Public Health England

Protecting and improving the nation's health

Diagnosis of urinary tract infections (UTIs)

Quick reference guide for primary care: For consultation and local adaptation

About Public Health England

Public Health England (PHE) exists to protect and improve the nation's health and wellbeing, and reduce health inequalities. It does this through world-class science, knowledge and intelligence, advocacy, partnerships, and the delivery of specialist public health services. PHE is an executive agency of the Department of Health, and is a distinct delivery organisation with operational autonomy to advise and support government, local authorities, and the NHS, in a professionally independent manner.

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Contents

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Foreword – Aims and adaptations

Audience

- primary care prescribers in general practice and out of hours settings; including doctors, nurses and pharmacists
- those giving first point of contact for urinary tract infections

Aims

- to provide a simple, effective, economical and empirical approach to the diagnosis and treatment of urinary tract infections
- to minimise the emergence of antibiotic resistance in the community

Implications

- the guidance should lead to more appropriate antibiotic use
- use of this guidance may influence laboratory workload, which may have financial implications for laboratories and primary care commissioners

Production

- the guidance has been produced in consultation with the Association of Medical Microbiologists, general practitioners, nurses, specialists, and patient representatives
- the guidance is in agreement with other publications, including CKS, SIGN and NICE
- the guidance is fully referenced and graded
- the guidance is not all-encompassing, as it is meant to be 'quick reference'
- if more detail is required we suggest referral to the websites and references cited
- the guidance will be updated every three years; or more frequently if there are significant developments in the field

Poster Presentation of Guidance

- the summary table is designed to be printed out as a poster for use in practice
- the rationale and evidence is designed to be used as an educational tool for you, and your colleagues and trainees, to share with patients as needed

Local Adaptation

- we would discourage major changes to the guidance, but the format allows minor changes to suit local service delivery and sampling protocols
- to create ownership agreement on the guidance locally, dissemination should be agreed and planned at the local level between primary care clinicians, laboratories and secondary care providers

We welcome opinions on the advice given. Please email any evidence or references that support your requests for change so that we may consider them at our annual review. Comments should be submitted to Professor Cliodna McNulty, Head of PHE Primary Care Unit, Microbiology Laboratory, Gloucestershire Royal Hospital, Great Western Road, Gloucester GL1 3NN.
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Review Due: April 2014 – Next Full Review Scheduled: December 2017

Quick reference guide

URINARY SYMPTOMS IN ADULT WOMEN <65: DO NOT CULTURE ROUTINELY[1B+,2C,3B+,4B+,5C]

In sexually active young people with urinary symptoms, consider *Chlamydia trachomatis*

Severe[2C] or ≥ 3 symptoms of UTI[4B+]

- dysuria
- frequency
- suprapubic tenderness
- urgency
- polyuria
- haematuria

- AND - NO vaginal discharge or irritation[2C,5C] → 90% culture positive → Give empirical antibiotic treatment

Mild or ≤ 2 symptoms of UTI (as above) → Obtain urine specimen → Urine NOT cloudy: 97% NPV[7B+,9B-] → Consider other diagnosis

URINE CLOUDY
Perform urine dipstick test with nitrite
When reading test, WAIT for the time recommended by the manufacturer

Positive nitrite, and leukocytes and blood 92% PPV[4B+] OR **positive** nitrite alone[4B+] → Probable UTI → Treat with first line agents on local or PHE guidance

Negative nitrite **Positive** leukocyte[12D] → UTI or other diagnosis equally likely → Review time of specimen (*morning is most reliable*) Treat if severe symptoms, or consider delayed antibiotic prescription and **send urine for culture**

Negative nitrite, leukocytes and blood 76% NPV[4B+] OR **negative** nitrite and leukocyte; **positive** blood[6A+] or protein[12D] → Laboratory microscopy for red cells is less sensitive than dipstick; UTI unlikely → Consider other diagnosis Reassure and give advice on management of symptoms

URINE CULTURE IN WOMEN AND MEN >65 YEARS

☑

- ☐ **Do not send urine for culture in asymptomatic elderly with positive dipsticks.**
- ☐ Only send urine for culture if two or more signs of infection, especially dysuria, fever >38°C, or new incontinence.[4B+,5C]
- ☐ Do not treat asymptomatic bacteriuria in the elderly as it is very common.[1B+]
- ☐ Treating does not reduce mortality or prevent symptomatic episodes, but does increase side-effects and antibiotic resistance.[2C,3B+]

URINE CULTURE IN WOMEN AND MEN WITH CATHETERS

☑

- ☐ **Do not treat asymptomatic bacteriuria in those with indwelling catheters, as bacteriuria is very common, and antibiotics increase side-effects and antibiotic resistance.**[1B+]
- ☐ Treatment does not reduce mortality or prevent symptomatic episodes, but does increase side-effects and antibiotic resistance.[2C,3B+]

Produced: 2002 – Reformat: June 2017
Review Due: April 2014 – Next Full Review Scheduled: December 2017

- ☐ Only send urine for culture in catheterised[7B-] if features of systemic infection.[1B+,5C,6C] However, always:
  - exclude other sources of infection[1C]
  - check that the catheter drains correctly and is not blocked
  - consider need for continued catheterisation
  - if the catheter has been in place for more than seven days, consider changing it before/when starting antibiotic treatment[1B+,6C,8B+]
- ☐ Do not give antibiotic prophylaxis for catheter changes unless history of symptomatic UTIs due to catheter change.[9B-,10B+]

WHEN ELSE SHOULD I SEND A URINE FOR CULTURE?

- ☐ Pregnancy: if symptomatic for investigation of positive UTI,[1B+] and at first antenatal visit, as asymptomatic bacteriuria associated with pyelonephritis and premature delivery.[1B+,2B+]
- ☐ Suspected pyelonephritis[3C] (loin pain and fever).
- ☐ Suspected UTI in men.[1B+,4C]
- ☐ Failed antibiotic treatment or persistent symptoms.[5A+,6B-]
  - *E. coli* with ESBL and CPE enzymes are increasing in the community
  - ESBLs are multi-resistant, but usually remain sensitive to nitrofurantoin or fosfomycin[7B+,8B+,9A+]
- ☐ Recurrent UTI, abnormalities of genitourinary tract, or renal impairment, as more likely to have a resistant strain.

SAMPLING IN WOMEN AND MEN

- ☑ ☐ **Refrigerate specimens to prevent bacterial overgrowth,[1B+] or use specimen pots with boric acid (fill to the line).[1B+]**
- ☐ Women: specimen should be midstream.[1C,2C] Cleansing with water[5B-] and holding the labia apart[3B+,4B-] are not essential. Cleansing with antiseptic leads to false negatives.[6B-]
- ☐ Men: specimen should be midstream.[1C,2C]
- ☐ People with catheters: using aseptic technique, drain a few mL of urine, then collect a sample from catheter sampling port.[1C]

HOW DO I INTERPRET A CULTURE RESULT?

- ☐ Usually indicates UTI in patient with urinary symptoms.[1B+] Higher counts have even higher positive predictive value.
  - single organism $\geq 10^4$ colony forming units (CFU)/mL[1B+]
  - $\geq 10^5$ mixed growth with one predominant organism
  - *Escherichia coli* or *Staphylococcus saprophyticus* $\geq 10^3$ CFU/mL[1B+]
- ☐ Do not treat asymptomatic bacteriuria in the elderly as it does not reduce mortality or prevent symptomatic episodes.
- ☐ White blood cells:[2C]
  - white cells $\geq 10^4$/mL are considered to represent inflammation
  - 'no white cells present' indicates no inflammation and reduces culture significance
  - pregnancy is associated with physiological pyuria
- ☐ Sterile pyuria:[2C]
  - in sterile pyuria, consider *Chlamydia trachomatis* (especially if 16-24 years), other vaginal infections, other non-culturable organisms, including TB or renal pathology
- ☐ Epithelial cells/mixed growth:[2C]
  - presence indicates perineal contamination, which reduces significance of culture
- ☐ Red cells:[3C]

Produced: 2002 – Reformat: June 2017
Review Due: April 2014 – Next Full Review Scheduled: December 2017

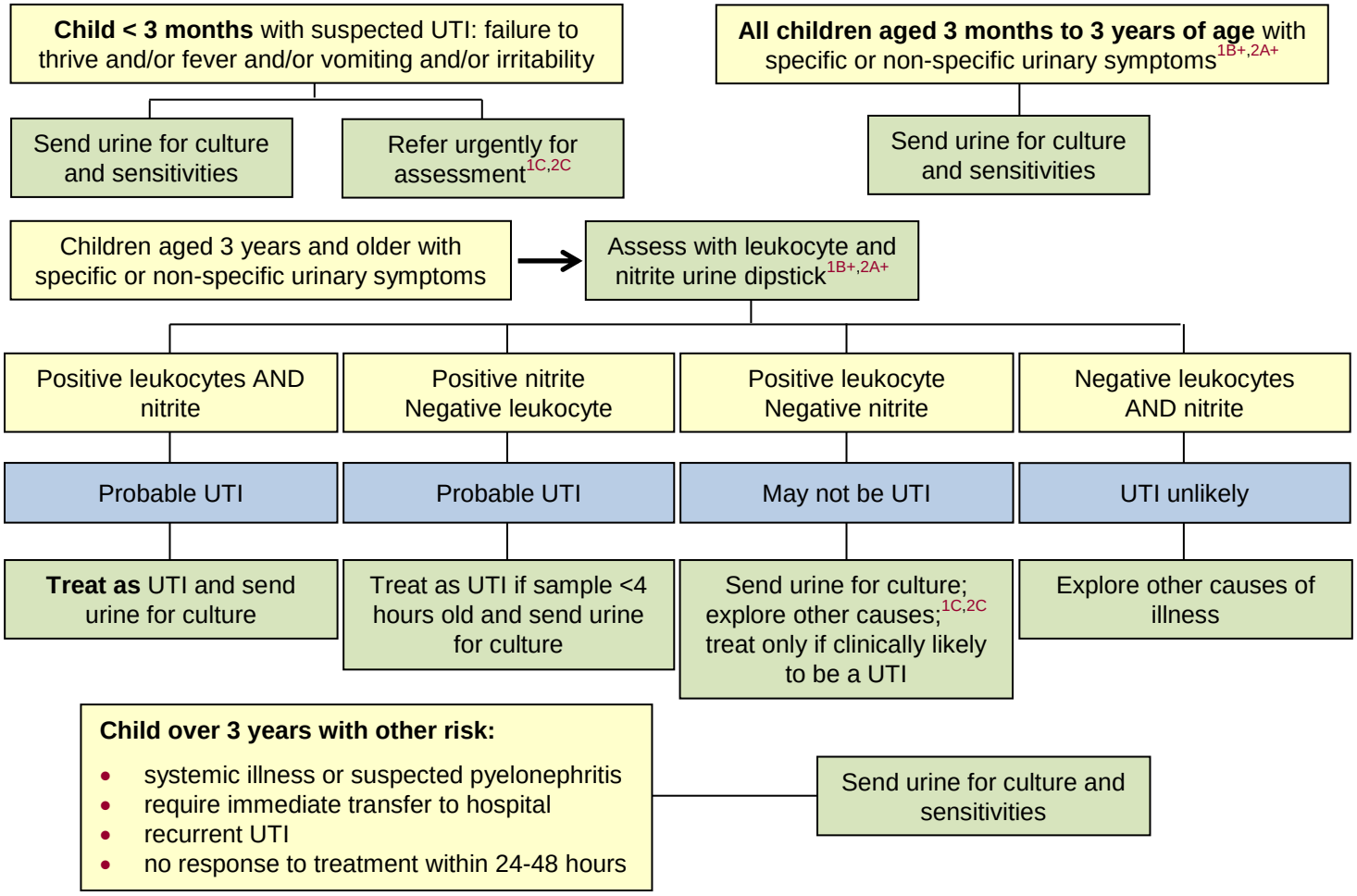
- may be present in UTI; refer patients with persistent haematuria post-UTI
- lab microscopy for red cells is less accurate than dipstick due to red cell lysis in transport

IS A FOLLOW-UP URINE SAMPLE NEEDED?

☐ Follow-up urine samples are not usually indicated, except when treating asymptomatic bacteriuria in pregnancy.

CHILDREN

Consider UTI in any sick child and every young child with unexplained fever[1B+,2A+]



☐ <u>Sampling in children:</u>

- in toddlers, clean catch urine using potties washed in hot water (60°C) with washing up liquid are suitable[1B-,2C]
- in infants, clean catch urine is preferable;[2C] a collection pad in a nappy may be used but is less accurate;[3B+] changing the pad every 30 minutes until urine is passed reduces contamination;[4A-] bag urines are less comfortable[2C,3B-]

☐ <u>Interpretation of culture results:</u>

- single organism $\geq 10^4$ CFU/mL indicates UTI;[1B+] suprapubic aspirates: growth is significant
- all children need clinical assessment for risk factors; if risk factors or non *E. coli* UTI, renal imaging needed[1D]
- white blood cells: in children, pyuria may be absent, or present (due to fever without UTI)[3C]

KEY: ☑ = good practice point

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GRADING OF GUIDANCE RECOMMENDATIONS

The strength of each recommendation is qualified by a letter in parenthesis. This is an altered version of the grading recommendation system used by SIGN.

STUDY DESIGN	RECOMMENDATION GRADE
Good recent systematic review and meta-analysis of studies	A+
One or more rigorous studies; randomised controlled trials	A-
One or more prospective studies	B+
One or more retrospective studies	B-
Non-analytic studies, eg case reports or case series	C
Formal combination of expert opinion	D

This guidance was originally produced in 2002 by the South West GP Microbiology Laboratory Use Group, in collaboration with the Association of Medical Microbiologists, general practitioners, nurses and specialists in the field. This guidance was reformatted in 2017 in line with PHE recommendations. For detailed information regarding the comments provided and action taken, please email sarah.alton@phe.gov.uk. Public Health England works closely with the authors of the Clinical Knowledge Summaries.

If you would like to receive a copy of this guidance with the most recent changes highlighted, please email sarah.alton@phe.gov.uk.

For detailed information regarding the search strategies implemented and full literature search results, please email sarah.alton@phe.gov.uk.

References

Adult women – acute uncomplicated UTI:

1. Car J. Urinary tract infections in women: diagnosis and management in primary care. *BMJ*. 2006 Jan; 332(7533):94-97. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1326933/pdf/bmj33200094.pdf.

2. Scottish Intercollegiate Guidelines Network (SIGN). Management of suspected bacterial urinary tract infection in adults. 2012 Jul. Available from: http://www.sign.ac.uk/pdf/sign88.pdf.
   RATIONALE: Expert consensus is that it is reasonable to start empirical antibiotics in women with symptoms of UTI without urine dipstick or urine culture. Expert consensus is that, in women with symptoms of vaginal itch or discharge, alternative diagnoses to UTI should be explored. Based on evidence from poor quality RCTs, the SIGN guideline group recommended that dipstick tests should only be used to diagnose bacteriuria in women with limited symptoms and signs (no more than two symptoms).

3. American College of Obstetricians and Gynaecologists (ACOG). ACOG practice bulletin no. 91: treatment of urinary tract infections in nonpregnant women. *Obstet Gynecol*. 2008 Mar; 111(3):785-794. Available from: https://www.ncbi.nlm.nih.gov/pubmed/18310389.
   RATIONALE: Expert consensus is that it is reasonable to start empirical antibiotics in women with symptoms of UTI without urine culture.

4. Little P, Turner S, Rumsby K, Warner G, Moore M, Lowes JA et al. Dipsticks and diagnostic algorithms in urinary tract infection: development and validation, randomised trial, economic analysis, observational cohort and qualitative study. *Health Technol Assess*. 2009 Mar; 13(19):1-73. Available from: https://www.ncbi.nlm.nih.gov/pubmed/19364448.
   RATIONALE: In women with uncomplicated UTI, the negative predictive value when nitrite, leukocytes, and blood are all negative was 76%. The positive predictive value for having nitrite and either blood or leukocytes was 92%. When clinical variables were examined, the positive predictive value was 82% for women with all three of cloudy urine, dysuria, and nocturia. The negative predictive value was 67% for none of these three features. When individual clinical features were considered alone, cloudy urine or dysuria were predictive of UTI, but nocturia or smelly urine were not.

5. Bent S, Nallamothu BK, Simel DL, Fihn SD, Saint S. Does this woman have an acute uncomplicated urinary tract infection? *JAMA*. 2002 May; 287(20):2701-2710. Available from: https://www.ncbi.nlm.nih.gov/pubmed/12020306.
   RATIONALE: A systematic review of diagnostic studies found that the presence of vaginal discharge or vaginal irritation substantially reduces the probability of UTI to around 20%.

6. Rodgers M, Nixon J, Hempel S, Aho T, Kelly J, Neal D et al. Diagnostic tests and algorithms used in the investigation of haematuria: systematic reviews and economic evaluation. *Health*

Technol Assess. 2006 Jun; 10(18):259. Available from: https://www.ncbi.nlm.nih.gov/pubmed/16729917.

RATIONALE: This systematic review found that it was not possible to define the most effective diagnostic strategy for the investigation of microscopic and macroscopic haematuria in adults, as insufficient data was currently available. The detection of microhaematuria was not found to be a useful test to either rule in or rule out the presence of a significant underlying pathology, such as urinary calculi or bladder cancer. An algorithm was therefore developed by expert consensus (see the appendices of the systematic review) to guide further investigations.

7. Bulloch B, Bausher JC, Pomerantz WJ, Connors JM, Mahabee-Gittens M, Dowd MD. Can urine clarity exclude the diagnosis of urinary tract infection? *Pediatrics*. 2000 Nov; 106(5):60. Available from: https://www.ncbi.nlm.nih.gov/pubmed/11061797.

   RATIONALE: This was a prospective cohort study of 159 children (aged from four weeks to 19 years) presenting to an emergency department with possible UTI. Catheterised or midstream clean-catch urine specimens were collected for culture. The finding of clear urine on visual inspection had a negative predictive value of 97.3%.

8. Flanagan PG, Rooney PG, Davies EA, Stout RW. Evaluation of four screening tests for bacteriuria in elderly people. *Lancet*. 1989 May; 1(8647):1117-1119. Available from: https://www.ncbi.nlm.nih.gov/pubmed/2566058.

   RATIONALE: This was a prospective cohort of urine samples from 418 elderly people admitted to hospital for any reason. A clear urine sample had a negative predictive value of 91.2%.

9. Phillips G, Fleming LW, Khan I, Stewart WK. Urine transparency as an index of absence of infection. *Br J Urol*. 1992 Aug; 70(2):191-195. Available from: https://www.ncbi.nlm.nih.gov/pubmed/1393442.

   RATIONALE: This was a prospective cohort study of urine samples from 363 adults attending a nephrology clinic over a six month period. A clear urine sample had a negative predictive value of 97%.

10. Czerwinski AW, Wilkerson RG, Merrill JA, Braden B, Colmore JP. Further evaluation of the Griess test to detect significant bacteriuria: Part II. *Am J Obstet Gynaecol*. 1971 Jul; 110(5):677-681. Available from: http://www.sciencedirect.com/science/article/pii/0002937871902535.

    RATIONALE: Nitrite is produced by the action of bacterial nitrate reductase in urine. As contact time between bacteria and urine is needed, morning specimens are most reliable. Early morning urines give more accurate nitrite results, as bacteria must be in contact with the urine for sufficient time to allow reduction of nitrates to nitrites.

11. Public Health England (PHE). Management of infection guidance for primary care for consultation and local adaptation. 2017 May. Available from: https://www.gov.uk/government/publications/managing-common-infections-guidance-for-primary-care.

12. European Confederation of Laboratory Medicine. European urinalysis guidelines. *Scand J Clin Lab Invest Suppl*. 2000 Jan; 231(1):1-86. Available from: https://www.ncbi.nlm.nih.gov/pubmed/12647764.

RATIONALE: Very extensive guidelines (aimed at laboratory staff) for interpretation of urine culture and microscopy. Reasons for false positive and negative results, see page 54. Other causes of leukocytes in urine: leukocyte esterase detects intact and lysed leukocytes produced in inflammation. Neutrophils are found in UTI and also glomerulonephritis, interstitial nephritis and aseptic cystitis. The appearance of lymphocytes in urine is associated with chronic inflammatory conditions, viral diseases and renal transplant rejection. Macrophages are also suggested to reflect inflammatory activity of renal disease. Other causes of haematuria: haematuria remains a major sign of urinary tract and renal disease. It may also reflect a general bleeding tendency, or be caused by strenuous exercise or menstruation. Other causes of proteinuria: protein is found in UTI and also in bladder or prostatic disease, and in vaginal discharge. Intermittent proteinuria may be due to fever, exercise, epileptic seizure, congestive heart failure, or be orthostatic (occurs in the upright position only). Persistent proteinuria can be due to rhabdomyolysis, acute haemolysis, IgA nephropathy, drug-induced nephropathy.

The elderly and people with catheters:

1. Scottish Intercollegiate Guidelines Network (SIGN). Management of suspected bacterial urinary tract infection in adults. 2012 Jul. Available from: http://www.sign.ac.uk/pdf/sign88.pdf.

RATIONALE: A SIGN guideline, providing advice on how to manage suspected bacterial urinary tract infections in the elderly and people with catheters. Symptomatic bacteriuria in the elderly: elderly women and men should not receive antibiotic treatment for asymptomatic bacteriuria. There is evidence that mortality and the number of symptomatic episodes are not reduced, but for every three people given antibiotics, one will experience adverse effects (such as rash or GI symptoms), NNH=3. Asymptomatic bacteriuria in people with catheters: catheterised people with asymptomatic bacteriuria should not receive antibiotic treatment. There is conflicting evidence on whether repeated treatment of asymptomatic bacteriuria prevents symptomatic episodes in people with long-term catheters. However, there is evidence that repeated treatment of asymptomatic bacteriuria prevents symptomatic episodes in people with long-term catheters. However, there is evidence that repeated treatment of asymptomatic bacteriuria increases the risk of colonisation by antibiotic resistant bacteria. When to send a sample for culture in people with catheters: expert opinion is that no constellation of symptoms and signs can accurately predict the likelihood of a symptomatic UTI in catheterised people (and therefore, the need to send a sample for culture). In catheterised people who present with fever, experts recommend looking for associated localising (loin or suprapubic tenderness) or systemic features and exclude other potential sources before sampling and considering antibiotic treatment. Catheter change before treating symptomatic infection: expert opinion, based on one small RCT, is that people with long-term indwelling catheters should have the catheter changed before starting antibiotic treatment for symptomatic UTI. Catheter change increases the likelihood of successful treatment.

2. Abrutyn E, Mossey J, Berlin JA, Boscia J, Levison M, Pitsakis P et al. Does asymptomatic bacteriuria predict mortality and does antimicrobial treatment reduce mortality in elderly ambulatory women: *Ann Intern Med*. 1994 May; 120(10):827-833. Available from: https://www.ncbi.nlm.nih.gov/pubmed/7818631.
   RATIONALE: This cohort study found that asymptomatic bacteriuria occurs in 25% of women >65 years and 10% of men >65 years. However, it was not a risk factor for mortality in elderly women without catheters. Those with asymptomatic bacteriuria were subsequently randomised to treatment or no treatment. There was no difference in the risk of mortality between the treated and untreated groups.

3. Nicolle LE, Mayhew WJ, Bryan L. Prospective randomized comparison of therapy and no therapy for asymptomatic bacteriuria in institutionalized elderly women. *Am J Med*. 1987 Jul; 83(1):27-33. Available from: https://www.ncbi.nlm.nih.gov/pubmed/3300325.
   RATIONALE: There was no difference in morbidity or mortality in those randomised to antibiotics or no antibiotics (50 participants). However, antibiotic treatment was associated with an increased risk of adverse effects.

4. Benton TJ, Young RB, Leeper SC. Asymptomatic bacteriuria in the nursing home. *ALTC*. 2008 Sep; 14(7):17-22. Available from: http://www.managedhealthcareconnect.com/article/5963.
   RATIONALE: A useful discussion of the difficulties in deciding when bacteriuria in the elderly requires treatment.

5. Loeb M, Bentley DW, Bradley S, Crossley K, Garibaldi R, Gantz N et al. Development of minimum criteria for the initiation of antibiotics in residents of long-term-care facilities: results of a consensus conference. *Infect Control Hosp Epidemiol*. 2001 Feb; 22(2):120-124. Available from: https://www.ncbi.nlm.nih.gov/pubmed/11232875.
   RATIONALE: Elderly people: expert consensus is that the minimum criteria for initiating antibiotics for bacteriuria include acute dysuria alone, or fever, and at least one of the following: new or worsening urgency, frequency, suprapubic pain, gross haematuria, costovertebral angle tenderness, or urinary incontinence. People with an indwelling catheter: expert consensus is that the minimum criteria for initiating antibiotics for bacteriuria include the presence of at least one of the following: fever, new costovertebral tenderness, rigors, or new onset delirium.

6. Tenke P, Kovacs B, Bjerklund Johansen TE, Matsumoto T, Tambyah PA, Naber KG. European and Asian guidelines on management and prevention of catheter-associated urinary tract infections. *Int J Antimicrob Agents*. 2008 Feb; 31(1):68-78. Available from: https://www.ncbi.nlm.nih.gov/pubmed/18006279.
   RATIONALE: When to send samples for culture: a sample is only needed if the person is symptomatic. Asymptomatic bacteriuria is common, but should generally be treated because bacteriuria will either not be eradicated or will return rapidly, and antibiotic treatment will contribute to antibiotic resistance, and cause adverse effects. Antibiotic treatment is recommended only in symptomatic infection. Systemic antibiotics should be

used for catheterised patients who are febrile and appear to be ill. Catheter change before treating symptomatic infection: owing to the likelihood of bacteria sequestered in a biofilm on the catheter surface, expert opinion is that it may be reasonable to replace or remove the catheter (if the indwelling catheter has been in place for more than seven days) before the therapy of symptomatic catheter-associated bacteriuria.

7. Tambyah PA, Maki DG. The relationship between pyuria and infection in patients with indwelling urinary catheters: a prospective study of 761 patients. *Arch Intern Med*. 2000 Mar; 160(5):673-677. Available from: https://www.ncbi.nlm.nih.gov/pubmed/10724053.
   RATIONALE: Pyuria is common in catheterised patients and it has no predictive value in this population. Dipstick testing should not, therefore, be used to diagnose UTI in catheterised patients.

8. Raz R, Schiller D, Nicolle LE. Chronic indwelling catheter replacement before antimicrobial therapy for symptomatic urinary tract infection. *J Urol*. 2000 Oct; 164(4):1254-1258. Available from: https://www.ncbi.nlm.nih.gov/pubmed/10992375.
   RATIONALE: This small (n = 54) randomised, open trial found that urine culture 72 hours after starting antibiotic treatment was more likely to be negative in people whose indwelling catheters were changed at the start of treatment (89%; 24 of 27), compared with those whose catheters were not changed (30%; 8 of 27), p = 0.001.

9. National Institute for Health and Care Excellence (NICE). Infection control: prevention of healthcare-associated infection in primary and community care. 2003 Jun. Available from: https://www.nice.org.uk/guidance/cg2.
   RATIONALE: The NICE recommendation not to use antibiotic cover during catheter changes is based on two studies which reported that not using prophylactic antibiotics did not increase the risk of UTI.

10. National Institute for Health and Care Excellence (NICE). Prophylaxis against infective endocarditis: antimicrobial prophylaxis against infective endocarditis in adults and children undergoing interventional procedures. 2008 Mar. Available from: https://www.nice.org.uk/guidance/cg64.
    RATIONALE: Based on a cost-effective analysis, NICE recommend that prophylactic antibiotic cover is NOT needed when changing catheters in people with a heart valve lesion, septal defect, patent ductus, or prosthetic valve.

Laboratory testing for culture and sensitivity:

1. Scottish Intercollegiate Guidelines Network (SIGN). Management of suspected bacterial urinary tract infection in adults. 2012 Jul. Available from: http://www.sign.ac.uk/pdf/sign88.pdf.
   RATIONALE: Screening for bacteriuria in pregnancy: there is evidence from a systematic review that dipstick testing is not sufficiently sensitive to be used as a screening test in pregnancy. Expert consensus is that urine culture should be performed routinely at the first antenatal visit. Women with bacteriuria should have a second urine culture. If

bacteriuria is confirmed by the second culture, give antibiotics and repeat urine culture at each antenatal visit until delivery. Women who do not have bacteriuria in the first trimester should not have repeat urine cultures unless symptomatic. Diagnosis in men: a urine sample is recommended because UTI in men is generally regarded as complicated (it results from an anatomic or functional abnormality), and there are no studies on the predictive values of dipstick testing in men.

2. National Institute for Health and Care Excellence (NICE). Antenatal care for uncomplicated pregnancies. 2008 Mar. Available from: https://www.nice.org.uk/guidance/CG62.
   RATIONALE: NICE recommend that women should be offered routine screening for bacteriuria by midstream urine culture early in pregnancy, because identification and treatment of asymptomatic bacteriuria reduces the risk of pyelonephritis and premature delivery.

3. Warrell DA, Cox TM, Firth JD. *Oxford Textbook of Medicine*. Oxford Medicine Online; 2017. Available from: http://oxfordmedicine.com/view/10.1093/med/9780199204854.001.1/med-9780199204854.
   RATIONALE: A diagnosis of pyelonephritis is usually made on the basis of flank pain (usually unilateral), fever, rigors, raised C-reactive protein (or erythrocyte sedimentation rate), and evidence of urine infection on a midstream urine sample.

4. Grabe M, Bjerklund-Johansen TE, Botto H, Cek M, Naber KG, Pickard RS et al. Guidelines on urological infections. 2013 Mar. Available from: https://uroweb.org/wp-content/uploads/18_Urological-infections_LR.pdf.
   RATIONALE: Diagnosis in men: a urine sample is recommended because UTI in men is generally regarded as complicated (it results from an anatomic or functional abnormality) and there are no studies on the predictive values of dipstick testing in men.

5. Costelloe C, Metcalfe C, Lovering A, Mant D, Hay AD. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. *BMJ*. 2010 May; 18(340):2096. Available from: https://www.ncbi.nlm.nih.gov/pubmed/20483949.
   RATIONALE: This systematic review found that individuals prescribed an antibiotic in primary care for a respiratory or urinary infection develop bacterial resistance to that antibiotic. The effect is greatest in the month immediately after treatment, but may persist for up to 12 months. In five studies of urinary tract bacteria (14,348 participants), the pooled odds ratio for bacterial resistance was 2,5 (95% CI 2.1 to 2.9) within two months of antibiotic treatment, and 1.33 (95% CI 1.2 to 1.5) within 12 months of treatment.

6. Vellinga A, Cormican M, Hanahoe B, Murphy AW. Predictive value of antimicrobial susceptibility from previous urinary tract infection in the treatment of re-infection. *Br J Gen Pract*. 2010 Jul; 60(576):511-513. Available from: https://www.ncbi.nlm.nih.gov/pubmed/20594440.
   RATIONALE: Analysis of susceptibility results from 3,413 patients who provided at least

two *E. coli* positive urine samples over the study period found that, if resistance to ampicillin, trimethoprim, or ciprofloxacin was detected, a recurrent UTI within three months of this sample is likely to be associated with an organism that is still resistant. However, if resistance to nitrofurantoin was detected, a recurrent UTI within three months has only a one in five chance of being a resistant organism. If the organism was susceptible to nitrofurantoin, ciprofloxacin, or trimethoprim, then a recurrent UTI within 12 months is likely to still be susceptible.

7. Naber KG, Schito G, Botto H, Palou J, Mazzei T. Surveillance study in Europe and Brazil on clinical aspects and Antimicrobial Resistance Epidemiology in Females with Cystitis (ARESC): implications for empiric therapy. *Eur Urol*. 2008 Nov; 54(5):1164-1175. Available from: https://www.ncbi.nlm.nih.gov/pubmed/18511178.
   RATIONALE: In all countries, susceptibility rate to *E. coli* above 90% (p<0.0001) was found only for fosfomycin, mecillinam, and nitrofurantoin.

8. Falagas ME, Kastoris AC, Kapaskelis AM, Karageorgopoulos DE. Fosfomycin for the treatment of multidrug-resistant, including extended-spectrum beta-lactamase producing, Enterobacteriaceae infections: a systematic review. *Lancet Infect Dis*. 2010 Jan; 10(1):43-50. Available from: https://www.ncbi.nlm.nih.gov/pubmed/20129148.
   RATIONALE: 97% of ESBL-producing *E. coli* isolates, and 81% of *Klebsiella pneumonia* ESBL-producing isolates were susceptible to fosfomycin.

9. Falagas ME, Vouloumanou EK, Togias AG, Karadima M, Kapaskelis AM, Rafailidis PI et al. Fosfomycin versus other antibiotics for the treatment of cystitis: a meta-analysis of randomized controlled trials. *J Antimicrob Chemother*. 2010 Sep; 65(9):1862-1877. Available from: https://www.ncbi.nlm.nih.gov/pubmed/20587612.
   RATIONALE: In this meta-analysis including 27 trials, 848 women received fosfomycin and 754 comparative agents. Efficacy of fosfomycin was similar to all the comparator agents including fluoroquinolones and trimethoprim. Five of the 27 trials included 502 pregnant women, in which side-effects for fosfomycin were lower than for non-pregnant women.

Sampling technique in men and women:

1. Public Health England (PHE). SMI B 41: Investigation of urine. 2014 Jul. Available from: https://www.gov.uk/government/publications/smi-b-41-investigation-of-urine.
   RATIONALE: Midstream urines are recommended for routine use. Delays and storage at room temperature allow organisms to multiply, which may generate false positive results. Where delays in processing are unavoidable, refrigeration is recommended. Use of a boric acid preservative may also be useful. Boric acid preservative may also be useful. Boric acid preservative holds the bacterial population steady for 48-96 hours. Toxicity to some organisms has been reported, but this often reflects under filling of the container.

2. European Confederation of Laboratory Medicine. European urinalysis guidelines. *Scand J*

Clin Lab Invest Suppl. 2000 Jan; 231(1):1-86. Available from: https://www.ncbi.nlm.nih.gov/pubmed/12647764.

RATIONALE: Very extensive guidelines (aimed at laboratory staff) for interpretation of urine culture and microscopy. Midstream urines are recommended because the first portion of urine is always contaminated by commensal urethral flora in both men and women.

3. Lifshitz E, Kramer L. Outpatient urine culture: does collection technique matter? *Arch Intern Med*. 2000 Sep; 160(16): 2537-2540. Available from: https://www.ncbi.nlm.nih.gov/pubmed/10979067.

   RATIONALE: This randomised study of 242 women who presented with symptoms suggestive of UTI found that there was no difference in contamination rates between samples obtained with no technique (not midstream and no cleansing: 29%; contaminated: n=77; samples obtained midstream with perineal cleansing and spreading of the labia: 32% contaminated: n=84; samples obtained midstream with perineal cleansing and a vaginal tampon in place: 31% contaminated; n=81).

4. Baerheim A, Digranes A, Hunskaar S. Evaluation of urine sampling technique: bacterial contamination of samples from women students. *Br J Gen Pract*. 1992 Jun; 42(359):241-243. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1372060/.

   RATIONALE: This prospective study obtained a series of urine samples (a new sample was obtained each day for eight days, using a different set of instructions each day) from 111 healthy young women. There was no statistically significant difference in contamination rates between the following techniques: no precautions (31%), midstream sample (23.9%), midstream sample with perineal cleansing (20.4%), midstream and holding labia apart (21.1%). However, holding the labia apart as the sole technique was associated with a lower contamination rate (13%) in this study.

5. Leisure MK, Dudley SM, Donowitz LG. Does a clean-catch urine sample reduce bacterial contamination? *N Engl J Med*. 1993 Jan; 328(4):289-290. Available from: https://www.ncbi.nlm.nih.gov/pubmed/8418419.

   RATIONALE: Standard practice for collecting a urine specimen from women for bacterial culture includes cleansing of the perineum and urethral meatus before collection. A midstream urine specimen and a midstream urine specimen with prior cleansing were obtained during consecutive urinations in a series of 105 asymptomatic female health care workers. 64% of samples obtained by each method were found to be contaminated.

6. Roberts AP, Robinson RE, Beard RW. Some factors affecting bacterial colony counts in urinary infection. *Br Med J*. 1967 Feb; 1(5537):400-403. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1841545/pdf/brmedj02123-0050.pdf.

   RATIONALE: Suprapubic specimens and midstream samples taken using perineal cleansing with chlorhexidine were both taken from a series of 20 women presenting with suspected UTI. The colony count was reduced in 12 of the midstream plus chlorhexidine cleaning samples compared with the suprapubic sample from the same woman.

7. National Institute for Health and Care Excellence (NICE). Infection control: prevention of healthcare-associated infection in primary and community care. 2003 Jun. Available from: https://www.nice.org.uk/guidance/cg2.

   RATIONALE: Expert opinion is that urine samples from catheters should be obtained from the catheter sampling port, to reduce the risk of contamination. Maintaining a sterile, continuously closed catheter system is central to the prevention of catheter-associated infection.

Interpretation of culture results in adults:

1. European Confederation of Laboratory Medicine. European urinalysis guidelines. *Scand J Clin Lab Invest Suppl*. 2000 Jan; 231(1):1-86. Available from: https://www.ncbi.nlm.nih.gov/pubmed/12647764.

   RATIONALE: The cut-offs for symptomatic urinary tract infection caused by primary pathogens (*E. coli* and *S. saprophyticus*) are set by the European Confederation of Laboratory Medicine at $\geq 10^3$ CFU/mL in midstream urine specimens. For secondary pathogens (such as Enterobacter species, Enterococcus species, *P. mirabilis*, *P. aeruginosa* etc) cut offs are set as $\geq 10^4$ CFU/mL for women and $\geq 10^3$ CFU/mL for men. Evaluating urine culture findings has long been dominated by Kass's criteria for significant bacteriuria. Kass found that 95% of women with pyelonephritis had $\geq 10^8$ CFB/L ($\geq 10^5$ CFU/mL) or one bacterial species in a clean-catch midstream urine, and that such a finding in two consecutive midstream urine specimens in asymptomatic women would, with 95% probability, give the same result in a third midstream urine specimen. Kass also showed that $<10^7$ CFB/L indicated contamination during sample collection, whereas bacterial concentration in the interval of 10^7 to $<10^8$ CFB/L was difficult to interpret. Despite the fact that the criteria were developed for acute pyelonephritis and asymptomatic bacteriuria in women, they began to be used generally, even for symptomatic lower urinary tract infection. Stamm et al examined 187 sexually active young women with dysuria and urinary urgency. Cultures of midstream urine samples were compared to urine cultures obtained through suprapubic aspiration or urethral catheterisation. Enterobacteriaceae were isolated from bladder urine in 98 (52%) women. *S. saprophyticis*, *S. aureus* and enterococci were cultured in 26 (14%). The women who had 'coliform' bacteria in bladder urine were further analysed regarding the number of CFB/L. If 10^8 CFB/L midstream urine was used as a cut-off for 'significant' bacteriuria, the sensitivity was 51%, and the negative predictive value was 65%. If, on the other hand, a cut-off of 10^5 CFB/L midstream urine was used, the sensitivity was 95% with a negative predictive value of 94%, whereas specificity declined from 99% to 85%. Thus, low cut-off of 'coliform' bacteria in midstream urine more accurately predicted bladder infection in symptomatic women than in asymptomatic. Many additional studies support the observation that low bacterial concentrations of *E. coli* in particular have diagnostic relevance, even in mixed flora. Findings of *E. coli* have been interpreted as the first phase in urethritis in an ascending infection.

2. Public Health England (PHE). SMI B 41: Investigation of urine. 2014 Jul. Available from:

https://www.gov.uk/government/publications/smi-b-41-investigation-of-urine.

RATIONALE: White blood cells: significant pyuria is defined by PHE as ≥10^4 WBC/mL, although higher numbers are often found in healthy, asymptomatic women. A level of ≥10^5 WBC/mL has been suggested to be more appropriate for discriminating infection. Sterile pyuria (ie pyuria in the presence of no growth on routine culture media) may be the result of many factors, including genital tract infection, infection with *C. trachomatis*, infection with a fastidious organism, prior treatment with an antibiotic, renal calculi, bladder neoplasm, catheterisation, renal tuberculosis, or lysis of WBC in alkaline urine (as occurs in infections with Proteus species).

3. Renal Association and British Association of Urological Surgeons. Joint consensus statement on the initial assessment of haematuria. 2008 Jul. Available from: http://www.renal.org/docs/default-source/what-we-do/RA-BAUS_Haematuria_Consensus_Guidelines.pdf?sfvrsn=0.

RATIONALE: This Joint Working Party agreed that urine testing for haematuria should only be performed for identifiable clinical reasons; there is currently no evidence to support opportunistic screening of the general population. Urine dipstick of a fresh voided urine sample, containing no preservative, is considered a sensitive means of detecting the presence of haematuria. Significant haematuria is considered to be 1+ or greater. Trace haematuria should be considered negative. Routine microscopy for confirmation of dipstick haematuria is not necessary. Significant haematuria is diagnosed if there is any single episode of visible haematuria; any single episode of non-visible haematuria (in absence of UTI or other transient causes); persistent (two out of three dipsticks positive); asymptomatic non-visible haematuria (in absence of UTI or other transient causes). Haematuria in association with UTI is not uncommon. Following treatment of UTI, a dipstick should be repeated to confirm the post-treatment absence of haematuria. Other causes of transient haematuria include exercise induced haematuria, rarely myoglobinuria and menstruation. Refer to urology: all patients with visible haematuria (any age). All patients with s-NVH (any age). All patients with a-NVH aged ≥40 years.

Children:

1. National Institute for Health and Care Excellence (NICE). Urinary tract infection in under 16s: diagnosis and management. 2007 Aug. Available from: https://www.nice.org.uk/guidance/cg54.

RATIONALE: Urine culture: evidence from systematic reviews is that urgent microscopy and culture is the preferred method of diagnosis in children aged three months to three years of age. However, antibiotics should be started while awaiting results of MSU in children with specific urinary symptoms. In those without specific urinary symptoms, use positive nitrite on dipstick testing to start empirical antibiotics. Evidence from systematic reviews is that, in children over the age of three years, dipstick testing is as useful as culture. MSU is only needed in this age group if UTI is recurrent, or the child has a high or intermediate risk of serious illness, or if only one of nitrite or leukocyte esterase is positive. Children under three months of age: expert opinion is that children under three months of

age with suspected UTI should be referred urgently for assessment.

2. Price E, Pallett A, Gilbert RD, Williams C. Microbiological aspects of the UK National Institute for Health and Clinical Excellence (NICE) guidance on urinary tract infection in children. *J Antimicrob Chemother*. 2010 May; 65(5):836-841. Available from: https://www.ncbi.nlm.nih.gov/pubmed/20202989.

Sampling technique in children:

1. Rees JC, Vernon S, Pedler SJ, Coulthard MG. Collection of urine from washed-up potties. *Lancet*. 1996 Jul; 348(9021):197. Available from: https://www.ncbi.nlm.nih.gov/pubmed/8684173.
   RATIONALE: This study tested four methods of cleaning the potty to reduce faecal contamination of the sample. Washing potties using washing up liquid with hot water at 60°C before taking a urine specimen was the most effective method of reducing faecal contamination. Cleaning potties with Dettol or bleach were less successful.

2. National Institute for Health and Care Excellence (NICE). Urinary tract infection in under 16s: diagnosis and management. 2007 Aug. Available from: https://www.nice.org.uk/guidance/cg54.
   RATIONALE: This guidance reviews all the evidence around sample collection in children, and suggests that clean catch and suprapubic aspirate provide the most diagnostically accurate samples.

3. Lynster LCT, Nayar DM, Pedler SJ, Coulthard MG. Home collection of urine for culture from infants by three methods: survey of parents' preferences and bacterial contamination rates. *BMJ*. 2000 May; 320(7245):1312-1313. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC27376/.
   RATIONALE: In this series of 44 infants, parents collected three urine samples using a urine pad, bag, and clean-catch method (in a randomised order). Urine contamination levels were similar between pads (16%) and bags (18%), but lower with clean-catch (2%). Parents disliked the clean-catch method (requiring nursing the infant with a bottle ready until they wee, which is both time consuming and messy). Parents found pads and bags easy to use, and preferred them to clean-catch. The pad was considered comfortable. However, the bag was distressing, particularly on removal, often leaking, and leaving red marks.

4. Rao S, Bhatt J, Houghton C, Macfarlane P. An improved urine collection pad method: a randomised clinical trial. *Arch Dis Child*. 2004 Aug; 89(8):773-775. Available from: https://www.ncbi.nlm.nih.gov/pubmed/15269081.
   RATIONALE: Febrile children under the age of two were randomised to either the same urine collection pad kept in the nappy until urine was passed, or to urine collection pads to be changed every 30 minutes until a urine was passed. From 80 children enrolled, a satisfactory sample was obtained from 68 of them (12 samples were unusable because of

faecal soiling). Heavy mixed growth (indicating contamination) occurred in 3% of the replaced urine collection pad group (one of 31), compared with 29% (10 of 35) in the single urine collection pad group (p=0.008).

Interpretation of culture results in children:

1. European Confederation of Laboratory Medicine. European urinalysis guidelines. *Scand J Clin Lab Invest Suppl*. 2000 Jan; 231(1):1-86. Available from: https://www.ncbi.nlm.nih.gov/pubmed/12647764.

   RATIONALE: The cut-offs for symptomatic urinary tract infection caused by primary pathogens (*E. coli* and *S. saprophyticus*) are set by the European Confederation of Laboratory Medicine at $\geq 10^3$ CFU/mL in midstream urine specimens. For secondary pathogens (such as Enterobacter species, Enterococcus species, Klebsiella species, *P. mirabilis*, *P. aeruginosa* etc) cut offs are set as $\geq 10^4$ CFU/mL for women and $\geq 10^3$ CFU/mL for men.

2. Public Health England (PHE). SMI B 41: Investigation of urine. 2014 Jul. Available from: https://www.gov.uk/government/publications/smi-b-41-investigation-of-urine.

   RATIONALE: White blood cells: significant pyuria is defined by PHE as $\geq 10^4$ WBC/mL, although higher numbers are often found in healthy, asymptomatic women. A level of $\geq 10^5$ WBC/mL has been suggested to be more appropriate for discriminating infection. Sterile pyuria (ie pyuria in the presence of no growth on routine culture media) may be the result of many factors including genital tract infection, infection with *C. trachomatis*, infection with a fastidious organism, prior treatment with an antibiotic, renal calculi, bladder neoplasm, catheterisation, renal tuberculosis, or lysis of WBC in alkaline urine (as occurs in infections with Proteus species).

3. National Institute for Health and Care Excellence (NICE). Urinary tract infection in under 16s: diagnosis and management. 2007 Aug. Available from: https://www.nice.org.uk/guidance/cg54.

   RATIONALE: Expert opinion is that pyuria may be absent in childhood UTI, and that non *E. coli* organisms are an atypical cause of UTI in children. NICE recommend urgent ultrasound imaging in this situation to exclude structural abnormalities of the genitourinary tract, and to guide management.

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Abbreviations

a-NVH = Asymptomatic non-visible haematuria

°C = Degrees centigrade

CFB = Colony forming bacteria

CFU = Colony forming units

CI = Confidence interval

CPE = Carbapenemase-producing enterobacteriaceae

C. trachomatis = *Chlamydia trachomatis*

E. coli = *Escherichia coli*

ESBL(s) = Extended-spectrum beta-lactamase(s)

GI = Gastrointestinal

IgA = Immunoglobulin A

L = Litres

mL = Millilitres

MSU = Midstream urine

NNH = Number needed to harm

NPV = Negative predictive value

PPV = Positive predictive value

P. aeruginosa = *Pseudomonas aeruginosa*

P. mirabilis = *Proteus mirabilis*

RCT(s) = Randomised controlled trial(s)

s-NVH = Symptomatic non-visible haematuria

S. saprophyticus = *Staphylococcus saprophyticus*

TB = Tuberculosis

UTI(s) = Urinary tract infection(s)

WBC = White blood cell

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