

Scottish Intercollegiate Guidelines Network

Supplementary material supporting

**SIGN 88: Management of suspected bacterial
urinary tract infection in adults**

A national clinical guideline



July 2006

S1 Statistical methods

S1.1 DEFINITIONS

<i>Absolute risk (AR)</i>	The observed or calculated probability of an event or outcome occurring in a study population. Study results may be reported as absolute risk reduction (ARR).
<i>Confidence interval (CI)</i>	An interval within which the population parameter (the true value) is expected to lie with a given degree of certainty (eg 95% or 99%).
<i>Number needed to treat (NNT)</i>	The number of patients that would have to be treated to benefit (NNTB) or harm (NNTH) one patient.
<i>Number needed to screen (NNS)</i>	The number of patients that would have to be screened for a given duration to prevent one death or adverse event. ¹

S1.2 CALCULATION OF NUMBER NEEDED TO TREAT

The number needed to treat (NNT) is a useful way of reporting results of randomised controlled trials (RCTs). In a trial comparing a new treatment with a standard one, NNT is the estimated number of patients who need to be treated with a new treatment rather than the standard treatment for one additional patient to benefit or to prevent one additional bad outcome, for example, a symptomatic UTI.

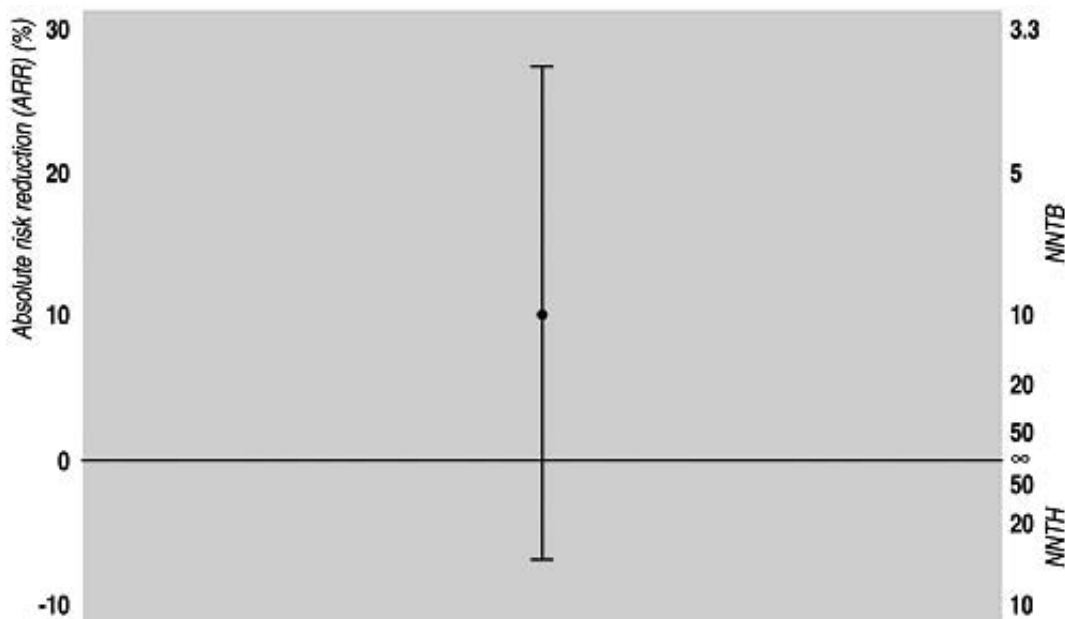
NNT can be obtained for any trial that has reported a binary outcome, for example, a Yes/No type response, with 'Yes' denoting whether a patient has experienced at least once episode of symptomatic UTI. If p_N denotes the proportion of patients with a 'Yes' response in the new treatment and p_S that of the standard treatment, then the difference ($p_N - p_S$) represents the absolute risk reduction (ARR).

NNT is the reciprocal of the absolute risk reduction (ARR) ie $NNT = 1/ARR$. A large treatment difference, in absolute terms, leads to a small NNT. When there is no treatment difference the ARR is zero and NNT is infinite.

When the treatment effect is significant at the 5% level, the 95% confidence interval (CI) for ARR will not include zero and hence the 95% CI for NNT, obtained simply by taking the reciprocals of the values defining the 95% CI for ARR, will not include infinity. When the treatment difference is not statistically significant, the 95% CI for ARR can include 0 and also be negative, giving rise to a CI for NNT which can include negative values and infinity.² To avoid confusion NNT is sometimes presented without a CI when the treatments are not statistically significantly different.

A negative NNT indicates that the new treatment has a harmful effect and is referred to as the number needed to harm (NNTH), whilst a positive NNT indicates that the new treatment has a beneficial effect and is referred to as number needed to benefit NNTB.²

Chart of 95% Confidence Intervals for AAR and NNT for a non-significant trial.²



The left hand axis shows the ARR and the right hand scale shows NNT. Note that the number needed to treat scale now goes from NNTH = 1 to NNTB = 1 via infinity. NNTB = 1 is an extreme and unattainable value, corresponding to the situation in which all patients experience at least one episode of symptomatic UTI if not given the new treatment and none if given the new treatment. NNTH = 1 corresponds to the case in which no patient experiences an episode of symptomatic UTI unless given the new treatment. The values NNTB = 1 and NNTH = 1 correspond to ARR = 100% and ARR = -100% respectively (not shown). The horizontal line denotes the case where the treatment makes no difference (ARR = 0 and NNT = ∞).

S1.3 EXAMPLES OF PRESENTATION OF NNT

The notation used to present CI for NNT distinguishes between NNTB and NNTH.

S1.3.1 TRIALS DEMONSTRATING SIGNIFICANT TREATMENT EFFECTS

Beneficial	
NNTB 7, (CI 4 to 25)	The treatment has a significant beneficial effect reported with confidence that one patient will benefit for every 25 treated.
Harmful	
NNTH 5, (CI 3 to 13)	The treatment has a significant harmful effect and only three patients may need to be treated for one patient to be harmed.

S1.3.2 TRIALS DEMONSTRATING NO SIGNIFICANT TREATMENT EFFECT

NNTB 45, (CI 17 to 10)	<p>Although the point estimate suggests a beneficial treatment the 95% confidence intervals include infinity which is indicative of no treatment effect.</p> <p>The number needed to treat to harm one patient is at least 17 and the number needed to treat to benefit one patient is at least 10.</p>
------------------------	---

S1.4 CALCULATION OF NUMBER NEEDED TO SCREEN

The number needed to screen (NNS) can be calculated from clinical trials that directly measure the effect of a screening strategy. Alternatively NNS can be estimated from clinical trials that measure treatment benefit, as the number needed to treat from the trial divided by the prevalence of unrecognised or untreated disease. Confidence intervals for the number needed to screen are derived from the CI for NNT.

S2 Prevalence of bacteriuria

S2.1 RISK FACTORS FOR ASYMPTOMATIC BACTERIURIA

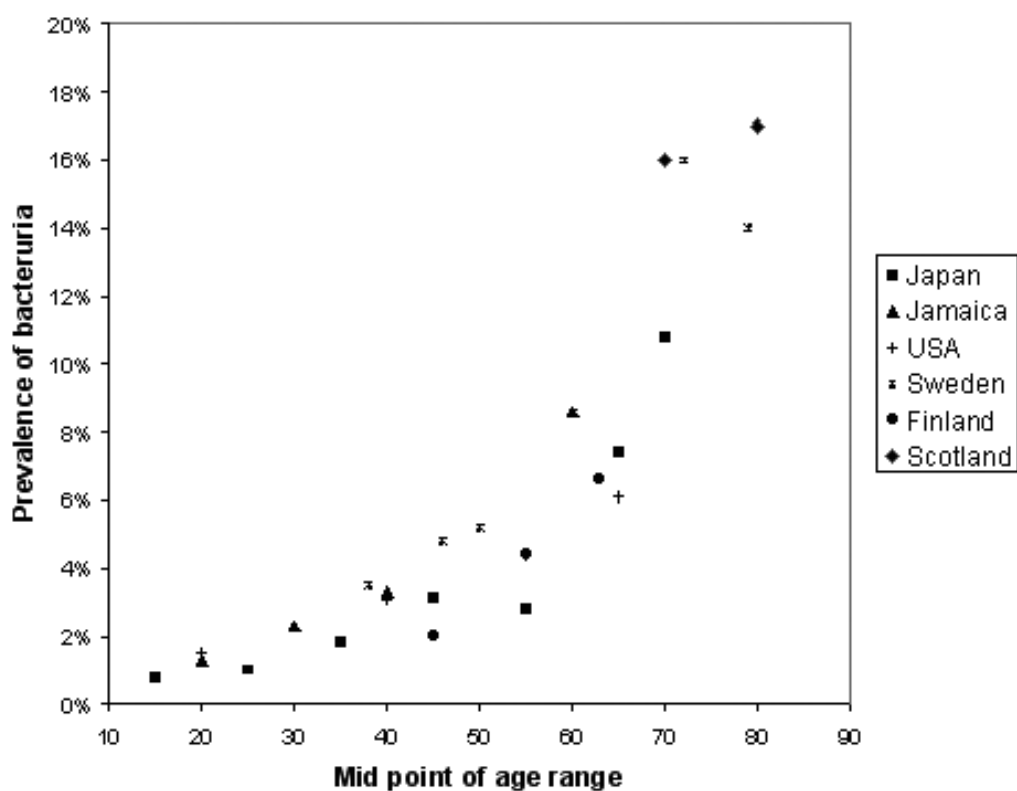
S2.1.1 SEXUAL ACTIVITY

Prevalence of asymptomatic bacteriuria by age in married women and nuns³

Age (years)	Married women	Nuns
24-44	4.6	0.7
55-64	6.3	2.7
> 65	6.5	5.8

S2.1.2 AGE

Prevalence of bacteriuria in non-pregnant adult women by age⁴⁻¹⁰



S2.2 PREVALENCE OF ASYMPTOMATIC BACTERIURIA

Prevalence of bacteriuria in non-pregnant women under 50 years of age with acute symptoms of UTI.¹¹⁻¹⁹

Reference	Total number of women	Number with bacteriuria	% with bacteriuria	Lower confidence interval (CI)	Upper confidence interval (CI)
Mond ¹²	83	37	44.6%	33.9%	55.3%
Buckwold ¹³	117	89	76.1%	68.3%	83.8%
Komaroff ¹⁴	137	105	76.6%	69.6%	83.7%
Ferry ¹⁵	170	146	85.9%	80.6%	91.1%
Rubin ¹⁶	218	142	65.1%	58.8%	71.5%
Jelheden ¹⁷	819	670	81.8%	79.2%	84.4%
Østerberg ¹⁸	1136	818	72.0%	69.4%	74.6%
Winkens ¹⁹	1388	902	65.0%	62.5%	67.5%
All studies combined	4,135	2960	71.6%	70.2%	73.0%

S3 Asymptomatic UTI in pregnant women

S3.1 ANTIBIOTIC TREATMENT OF ASYMPTOMATIC UTI

A systematic review identified fourteen well designed clinical trials that provide evidence that treatment of asymptomatic bacteriuria in pregnancy reduces the risk of pyelonephritis and of premature delivery and low birth weight.²⁰

There were potentially important differences in the criteria for diagnosis of bacteriuria between trials. Three trials included women with bacteriuria in a single specimen²¹⁻²³ whereas nine trials only included women with bacteriuria in two MSUs²⁴⁻³¹ or a catheter specimen of urine (CSU).³² The remaining two trials did not specify how bacteriuria was diagnosed.^{33,34}

The diagnostic criteria are important because a single CSU specimen has a false positive rate of up to 40% for diagnosis of asymptomatic bacteriuria in pregnancy.^{35,36} Such misclassification can influence the outcome of RCTs of treatment of asymptomatic bacteriuria. Separating out the trials that used two urine samples to diagnose asymptomatic bacteriuria suggests that inclusion of the other trials biases the results towards being less clinically effective.

False positive rates for diagnosis of asymptomatic bacteriuria in pregnancy by single midstream specimen of urine (MSU) specimen.

Reference	Time of screening	Positive single MSU	Confirmatory test	Confirmed positive	False positive	% false positive single MSU
Campbell-Brown ³⁵	First antenatal visit	198	SPA or CSU or second MSU	88	110/198	56%
Campbell-Brown ³⁷	First antenatal visit	87	SPA	51	36/87	41%
Gratacos ³⁶	First antenatal visit	134	Second MSU	77	57/134	43%
Persson ³⁸	Any of three antenatal visits	54	Second MSU	43	11/54	20%
Stenquist ³⁹	Any of three antenatal visits	67	Second MSU	57	10/67	15%

Most of the trials in this review were of continuous antibiotic therapy from diagnosis of asymptomatic bacteriuria until the end of pregnancy.²⁰ Only one of five trials with pyelonephritis as an outcome reported using two urine specimens to establish the diagnosis of bacteriuria. The results suggested that short course treatment is effective at preventing pyelonephritis.³⁰ The pooled results of the other four trials show no significant effect.

Only one of three trials of short course treatment with pre-term delivery or low birth weight as outcomes reported using two urine samples to diagnose bacteriuria.³¹ The results showed significant risk reduction (5/83 treatment versus 15/90 control, NNTB 9.4, CI NNTB 5.0 to NNTB 71.6). The pooled results of the other two trials showed a similar risk reduction but one of these trials was restricted to women with bacteriuria caused by Group B streptococci.²³

Numbers Needed to Treat (NNT) to prevent pyelonephritis by treating asymptomatic bacteriuria in pregnancy²⁰

Treatment	Diagnosis	NNT to prevent one outcome		
		NNT	LCI	UCI
Any antibiotic	Any bacteriuria	7.2	6.1	9.0
	Bacteriuria in 2 MSUs or 1 CSU	6.3	5.2	8.1
	Bacteriuria in 1 MSU	12.4	7.9	28.3
Short course (3-7 days)	Any bacteriuria	12.0	8.0	24.1
	Bacteriuria in 2 MSUs or 1 CSU	5.8	3.6	15.2
	Bacteriuria in 1 MSU	No significant difference		

A second review comparing the effectiveness of single dose therapy with four to seven days antibiotic treatment for asymptomatic bacteriuria in pregnancy included eight trials, of which seven used two urine specimens to diagnose asymptomatic bacteriuria.⁴⁰ The quality of the trials was poor and the results were heterogeneous. There is insufficient evidence to evaluate whether single dose treatment is as effective as 4-7 days treatment.

S4 Cost effectiveness

S4.1 COST EFFECTIVENESS OF CRANBERRY PRODUCTS FOR PREVENTING UTI IN NON-PREGNANT WOMEN

One Canadian clinical trial from 2002 included comprehensive measurement of direct patient costs based on interviews, collection of receipts and access to medical records.⁴¹ Direct patient costs are costs arising from the disease or its treatment. Indirect patient costs (loss of productivity) were based on time absent from work and the average weekly wage for the study participants.

Cost effectiveness of cranberry products for preventing UTI in non-pregnant women

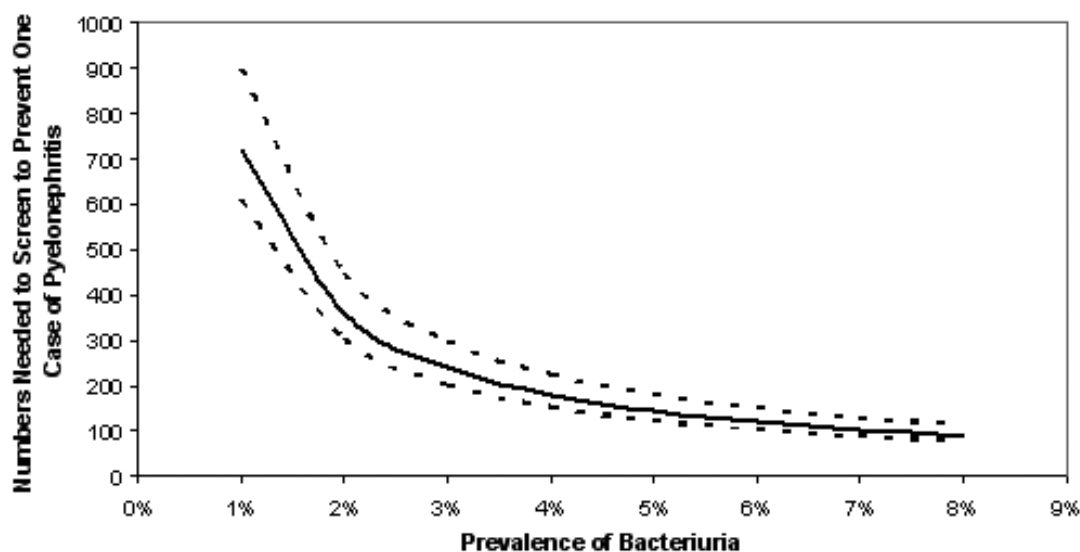
Annual cost of prophylaxis	Cost per UTI prevented	Direct patient costs	Indirect patient costs	Direct health sector costs
Cranberry tablets				
CDN\$624	CDN\$1,890	73%	5%	21%
Cranberry juice				
CDN\$1,400	CDN\$3,333	82%	6%	11%

- In 2005 the costs for one year of treatment in the UK are from £42 to £125 for cranberry tablets or capsules and £175 to £257 for cranberry juice.
- Cost per UTI prevented is lower in the UK because of the lower cost of cranberry products at around £250 to £750.

S4.2 COST-EFFECTIVE SCREENING OF PREGNANT WOMEN

Treatment of asymptomatic bacteriuria in pregnancy is extremely effective at preventing pyelonephritis but because the prevalence of bacteriuria is low (2-9%) in pregnant women a large number of women have to be screened in order to prevent one case of pyelonephritis.

Number of pregnant women that have to be screened for bacteriuria in order to prevent one case of pyelonephritis by antibiotic treatment of bacteriuric women (Dotted lines show the 95% confidence intervals)



A longitudinal study showed that most women acquire bacteriuria in the first trimester of pregnancy and that screening between 16-20 weeks is the optimal timing for diagnosis.³⁹ A large observational study demonstrated the effectiveness of a screening programme based on diagnosis of asymptomatic bacteriuria with two urine cultures in the first trimester.³⁶ Confirmed bacteriuria was found in 77 of 1652 (4.7%) women of whom 70 accepted antibiotic treatment. Pyelonephritis occurred in two of the 70 (2.8%) bacteriuric women who took antibiotic treatment, two of the seven (28.6%) bacteriuric women who did not take antibiotics and five of the 1,575 (0.3%) who did not have bacteriuria in the first trimester.

A decision analysis of screening based on urine culture concluded that it was likely to be cost saving to the health service unless the prevalence of asymptomatic bacteriuria was < 2%.⁴² The decision analysis assumed that 30% of women would develop pyelonephritis if they had untreated bacteriuria, which would fall to 6% (one fifth) with antibiotic treatment and that 1.8% of women without bacteriuria would develop pyelonephritis. The risk reductions used in this analysis were relatively conservative compared with those observed by another study which assumed that 28.6% of women would develop pyelonephritis compared to 2.8% (one tenth) with antibiotic treatment and that 0.3% of women without bacteriuria would develop pyelonephritis.³⁶

Two decision analyses compared the cost effectiveness of screening with dipstick testing compared with urine culture.^{43,44} Both analyses were based on culture of single urine samples, which is not the gold standard for diagnosis of asymptomatic bacteriuria in pregnancy (two urine samples).

The National Institute for Health and Clinical Excellence (NICE) guideline concludes that dipstick screening would have to be at least 91% sensitive to be cost effective.⁴⁴ Dipstick testing is cheaper than urine culture and has been adopted by some sectors of the NHS for that reason.⁴⁵ False negative dipstick tests can have significant adverse impact on women's health and may increase the risk of pre-term delivery.

The evidence supports screening for bacteriuria in pregnancy by culture of urine and treatment of women with bacteriuria.

S4.3 COST-EFFECTIVE SCREENING FOR ASYMPTOMATIC BACTERIURIA IN CATHETERISED PATIENTS

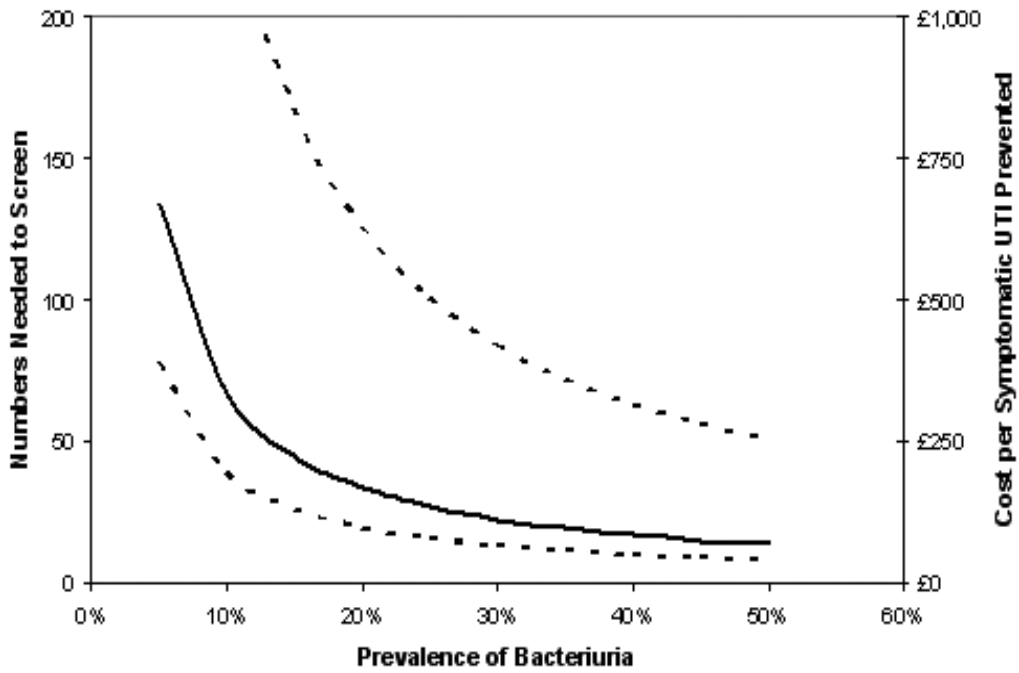
Symptomatic UTI is common both during and after short term catheterisation of the urinary tract and early identification of asymptomatic bacteriuria may prevent subsequent episodes of symptomatic UTI.

A prospective study of daily bacteriologic monitoring of 1,140 catheterised patients identified those in whom bacteriuria was either already present at the time of catheterisation or was acquired after catheterisation and those who had symptomatic UTI.⁴⁶ There were only 24 preventable symptomatic episodes among 1,140 catheterisations (2% prevalence) suggesting that daily urine culture is unlikely to be cost effective.

Single dose treatment of women with asymptomatic bacteriuria after short term catheterisation significantly reduces the risk of symptomatic episodes in the subsequent two weeks (NNTB 7, CI NNTB 4 to NNTB 25). The numbers needed to screen to prevent one symptomatic UTI has very wide confidence intervals because the evidence is based on a single RCT.⁴⁶

With modern standards of infection control and closed drainage systems the risk of bacteriuria from a single short term catheterisation is only 1-5% and may be as low as 20% even after 14 days.^{47,48} Laboratory testing and follow up of results account for most of the cost of screening, as the cost of a single dose of antibiotic is negligible. In the study two urine specimens confirmed the presence of bacteriuria. The cost per symptomatic UTI prevented was calculated using an estimated cost of £5 per patient screened assuming a single urine culture and one dose of trimethoprim.⁴⁹

Number of patients that have to be screened for bacteriuria and estimated cost to prevent one symptomatic UTI by single dose treatment of bacteriuric patients (Dotted lines show the 95% confidence intervals).



Abbreviations

AR	absolute risk
ARR	absolute risk reduction
CI	confidence interval
LE	leucocyte esterase
LCI	lower confidence interval
LUTI	lower urinary tract infection
MSU	midstream specimen of urine
CSU	catheter specimen of urine
NICE	National Institute for Health and Clinical Excellence
NNS	number needed to screen
NNT	number needed to treat
NNTH	number needed to harm
NNTB	number needed to benefit
RCT	randomised controlled trial
SPA	suprapubic aspirate
UCI	upper confidence interval
UTI	urinary tract infection
UUTI	upper urinary tract infection

References

1. Rembold CM. Number needed to screen: development of a statistic for disease screening. *BMJ* 1998;317(7154):307-12.
2. Altman DG. Confidence intervals for the number needed to treat. *BMJ* 1998;317:1309-12.
3. Kunin CM, McCormack RC. An epidemiologic study of bacteriuria and blood pressure among nuns and working women. *N Engl J Med* 1968;278(12):635-42.
4. Miall WE, Kass EH, Ling J, Stuart KL. Factors influencing arterial pressure in the general population in Jamaica. *BMJ* 1962;5303:497-506.
5. Evans DA, Kass EH, Hennekens CH, Rosner B, Miao L, Kendrick MI, et al. Bacteriuria and subsequent mortality in women. *Lancet* 1982;1(8264):156-8.
6. Freedman LR, Phair JP, Seki M, Hamilton HB, Nefzger MD. The epidemiology of urinary tract infections in Hiroshima. *Yale J Biol Med* 1965;37:262-82.
7. Bengtsson C, Bengtsson U, Bjorkelund C, Lincoln K, Sigurdsson JA. Bacteriuria in a population sample of women: 24-year follow-up study. Results from the prospective population-based study of women in Gothenburg, Sweden. *Scand J Urol Nephrol* 1998;32(4):284-9.
8. Takala J, Jousimies H, Sievers K. Screening for and treatment of bacteriuria in a middle-aged female population. II. Results of short-term nitrofurantoin therapy and one-year follow-up. *Acta Med Scand* 1977;202(1-2):75-9.
9. Nordenstam G, Sundh V, Lincoln K, Svanborg A, Eden CS. Bacteriuria in representative population samples of persons aged 72-79 years. *Am J Epidemiol* 1989;130(6):1176-86.
10. Akhter A, Andrews G, Caird F, Fallon R. Urinary tract infection in the elderly: a population study. *Age Aging* 1972;1:48-54.
11. Ditchburn RK, Ditchburn JS. A study of microscopical and chemical tests for the rapid diagnosis of urinary tract infections in general practice. *Br J Gen Pract* 1990;40(339):406-8.
12. Mond NC, Percival A, Williams JD, Brumfitt W. Presentation, diagnosis, and treatment of urinary-tract infections in general practice. *Lancet* 1965;19:514-6.
13. Buckwold FJ, Ludwig P, Harding GK, Thompson L, Slutchuk M, Shaw J, et al. Therapy for acute cystitis in adult women. Randomized comparison of single-dose sulfisoxazole vs trimethoprim-sulfamethoxazole. *JAMA* 1982;247(13):1839-42.
14. Komaroff AL, Pass TM, McCue JD, Cohen AB, Hendricks TM, Friedland G. Management strategies for urinary and vaginal infections. *Arch Intern Med* 1978;138(7):1069-73.
15. Ferry S, Andersson SO, Burman LG, Westman G. Optimized urinary microscopy for assessment of bacteriuria in primary care. *J Fam Pract* 1990;31(2):153-61.
16. Rubin RH, Fang LS, Jones SR, Munford RS, Slepach JM, Varga PA, et al. Single-dose amoxicillin therapy for urinary tract infection. Multicenter trial using antibody-coated bacteria localization technique. *JAMA*. 1980;244(6):561-64.
17. Jellheden B, Norrby RS, Sandberg T. Symptomatic urinary tract infection in women in primary health care. Bacteriological, clinical and diagnostic aspects in relation to host response to infection. *Scand J Primary Health Care*. 1996;14(2):122-8.
18. Osterberg E, Hallander HO, Kallner A, Lundin A, Svensson SB, Aberg H. Female urinary tract infection in primary health care: bacteriological and clinical characteristics. *Scand J Infect Dis* 1990;22(4):477-84.
19. Winkens RA, Leffers P, Trienekens TA, Stobberingh EE. The validity of urine examination for urinary tract infections in daily practice. *Fam Pract* 1995;12(3):290-3.
20. Smail F. Antibiotics for asymptomatic bacteriuria in pregnancy (Cochrane Review). In: *The Cochrane Library*, Issue 2 2000. Chichester, UK: John Wiley and Sons Ltd.
21. Foley ME, Farquharson R, Stronge JM. Is screening for bacteriuria in pregnancy worthwhile? *BMJ (Clin Res ed)* 1987;295(6592):270.
22. Kincaid-Smith P, Bullen M. Bacteriuria in Pregnancy. *Lancet* 1965;191:395-9.
23. Thomsen AC, Morup L, Hansen KB. Antibiotic elimination of group-B streptococci in urine in prevention of preterm labour. *Lancet* 1987;1(8533):591-3.
24. Elder HA, Santamarina BA, Smith S, Kass EH. The natural history of asymptomatic bacteriuria during pregnancy: the effect of tetracycline on the clinical course and the outcome of pregnancy. *Am J Obstet Gynecol* 1971;111(3):441-62.
25. Furness ET, McDonald PJ, Beasley NV. Urinary antiseptics in asymptomatic bacteriuria of pregnancy. *N Z Med J* 1975;81(539):417-9.
26. Gold EM, Traub FB, Daichman I, Terris M. Asymptomatic bacteriuria during pregnancy. *Obstet Gynecol* 1966;27(2):206-9.
27. Kass EH. Pyelonephritis and bacteriuria. A major problem in preventive medicine. *Ann Intern Med* 1962;56:46-53.
28. Little PJ. The incidence of urinary infection in 5000 pregnant women. *Lancet* 1966;2(7470):925-8.
29. Pathak UN, Tang K, Williams LL, Stuart KL. Bacteriuria of pregnancy: results of treatment. *J Infect Dis* 1969;120(1):91-103.
30. Williams GL, Campbell H, Davies KJ. Urinary concentrating ability in women with asymptomatic bacteriuria in pregnancy. *BMJ* 1969;3(664):212-5.
31. Wren BG. Subclinical renal infection and prematurity. *Med J Aust* 1969;2(12):596-600.
32. Leblanc AL, McGanly WJ. The Impact of Bacteriuria in Pregnancy; a Survey of 1300 Pregnant Patients. *Tex Rep Biol Med* 1964;22:336-47.
33. Brumfitt W. The effects of bacteriuria in pregnancy on maternal and fetal health. *Kidney Int Suppl* 1975;4:S113-9.
34. Mulla N. Bacteriuria in pregnancy. *Obstet Gynecol* 1960;16:89-92.
35. Campbell-Brown M, McFadyen IR, Seal DV, Stephenson ML. Is screening for bacteriuria in pregnancy worth while? *BMJ (Clin Res ed)* 1987;294:1579-82.
36. Gratacos E, Torres PJ, Vila J, Alonso PL, Cararach V. Screening and treatment of asymptomatic bacteriuria in pregnancy prevent pyelonephritis. *J Infect Dis* 1994;169(6):1390-2.
37. Campbell-Brown M, McFadyen IR. Bacteriuria in pregnancy treated with a single dose of cephalexin. *Br J Obstet Gynaecol* 1983;90(11):1054-9.
38. Persson K, Christensen KK, Christensen P, Forsgren A, Jorgensen C, Persson PH. Asymptomatic bacteriuria during pregnancy with special reference to group B streptococci. *Scand J Infect Dis* 1985;17(2):195-9.
39. Stenqvist K, Dahlen-Nilsson I, Lidin-Janson G, Lincoln K, Oden A, Rignell S, et al. Bacteriuria in pregnancy. Frequency and risk of acquisition. *Am J Epidemiol* 1989;129(2):372-9.
40. Villar J, Lydon-Rochelle MT, Gulmezoglu AM, Roganti A. Duration of treatment for asymptomatic bacteriuria during pregnancy. (Cochrane Review). In: *The Cochrane Library*, Issue 2 2000. Chichester, UK: John Wiley and Sons Ltd.
41. Stothers L. A randomized trial to evaluate effectiveness and cost effectiveness of naturopathic cranberry products as prophylaxis against urinary tract infection in women. *Can J Urol*. 2002;9(3):1558-62.
42. Wadland WC, Plante DA. Screening for asymptomatic bacteriuria in pregnancy. A decision and cost analysis. *J Fam Pract* 1989;29(4):372-6.
43. Rouse D, Andrews W, Goldenberg R, Owen J. Screening and treatment of asymptomatic bacteriuria of pregnancy to prevent pyelonephritis: a cost-effectiveness and cost-benefit analysis. *Obstet Gynecol* 1995;86(1):119-23.
44. National Institute for Health and Clinical Excellence. Antenatal care: routine care for the healthy pregnant woman. London: NICE; 2003. (Clinical Guideline 6)
45. Barker M. Clinical audits. Summary 1: routine urine culture. *Practice Nurse* 1999;17(9):648.
46. Garibaldi R, Mooney B, Epstein B, Britt M. An evaluation of daily bacteriologic monitoring to identify preventable episodes of catheter-associated urinary tract infection. *Infect Control* 1982;3(6):466-70.
47. Schaeffer A. Catheter-associated bacteriuria. *Urol Clin North Am* 1986;13:735-47.
48. Macfarlane D. Catheter-associated urinary tract infections. Part I: Epidemiology, pathogenesis and bacteriology. *West Indian Med J* 1984;33(3):146-50.
49. Fenwick E, Briggs A, Hawke CI. Management of urinary tract infection in general practice: a cost-effectiveness analysis. *Br J Gen Pract* 2000;50(457):635-9.

© Scottish Intercollegiate Guidelines Network
First published 2006

SIGN consents to the photocopying of this guideline for the
purpose of implementation in NHSScotland

Scottish Intercollegiate Guidelines Network
28 Thistle Street, Edinburgh EH2 1EN

www.sign.ac.uk