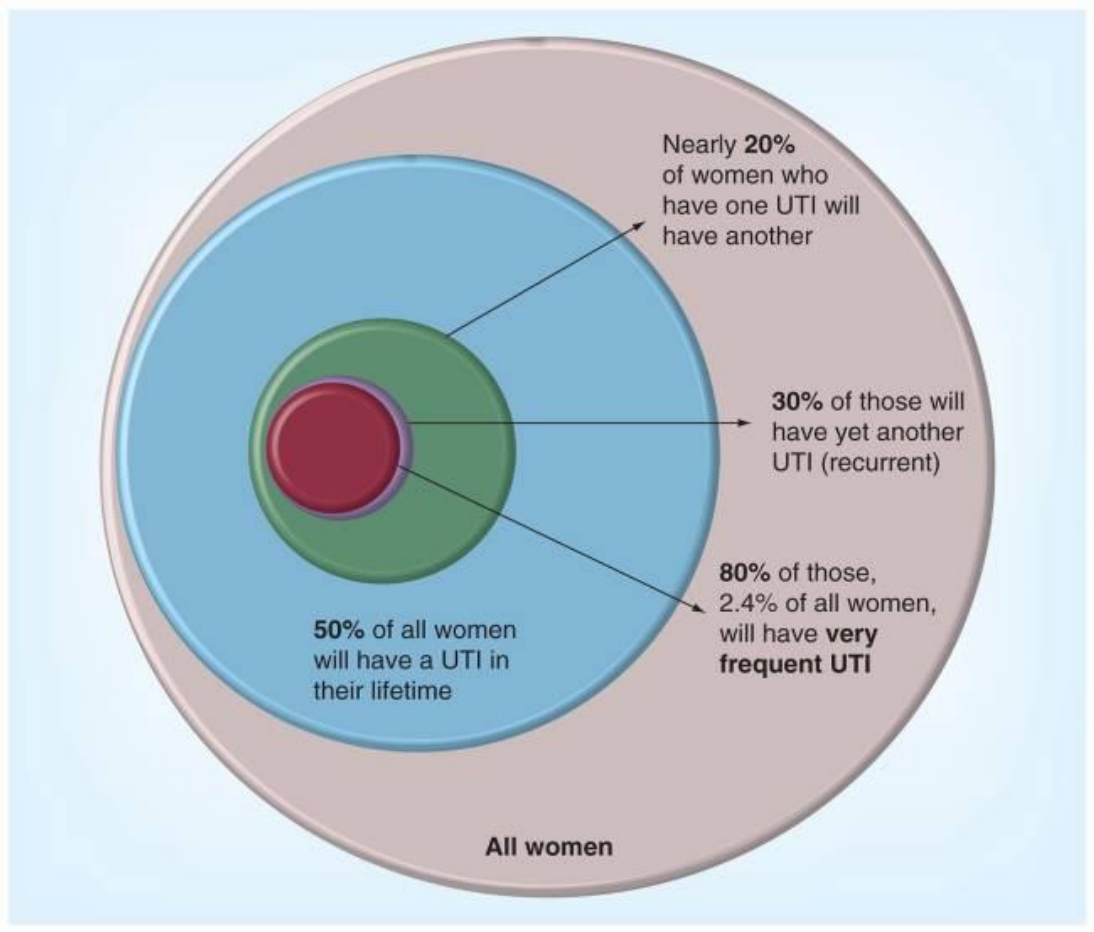
Mabeck *et al* Postgrad Med J 1972.

Brumbaugh and Mobley Expert Rev Vaccines. 2012.

- Finnish study showed older (>55yrs) more likely to have recurrence in first year (53% vs 36%)

Ikaheimo Clin Infect Dis 1996

COMMON PROBLEM



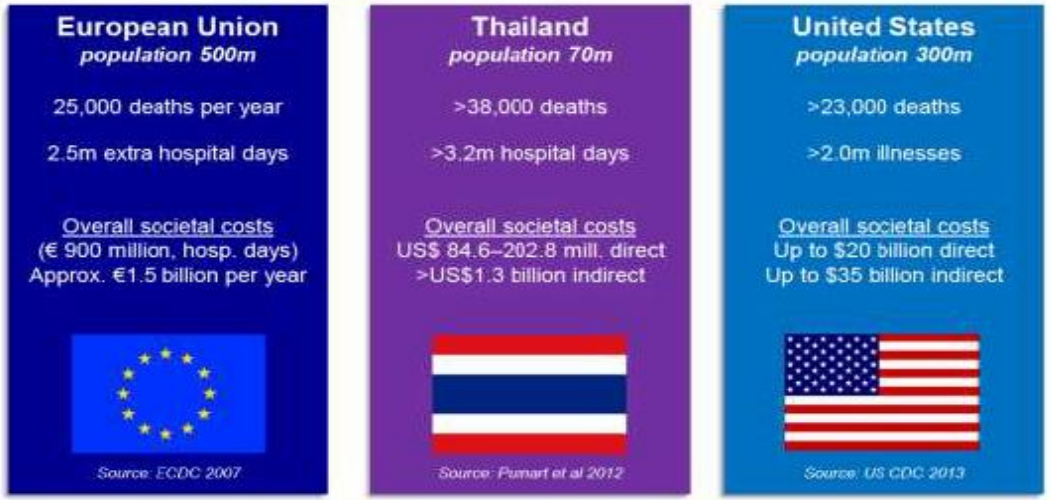
Expert Rev Vaccines. 2012; 11(6): 663–676.

Antimicrobial resistance....

- Successful surgery
- Cancer chemotherapy
- Immunotherapies

} AMR the end of modern medicine

Estimates of Burden of Antibacterial Resistance



Global information is insufficient to show complete disease burden impact and costs

WHO Antimicrobial Resistance Global Report on Surveillance 2014

Antimicrobial resistance by 2050 threatens:

- A reduction in the world economy of 0.1-3.1%

Taylor J, et al. Estimating the economic costs of antimicrobial resistance: model and results. 2015. http://www.rand.org/randeurope/research/projects/antimicrobial-resistance-costs.html

Taken from ARK-hospital presentation – Elizabeth Cross 2017

URINE DIPSTICK TESTING / MC&S

URINE DIPSTICK / MC&S

- Diagnosis of UTI should be based on a combination of:
  - clinical diagnosis based on typical symptoms
  - microbiological diagnosis by appropriate use of urine dipsticks and urine culture where indicated
  - past response to antibiotic treatment of isolated episodes of acute UTI

- A diagnosis of UTI can be considered if the patient has a strong symptom profile, even in the absence of culture-positive urine or dipstick confirmation
  - fever can be useful to differentiate inflammatory and infective causes
  - previous response to antibiotics for similar symptoms also supports this diagnosis

Prevalence of asymptomatic bacteriuria in seniors over 70:

- in long term care 50%
- in the community 19%

It's Hard to Ignore A Positive Test

Habitual Testing + Prevalent Colonization = Unnecessary prescriptions & missing the real diagnosis

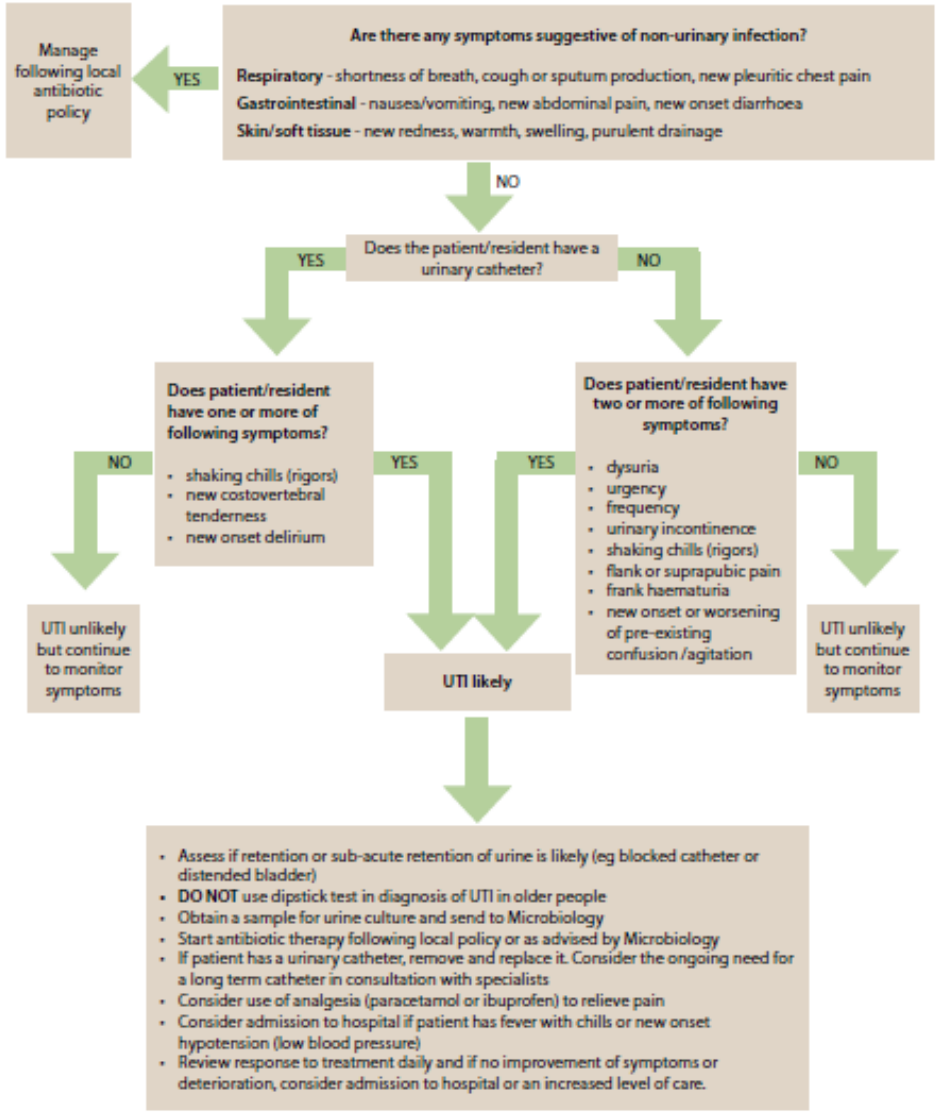
High Prevalence of Asymptomatic Bacteriuria

- The bladder is normally colonized in many elderly people
- A positive urinalysis or culture in the absence of symptoms reveals **colonization not infection**
- Treatment of asymptomatic bacteriuria is **not recommended**

Myth	Fact
Positive urine culture and abnormal urinalysis (positive nitrates or leukocytes, increased white blood cells or pyuria) always indicates a urinary tract infection and requires antibiotics.	Positive urine culture and abnormal urinalysis in a resident without symptoms is consistent with asymptomatic bacteriuria – that is, colonization – not infection. Treatment with antibiotics is not indicated.
Positive urine culture in resident with chronic indwelling catheter always indicates a urinary tract infection and requires antibiotics.	A chronic indwelling catheter is associated with bacteriuria 100% of the time. There is no need to treat unless the resident has symptoms of a UTI.
Elderly residents often have urinary tract infection with no symptoms except a change in mental status or delirium.	• A change in mental status or delirium is a non-specific symptom and may accompany a change in conditions such as dehydration, constipation, adverse drug effect, pneumonia, urinary retention, metabolic problems, head trauma, environmental changes or sensory deprivation. • Mental status change requires an exploration of alternative causes and may not require antibiotics for UTI unless there are more specific signs or symptoms that point to that diagnosis.
In an elderly population, urinary tract infections often present with nonspecific symptoms (e.g., falls, functional decline).	Nonspecific symptoms can be seen in many conditions such as dehydration or adverse drug effect. Diagnosing and treating UTIs based on these nonlocalizing symptoms not only results in inappropriate antibiotic use, it also completely misses the real diagnosis.
Cloudy or malodorous urine is always diagnostic of a urinary tract infection.	These changes may be seen in asymptomatic bacteriuria. Other causes can include dehydration, certain medications and diet.

DIAGNOSIS AND MANAGEMENT OF SUSPECTED UTI IN OLDER PEOPLE

Decision aid to guide management of patients/residents with fever defined as temperature >37.9°C or 1.5°C increase above baseline occurring on at least two occasions in last 12 hours.
Hypothermia (low temperature of <36°C) may also indicate infection, especially those with comorbidities.
Be alert to non-specific symptoms of infection such as abdominal pain, alteration of behaviour or loss of diabetes control.



Developed by the Scottish Antimicrobial Prescribing Group • www.scottishmedicines.org.uk/SAPG/

DIAGNOSIS AND MANAGEMENT OF SUSPECTED UTI IN OLDER PEOPLE

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Be alert to non-specific symptoms of infection such as abdominal pain, alteration of behaviour or loss of diabetes control.

Are there any symptoms suggestive of non-urinary infection?

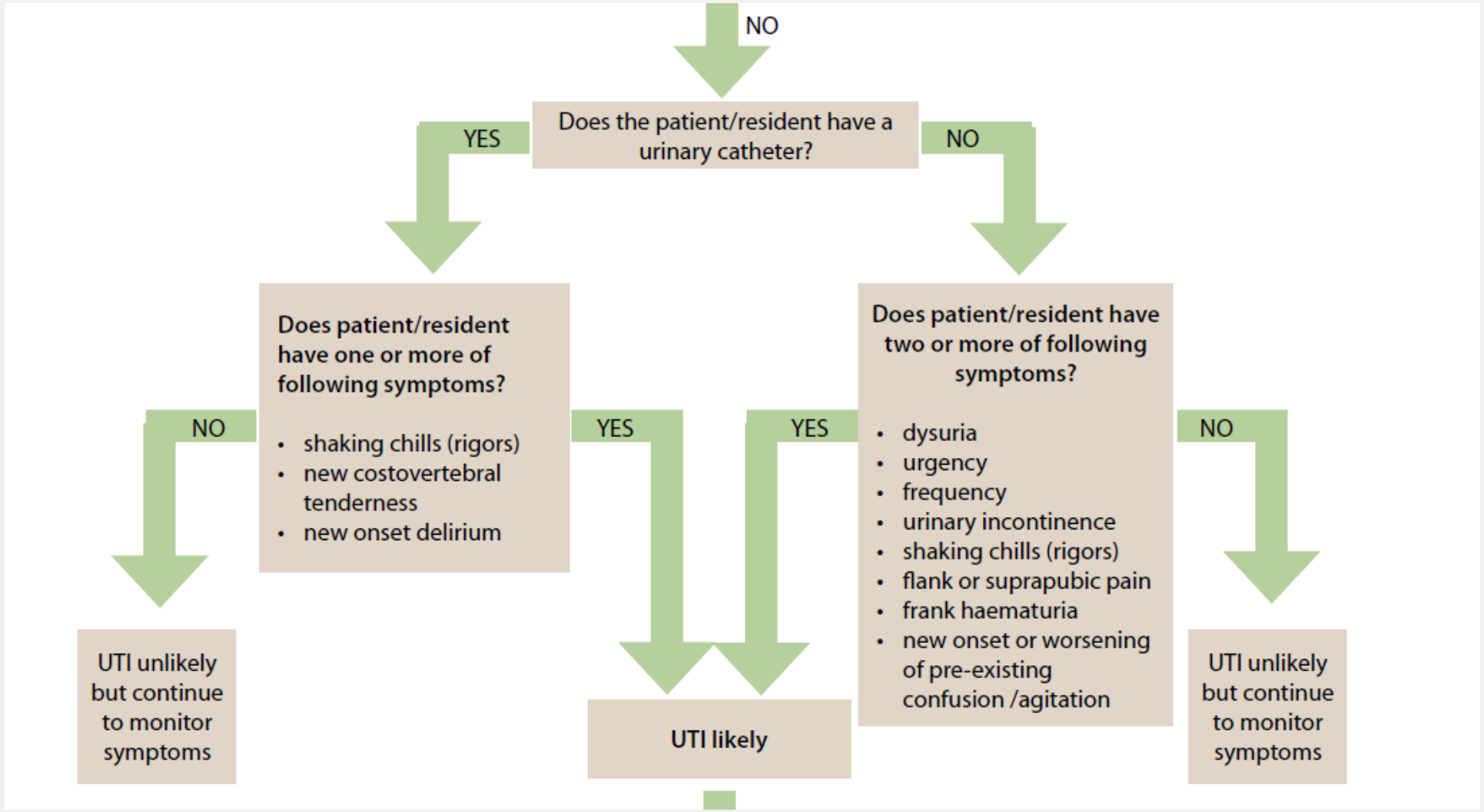
Respiratory - shortness of breath, cough or sputum production, new pleuritic chest pain

Gastrointestinal - nausea/vomiting, new abdominal pain, new onset diarrhoea

Skin/soft tissue - new redness, warmth, swelling, purulent drainage

YES → Manage following local antibiotic policy

NO


NO
Does the patient/resident have a urinary catheter?
YES
NO
Does patient/resident have one or more of following symptoms?
• shaking chills (rigors)
• new costovertebral tenderness
• new onset delirium
NO
YES
YES
Does patient/resident have two or more of following symptoms?
• dysuria
• urgency
• frequency
• urinary incontinence
• shaking chills (rigors)
• flank or suprapubic pain
• frank haematuria
• new onset or worsening of pre-existing confusion /agitation
NO
UTI unlikely but continue to monitor symptoms
UTI likely
UTI unlikely but continue to monitor symptoms

UTI likely

- Assess if retention or sub-acute retention of urine is likely (eg blocked catheter or distended bladder)
- DO NOT use dipstick test in diagnosis of UTI in older people
- Obtain a sample for urine culture and send to Microbiology
- Start antibiotic therapy following local policy or as advised by Microbiology
- If patient has a urinary catheter, remove and replace it. Consider the ongoing need for a long term catheter in consultation with specialists
- Consider use of analgesia (paracetamol or ibuprofen) to relieve pain
- Consider admission to hospital if patient has fever with chills or new onset hypotension (low blood pressure)
- Review response to treatment daily and if no improvement of symptoms or deterioration, consider admission to hospital or an increased level of care.

Developed by the Scottish Antimicrobial Prescribing Group • www.scottishmedicines.org.uk/SAPG/

WHO TO SCAN?

- Consider referral for urinary tract ultrasound (including post-void residual volume) in patients:
  - with very frequent infections
  - with recurrent *Proteus* infections (due to their association with renal calculi)
  - who do not respond to treatment
  - with post-micturition symptoms, such as a sensation of incomplete emptying, or those with a palpable bladder

CASE STUDY 1

- Fiona is a 23 year old female. Over the last 12 months, she has had multiple urinary tract infections. She is sometimes able to self manage these, buying ‘sachets’ over the counter and increasing fluid intake – but has also had to take time off work on 5 occasions to see her GP for an antibiotic prescription. She is fed up.

- What would you do?

CASE STUDY 2

- Maggie is a 52 year old female. Over the last 18 months she has been increasingly bothered by recurrent episodes of 'cystitis'. She has not had a problem with UTI's in the past. She has had several courses of antibiotics. MSU's show pyuria, often with growth of E coli.

- What would you do?

CASE STUDY 3

- Anne is 64. She has had a number of episodes recently of cystitis like symptoms – frequency, urgency, dysuria. Her urine is cloudy during these episodes. Urine dip sometimes shows pyuria, lab tests are often negative. Her symptoms respond to short courses of antibiotics, but never completely settle. Within 2 or 3 weeks after completing a course of antibiotics, her symptoms return. She does not have any haematuria, either visibly or on dipstick testing.

- What would you do?

ANTIBIOTICS

SELF START ANTIBIOTICS

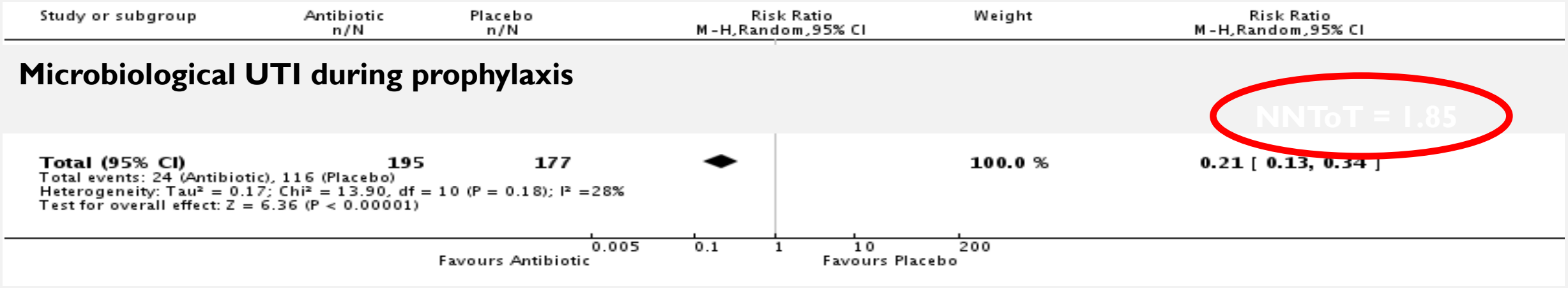
- 85-95% of women with previous UTI can self diagnose successfully (Gupta *et al.* Ann Intern Med 2001)
- Clinical and Microbiological cure rates > 90%
- Best used in motivated women with previous culture confirmed cystitis (Hooton NEJM 2012)

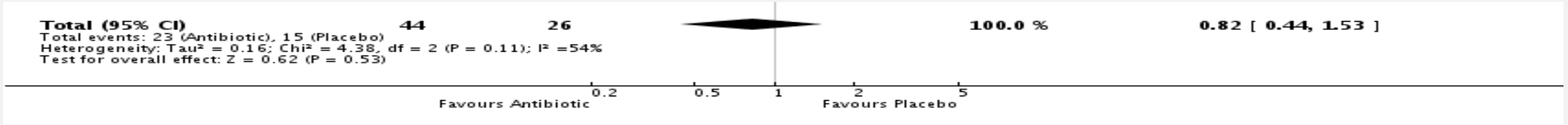
- Advantages are less antimicrobial exposure and high patient satisfaction rates
- Post coital antibiotics reserved for group where it has been identified as the dominant risk factor.

PROPHYLACTIC ANTIBIOTICS

- Single dose antibiotic prophylaxis – for triggers
- Long term prophylaxis can range from 4 mths to 5 yrs!!
- 95% will remain UTI free but 50% relapse following cessation (Nicolle *et al.* Am J Med 2002)
- Cochrane review of RCT's - RR 0.21 for single recurrence (NNT 1.85) but RR after prophylaxis 0.82 (Albert *et al.* Cochrane Database 2004)
- Single randomised study found prophylactic nitrofurantoin superior to oestrogen (Raz *et al* Clin Infect Dis 2003)

ANTIBIOTIC PROPHYLAXIS



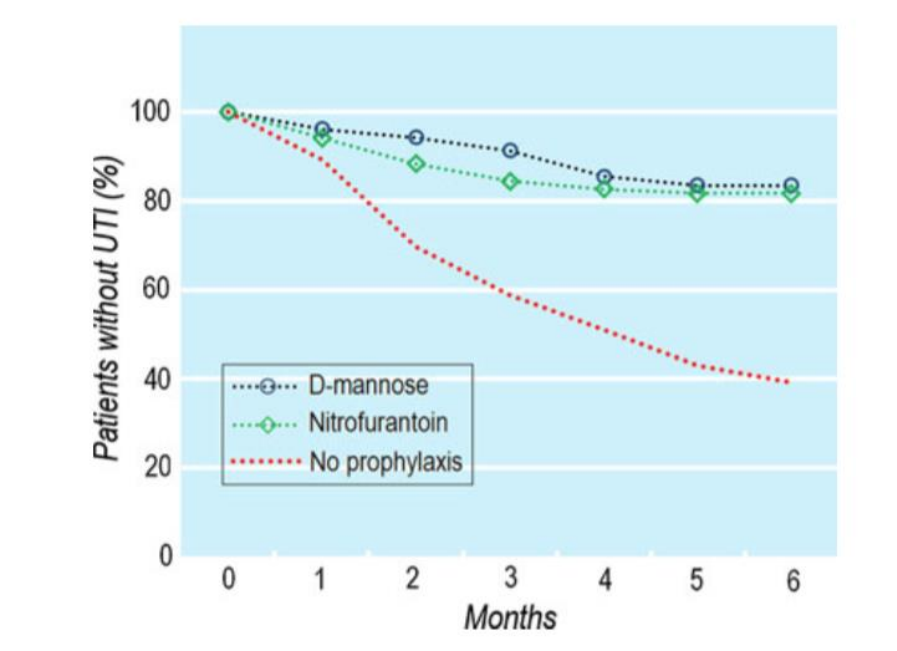


Albert *et al* . Cochrane Database Syst Rev. 2004;(3):CD001209

NON-ANTIBIOTIC MEASURES

D-MANNOSE

- Sugar – postulated to inhibit bacterial adherence to urothelium
- 1 x RCT: vs Nitrofurantoin vs nothing
- 308 women with hx of rUTI
- 98 had continued rUTI:
  - 15 in D-mannose arm
  - 21 in NF arm
  - 62 in no treatment arm



Kranjcec et al. World J Urol 2014; 32: 79-84

CRANBERRY

- Postulated to acidify urine and reduce bacterial adhesion/prevent fimbrial expression
- Some evidence that rUTIs reduced but optimum dose /duration unclear.
- Original Cochrane review (2008) identified *some benefit*

  BUT

  Meta-analyses in updated review (2012) showed that compared with placebo, water or non-treatment,

  "cranberry products did not significantly reduce the occurrence of symptomatic UTI overall" (RR 0.86, 95% CI 0.71 to 1.04)

  Jepson *et al.* Cochrane Database 2012

- Recent evidence review: 3 new papers suggesting cranberry does have a protective effect

  Kranz et al Eur Urol Focus 2018

TOPICAL OESTROGENS

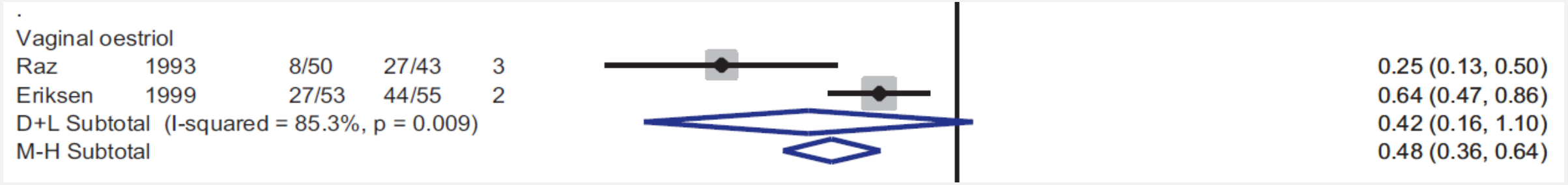
- Falling oestrogen levels lead to a change in vaginal flora and pH

- Local oestrogen can reverse this without SE of systemic oestrogen

Esposito *et al.* Gynaecological Endocrinology 1991

- Systematic review found no reduction in UTIs with oral oestrogen but showed vaginal preparations superior to placebo (RR 0.25/0.64)

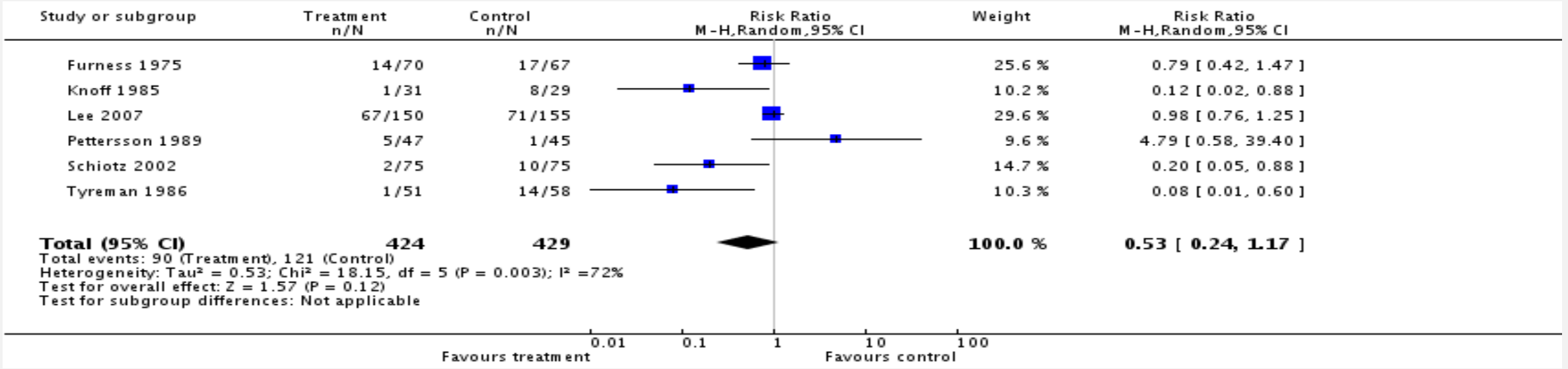
Perrotta *et al.* Cochrane Database 2008



METHENAMINE HIPPURATE

- Methenamine has antibacterial properties - hydrolysed to formaldehyde in acid urine
- Systematic review highlighted heterogeneity of data *but* **some studies report reduction in symptomatic UTIs (RR 0.24)**
- ?Ineffective in pts with neuropathic bladder / abnormal renal tract.
- **"There is a need for further large well-conducted RCTs to clarify…"**

Lee *et al.* Cochrane Database 2012



WHO TO REFER

- ‘Consider non-urgent referral for bladder cancer in people aged 60 and over with recurrent or persistent unexplained urinary tract infection’[1]

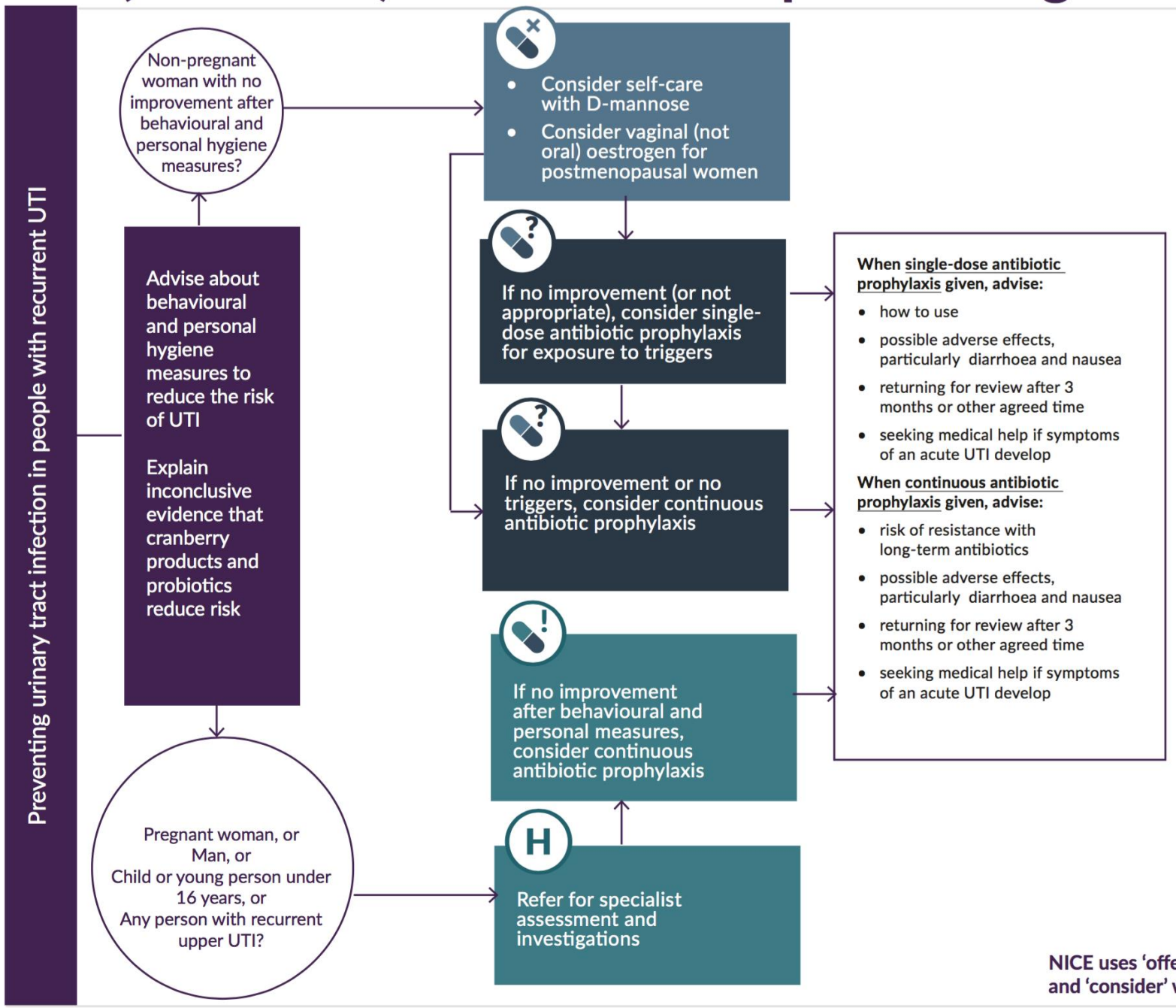
1. NICE Suspected Cancer Referral Guidelines 2015

WHO TO REFER

- pregnant women
- men with 2 or more UTI
- patients with recurrent or severe pyelonephritis
- patients infected with resistant bacteria
- patients with recurrent UTI associated with structural or functional abnormalities of the urinary tract
- patients with recurrent UTI associated with atypical infections, such as tuberculosis or schistosomiasis
- catheterised patients, in whom misdiagnosis is common because of colonisation (treat only when symptomatic)
- patients with immunity compromised as a result of drugs or diseases
- patients with chronic renal failure with oliguria, who should be seen by the renal team because of the risk of renal deterioration

UTI (recurrent): antimicrobial prescribing

NICE National Institute for Health and Care Excellence



Self-care

- Behavioural and personal hygiene measures include adequate fluid intake, not delaying urination, wiping from front to back, not douching or wearing tight underwear
- When considering D-mannose, take account of severity and frequency of symptoms, risk of complications, and preference for self-care
- Triggers include sexual intercourse

Treatments

- When considering vaginal oestrogen, take account of severity and frequency of symptoms, risk of complications, benefits for other symptoms (vaginal dryness), possible adverse effects (breast tenderness and vaginal bleeding), unknown long-term endometrial safety and preferences for treatment
- Review vaginal oestrogen treatment at least every 6 months
- When considering antibiotics, take account of severity and frequency of symptoms, risk of complications and long-term antibiotic use, previous results of urine culture and susceptibility, previous antibiotic use and preferences for treatment

Background

- Recurrent UTI includes lower UTI (cystitis) and upper UTI (acute pyelonephritis)
- Recurrent UTI may be due to relapse (same strain of bacteria) or reinfection (different strain or species of bacteria)

NICE uses 'offer' when there is more certainty of benefit and 'consider' when evidence of benefit is less clear.

UTI (recurrent): antimicrobial prescribing

NICE National Institute for Health and Care Excellence

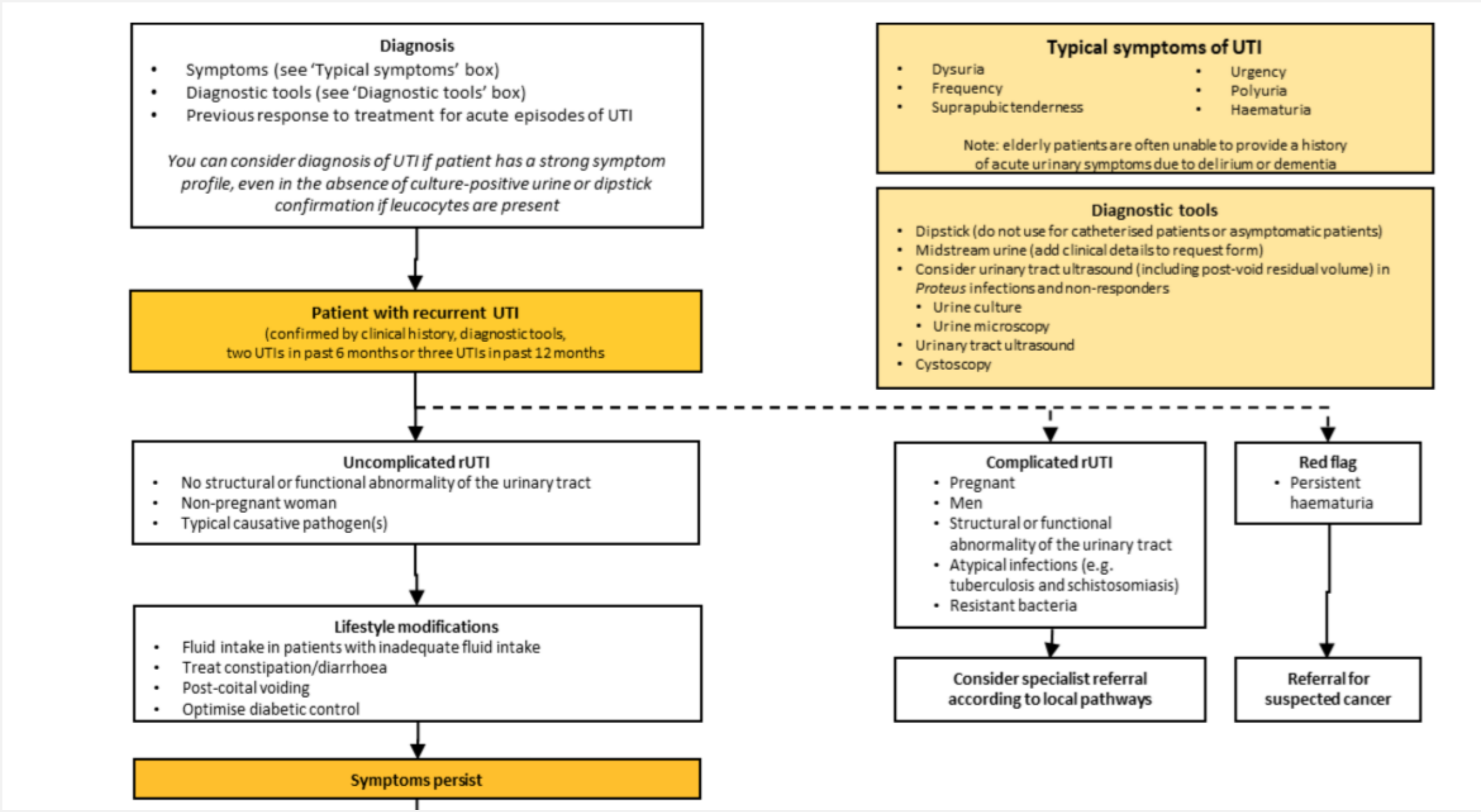
Choice of antibiotic: people aged 16 years and over

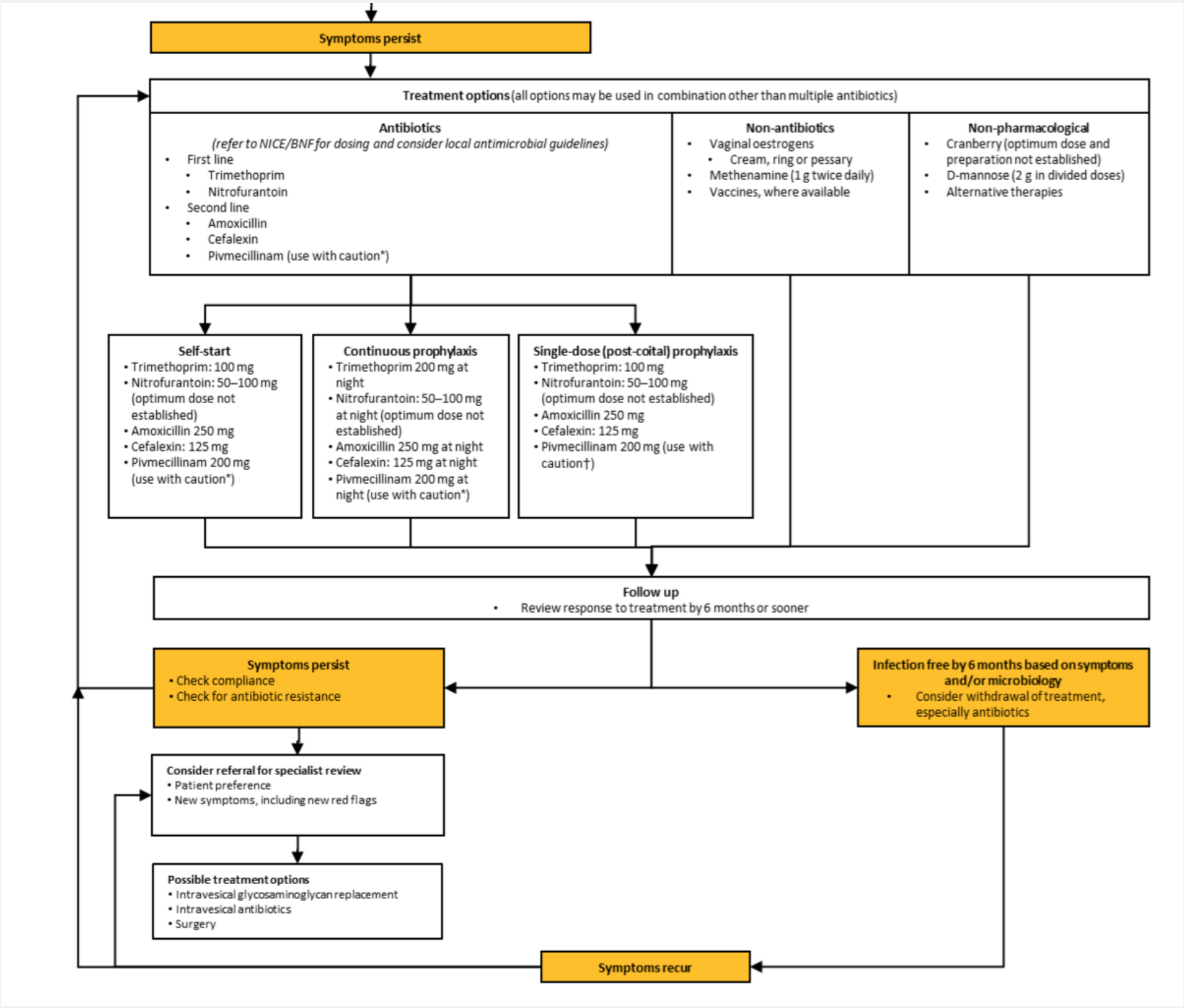
Antibiotic prophylaxis[1, 2]	Dosage and course length[3]
First choice	
Trimethoprim[4]	100 mg single dose, **or** 100 mg at night continuously
Nitrofurantoin - if eGFR ≥45 ml/minute[5]	50 to 100 mg single dose, **or** 50 to 100 mg at night continuously
Second choice	
Amoxicillin	250 mg single dose, **or** 250 mg at night continuously
Cefalexin	125 mg single dose, **or** 125 mg at night continuously
Pivmecillinam[6]	200 mg single dose, **or** 200 mg at night continuously
[1] See BNF for appropriate use and dosing in specific populations, for example, hepatic impairment, renal impairment, pregnancy and breast-feeding. [2] Choose antibiotics according to recent culture and susceptibility results where possible, with rotational use based on local policies. Select a different antibiotic for prophylaxis if treating an acute UTI. [3] Doses given are by mouth using immediate-release medicines, unless otherwise stated. [4] Teratogenic risk in first trimester of pregnancy (folate antagonist; BNF, April 2018). Manufacturers advise contraindicated in pregnancy (trimethoprim summary of product characteristics). [5] Avoid at term in pregnancy; may produce neonatal haemolysis (BNF, April 2018). [6] Not known to be harmful in pregnancy, but manufacturer advises avoid (BNF, April 2018).	
Abbreviations: eGFR, estimated glomerular filtration rate.	

Choice of antibiotic: children and young people under 16 years

Antibiotic prophylaxis[1, 2]	Dosage and course length[3]
Children under 3 months	
Refer to paediatric specialist	
Children aged 3 months and over (specialist advice only)	
First choice	
Trimethoprim	3 to 5 months, 2 mg/kg at night (maximum 100 mg per dose) **or** 12.5 mg at night 6 months to 5 years, 2 mg/kg at night (maximum 100 mg per dose) **or** 25 mg at night 6 to 11 years, 2 mg/kg at night (maximum 100 mg per dose) **or** 50 mg at night 12 to 17 years, 100 mg at night
Nitrofurantoin – if eGFR ≥45 ml/minute	3 months to 11 years, 1 mg/kg at night 12 to 17 years, 50 to 100 mg at night
Second choice	
Cefalexin	12.5 mg/kg at night (maximum 125 mg per dose)
Amoxicillin	1 to 11 months, 62.5 mg at night 1 to 4 years, 125 mg at night 5 to 17 years, 250 mg at night
[1] See BNF for children for appropriate use and dosing in specific populations, for example, hepatic impairment and renal impairment. [2] Choose antibiotics according to recent culture and susceptibility results where possible. If 2 or more antibiotics are appropriate, choose the antibiotic with the lowest acquisition cost. [3] The age bands apply to children of average size and, in practice, the prescriber will use the age bands in conjunction with other factors such as the severity of the condition and the child's size in relation to the average size of children of the same age. Doses given are by mouth using immediate release medicines, unless otherwise stated.	
Abbreviations: eGFR, estimated glomerular filtration rate.	

When exercising their judgement, professionals and practitioners are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or the people using their service. It is not mandatory to apply the recommendations, and the guideline does not override the responsibility to make decisions appropriate to the circumstances of the individual, in consultation with them and their families and carers or guardian.


Diagnosis
Symptoms (see 'Typical symptoms' box)
Diagnostic tools (see 'Diagnostic tools' box)
Previous response to treatment for acute episodes of UTI
You can consider diagnosis of UTI if patient has a strong symptom profile, even in the absence of culture-positive urine or dipstick confirmation if leucocytes are present
Typical symptoms of UTI
Dysuria
Frequency
Suprapubic tenderness
Urgency
Polyuria
Haematuria
Note: elderly patients are often unable to provide a history of acute urinary symptoms due to delirium or dementia
Diagnostic tools
Dipstick (do not use for catheterised patients or asymptomatic patients)
Midstream urine (add clinical details to request form)
Consider urinary tract ultrasound (including post-void residual volume) in Proteus infections and non-responders
Urine culture
Urine microscopy
Urinary tract ultrasound
Cystoscopy
Patient with recurrent UTI
(confirmed by clinical history, diagnostic tools, two UTIs in past 6 months or three UTIs in past 12 months
Uncomplicated rUTI
No structural or functional abnormality of the urinary tract
Non-pregnant woman
Typical causative pathogen(s)
Complicated rUTI
Pregnant
Men
Structural or functional abnormality of the urinary tract
Atypical infections (e.g. tuberculosis and schistosomiasis)
Resistant bacteria
Red flag
Persistent haematuria
Lifestyle modifications
Fluid intake in patients with inadequate fluid intake
Treat constipation/diarrhoea
Post-coital voiding
Optimise diabetic control
Consider specialist referral according to local pathways
Referral for suspected cancer
Symptoms persist


Symptoms persist
Treatment options (all options may be used in combination other than multiple antibiotics)
Antibiotics
(refer to NICE/BNF for dosing and consider local antimicrobial guidelines)
First line
Trimethoprim
Nitrofurantoin
Second line
Amoxicillin
Cefalexin
Pivmecillinam (use with caution*)
Non-antibiotics
Vaginal oestrogens
Cream, ring or pessary
Methenamine (1 g twice daily)
Vaccines, where available
Non-pharmacological
Cranberry (optimum dose and preparation not established)
D-mannose (2 g in divided doses)
Alternative therapies
Self-start
Trimethoprim: 100 mg
Nitrofurantoin: 50–100 mg (optimum dose not established)
Amoxicillin 250 mg
Cefalexin: 125 mg
Pivmecillinam 200 mg (use with caution*)
Continuous prophylaxis
Trimethoprim 200 mg at night
Nitrofurantoin: 50–100 mg at night (optimum dose not established)
Amoxicillin 250 mg at night
Cefalexin: 125 mg at night
Pivmecillinam 200 mg at night (use with caution*)
Single-dose (post-coital) prophylaxis
Trimethoprim: 100 mg
Nitrofurantoin: 50–100 mg (optimum dose not established)
Amoxicillin 250 mg
Cefalexin: 125 mg
Pivmecillinam 200 mg (use with caution†)
Follow up
Review response to treatment by 6 months or sooner
Symptoms persist
Check compliance
Check for antibiotic resistance
Infection free by 6 months based on symptoms and/or microbiology
Consider withdrawal of treatment, especially antibiotics
Consider referral for specialist review
Patient preference
New symptoms, including new red flags
Possible treatment options
Intravesical glycosaminoglycan replacement
Intravesical antibiotics
Surgery
Symptoms recur

CASE STUDY 1

- Fiona is a 23 year old female. Over the last 12 months, she has had multiple urinary tract infections. She is sometimes able to self manage these, buying ‘sachets’ over the counter and increasing fluid intake – but has also had to take time off work on 5 occasions to see her GP for an antibiotic prescription. She is fed up.

- What would you do?

CASE STUDY 2

- Maggie is a 52 year old female. Over the last 18 months she has been increasingly bothered by recurrent episodes of 'cystitis'. She has not had a problem with UTI's in the past. She has had several courses of antibiotics. MSU's show pyuria, often with growth of E coli.

- What would you do?

CASE STUDY 3

- Anne is 64. She has had a number of episodes recently of cystitis like symptoms – frequency, urgency, dysuria. Her urine is cloudy during these episodes. Urine dip sometimes shows pyuria, lab tests are often negative. Her symptoms respond to short courses of antibiotics, but never completely settle. Within 2 or 3 weeks after completing a course of antibiotics, her symptoms return. She does not have any haematuria, either visibly or on dipstick testing.

- What would you do?

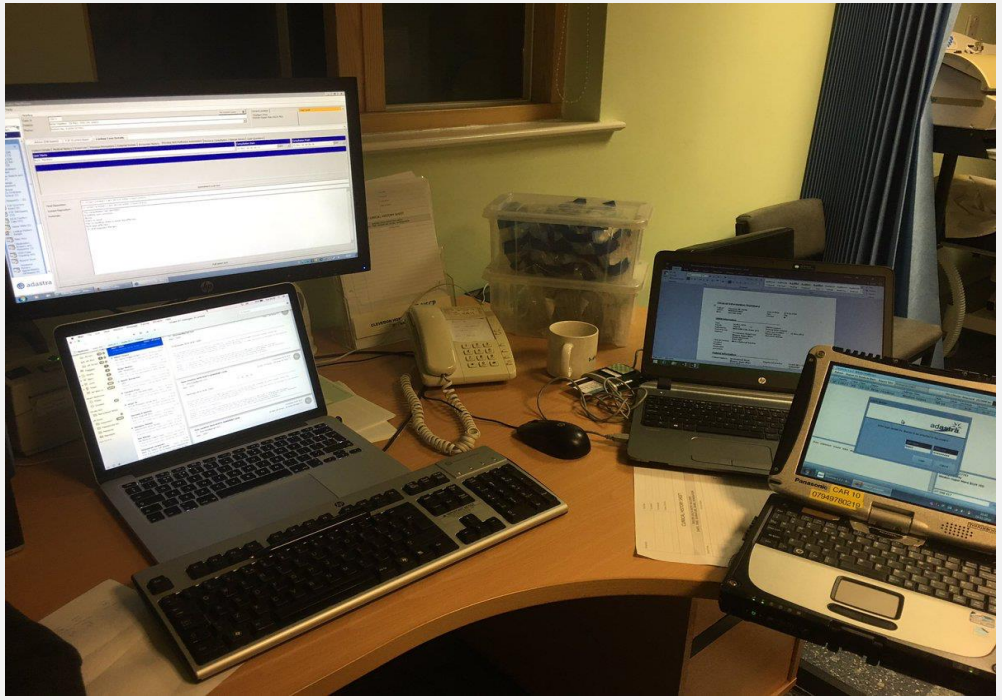
THE FUTURE

"Computers in the future may weigh no more than 1.5 tons"

Popular Mechanics, 1949

I think there is a world market for maybe 5 computers"

Thomas Watson, Chairman of IBM, 1943



SUMMARY

- Avoid treating ASB as recurrent UTI
- A negative dip / MSU does NOT exclude UTI
- Women with recUTI know when they have an infection – believe them
- Think non-antibiotic prophylaxis wherever possible
- Refer complicated recUTI for urological ssessment

Primary Care Urology Society