Managing Common Infections

Urinary tract infections (lower): antimicrobial prescribing

08/05/2017 – 05/06/2018

ID	ORGANISATION NAME	DOCUMENT	PAGE NO.	LINE NO.	COMMENTS Please insert each new comment in a new row	DEVELOPER'S RESPONSE Please respond to each comment
1	British Infection Association	Guideline	7	Table 1	Why is the pivmecillinam dosage the BNF dose rather than the PHE recommended 400 tds? NICE and PHE guidance need to be consistent with each other to reduce confusion amongst prescribers and also those formulating local/regional policies.	Thank you for your comment. NICE uses the BNF for dosages when making recommendations. NICE will contact the BNF about this issue. NICE antimicrobial prescribing guidelines will replace the PHE guidance as they are published.
2	British Infection Association	Guideline	General		There is no discussion of the possibility of contamination in the context of asymptomatic bacteriuria in pregnancy.	Thank you for your comment. The remit of this guidance is the management of common infections not diagnosis, therefore further detail on contamination in the context of asymptomatic bacteriuria is out of scope.
3	British Infection Association	Guideline	General		The antibiotic choices make no reference to local resistance rates or for come choices national data (many areas have high co-amoxiclav resistance rates as does the recent national E coli BSI dataset)	Thank you for your comment. The committee discussed the comment and added a recommendation to: take account of local antimicrobial resistance data when prescribing antibiotic treatment.
4	British Infection Association	Guideline	General		Advises high risk antibiotics for inpatient treatment from the C. difficile point of view	Thank you for your comment. The committee discussed, as outlined in the rationale, that, if an antibiotic is needed to treat an infection that is not life threatening, a narrow-spectrum antibiotic should generally be first choice. Indiscriminate use of broad-spectrum antibiotics creates a selective advantage for bacteria resistant even to these 'last-line'

						broad-spectrum agents, and also kills normal commensal flora leaving people susceptible to antibiotic-resistant harmful bacteria such as Clostridium difficile. For infections that are not life threatening, broad-spectrum antibiotics need to be reserved for second-choice treatment when narrow-spectrum antibiotics are ineffective. Cefalexin is only a second-choice antibiotic in pregnant women and children.
5	British Infection Association	Guideline	2	Section 1.1.5	'If a urine sample has been sent for culture' – need to state when a urine sample should be sent for culture.	Thank you for your comment. The remit of this guidance is the management of common infections not diagnosis, therefore further detail on when urine samples should be sent for culture is out of scope. Please note that this part of the recommendation refers to cases when samples have been sent during diagnosis according to usual best practice.
6	British Infection Association	Guideline	7	Table 2	The choices recommended are not in line with the Public Health England guidance that trimethoprim can be used as second line even in the first trimester with folate supplementation unless on a folate antagonist or known to be folate deficient. NICE and PHE guidance need to be consistent with each other to reduce confusion amongst prescribers and also those formulating local/regional policies.	Thank you for your comment. NICE are aware of the important role played by Public Health England guidance on the treatment of UTI. We have worked closely with Public Health England to produce this guideline and the NICE antimicrobial prescribing guidelines will replace the PHE guidance as they are published. The committee agreed not to recommend trimethoprim during pregnancy because it is contraindicated in pregnancy. Trimethoprim is a folate antagonist and there is a teratogenic risk in the

						first trimester. This recommendation is in line with the safety warning in the BNF and the summary of product characteristics. Further wording has been added to the rationale 'However, the committee acknowledged that trimethoprim is sometimes used in pregnancy when given with folic acid 5 mg daily in the first trimester (NICE clinical knowledge summary on UTI (lower) – women).'
7	British Infection Association	Guideline	8	Table 3	It is unclear why the choices and order of choice given for male patients are different to that for non-pregnant female patients. They should be the same.	Thank you for your comment. The committee has discussed your comment and made no changes to the recommendation. As outlined in the rationale, trimethoprim or nitrofurantoin are recommended. The committee agreed based on experience that trimethoprim generally has a lower risk of resistance in men than women, and can reach therapeutic prostate levels. Nitrofurantoin is not recommended for men with suspected prostate involvement because it is unlikely to reach therapeutic levels in the prostate.
8	Scottish Antimicrobial Prescribing Group	Visual summary	General	General	Signs and symptoms of lower UTI would be helpful. This should also include differential diagnosis in particular STI when there is vaginal discharge.	Thank you for your comment. The remit of this guidance is the management of common infections not diagnosis. Providing further details on diagnostic signs and symptoms in the guideline is out of scope, but further background information on signs and symptoms is given in the evidence review.

9	Scottish Antimicrobial Prescribing Group	Visual summary	General	General	Would be helpful to indicate when immediate antibiotics should be used rather than delayed i.e. based on symptom severity and duration of symptoms.	Thank you for your comment. As outlined in the rationale, either a back-up antibiotic prescription or an immediate antibiotic prescription can be prescribed for non-pregnant women with a lower UTI. Decisions should be individualised, taking account of the severity of symptoms, the risk of developing complications or having treatment failure. Further wording has been added to the recommendation that the evidence for back-up prescriptions is only in non-pregnant women with a lower UTI, where immediate antibiotic treatment was not necessary. Further wording has been added to the rationale that women included in the study had a mean age of 39 to 45 years and had moderate symptoms on average.
10	Scottish Antimicrobial Prescribing Group	Visual summary	General	General	Provide guidance on when backup prescription should be used – ie mild UTI or few symptoms. A back up prescription should only be considered where symptoms are mild or few (2 or less) I think back up comes under the general consideration of safety netting and should not be a direct step in the flow chart. We would like to encourage delayed prescribing in the small amount of patients where there is diagnostic uncertainty and where there is likely to be direct need to have the prescription should they deteriorate. At present it seems over emphasized in the guidance rather than an option in certain circumstances.	Thank you for your comment. As outlined in the rationale, either a back-up antibiotic prescription or an immediate antibiotic prescription can be prescribed for non-pregnant women with a lower UTI. Decisions should be individualised, taking account of the severity of symptoms, the risk of developing complications or having treatment failure. Further wording has been added to the recommendation that the evidence for back-up prescriptions is only in non-pregnant women with a lower UTI, where immediate antibiotic treatment was not necessary. Further wording has been added to the rationale that women included in the study had a

						mean age of 39 to 45 years and had moderate symptoms on average.
11	Scottish Antimicrobial Prescribing Group	Visual summary	General	General	It talks about reviewing the antibiotics once sensitivities are available but makes no mention of needing to check the patient is still symptomatic at this point. As lower UTI is self-limiting we wouldn't want people reacting to the results rather than the patient.	Thank you for your comment. The committee refer to the visual summary which states: 'change antibiotic for children and young people, men and non-pregnant women if bacteria resistant and symptoms not improving.'
12	Scottish Antimicrobial Prescribing Group	Visual summary	General	General	No mention of role of urinalysis in < 65s or the lack of need in >65s. No mention in general of how to manage older adults. No cross linking with PHE algorithms that are also out for consult.	Thank you for your comment. The remit of this guidance is the management of common infections not diagnosis, therefore further details on the role of urinalysis is out of scope. Please note older women are within the non-pregnant women population. The rationale states based on evidence, experience and resistance data, the committee agreed that a 3-day course of all the recommended antibiotics (apart from fosfomycin where a single dose is given) was sufficient to treat lower UTI in non-pregnant women of any age, with no longer duration of treatment required for older women.
13	Scottish Antimicrobial Prescribing Group	Visual summary	General	General	Non pregnant women with multiple or severe symptoms should be offered an antibiotic – it would be useful to stratify the different patient groups and also consider the role of dipstick testing in lower UTI in non-pregnant women as per SAPG & SIGN algorithms.	Thank you for your comment. The remit of this guidance is the management of common infections not diagnosis, therefore further details on the role of dipstick testing is out of scope. As outlined in the rationale, either a back-up antibiotic prescription or an immediate antibiotic prescription can

						be prescribed for non-pregnant women with a lower UTI, with decisions individualised, taking account of the severity of symptoms, the risk of developing complications or having treatment failure.
14	Scottish Antimicrobial Prescribing Group	Visual summary	General	General	Add information about safety netting if the patient develops signs of upper UTI / pyelonephritis.	Thank you for your comment. The committee refer to the table footnotes and rationale section on choice of antibiotic, which state 'If there are symptoms of pyelonephritis, or the person has a complicated UTI (associated with a structural or functional abnormality, or underlying disease, which increases the risk of a more serious outcome or treatment failure), see the recommendations on choice of antibiotic in the NICE guideline on acute pyelonephritis.' And also the recommendation on reassessment which states 'Reassess at any time if symptoms worsen rapidly or significantly..., taking account of: ..any symptoms or signs suggesting a more serious illness or condition, such as pyelonephritis.
15	Scottish Antimicrobial Prescribing Group	Visual summary	General	General	In antibiotics for pregnant women I assume note 4 refers to use of nitrofurantoin but there is no 4 (superscript) in the table.	Thank you for your comment. We have amended the relevant table.
16	Scottish Antimicrobial Prescribing Group	Visual summary	General	General	"change antibiotic for pregnant women if bacteria resistant • change antibiotic for children and young people, men and non-pregnant women if bacteria resistant and symptoms not improving" All antibiotic courses which are resistant should be changed to a sensitive agent for all population groups. The recommendation is to change antibiotics in pregnant women if the bacteria are resistant but not in men,	Thank you for your comment. The committee discussed the comment and made no changes to the recommendation. However more detail on the reason for the recommendation was added to the rationale. The committee agreed that for children and young people, men and non-pregnant women, it is

					children or young people if their symptoms are improving. This is poor stewardship and the antibiotic should either be stopped or changed depending on the condition of the patient.	appropriate to only change antibiotics according to susceptibility results if symptoms are not already improving. Often, susceptibility results may not be back for some days (when short courses of antibiotics may be completed), and because of differences between the in vitro and in vivo effectiveness of antibiotics, susceptibility results may not always be accurate. For some populations, where symptoms of the UTI are already improving, an additional course of antibiotics may be unnecessary treatment.
17	Scottish Antimicrobial Prescribing Group	Guideline	General	General	Would be useful to have signs & symptoms of lower UTI Appreciate this guideline is about antibiotic prescribing rather than diagnosis of UTI but would be helpful to have some mention of dipstick testing to highlight when it should and should not be used.	Thank you for your comment. The remit of this guidance is the management of common infections not diagnosis. Providing further details on diagnostic signs and symptoms in the guideline is out of scope, but further background information on signs and symptoms is given in the evidence review.
18	Scottish Antimicrobial Prescribing Group	Guideline	General	General	Self-care with ibuprofen – note recent study in PLOS Medicine by Vik et all showing higher rates of pyelonephritis with ibuprofen compared to pivmecillinam.	Thank you for your comment. The committee refer to the 'committee discussion on self-care' section, which states 'The committee agreed, based on the evidence and their experience, that it was also reasonable to consider ibuprofen for managing pain in adults, young people and children with lower UTI if this was preferred and suitable, taking account of safety concerns with NSAIDs, for example renal impairment.' Please note that NICE recommends analgesics for the management of pain within the self-

						care options. Analgesics are not recommended instead of antibiotics. The study by Vik et al. 2018 was published after the search cut-off date for this guideline and was therefore not included. NICE has reviewed this study following your comment, and as antibiotic treatment is recommended as well as ibuprofen (which is recommended for the self-care management of pain), the conclusions from this study that pivmecillinam is more effective than ibuprofen are the same conclusions which had already been considered by the committee. Therefore it would not impact the current recommendations. For this reason, the study by Vik et al. 2018 has not been included in the evidence review.
19	Scottish Antimicrobial Prescribing Group	Guideline	General	General	Course length of nitrofurantoin – note that meta-analysis by Huttner JAC 2015 not included and not identified in the search. This suggests that courses longer than 3 days are superior and given that nitrofurantoin is being recommended first line should this study be included.	Thank you for your comment. We identified Huttner et al. 2015 in the literature search. However, we deprioritised this analysis during our prioritisation process (see our interim process guide for more information). This was because higher quality systematic reviews (which only included RCTs, included more outcomes and reported more comprehensive analysis) covered the same comparisons and some of the same data that was covered by Huttner et al. 2015, namely nitrofurantoin versus placebo and nitrofurantoin versus other antibiotics. Falagas et al 2009 was a higher quality systematic review covering

						antibiotics compared with placebo, including nitrofurantoin for 3 days versus placebo (including data from Christiaens et al, 2002 which is included in Huttner et al. 2015). Falagas et al 2009 found that antibiotics were significantly better than placebo for clinical cure of lower UTI. While the individual analysis of 3 day nitrofurantoin versus placebo was not statistically significantly different for clinical cure, 3 day nitrofurantoin was significantly better than placebo for microbiological success. Zalmanavoci-Trestioreanu et al. 2010 was a higher quality systematic review, covering antibiotics compared with other antibiotics, including nitrofurantoin for 3 days compared with 3 days co-trimoxazole. Zalmanovoci-Trestioreanu et al. 2010 showed overall that there is no difference in efficacy between different antibiotics for lower UTI (including data from Hooton et al. 1995 which is included in Huttner et al. 2015). The data included on 3 day nitrofurantoin compared with 3 day co-trimoxazole does show borderline significant benefit of 3 day co-trimoxazole for short term bacteriological cure, but there is no significant difference for long term bacteriological cure. No evidence was identified specifically on 3 day nitrofurantoin compared with longer courses of nitrofurantoin. A systematic review

						(Milo et al. 2005) was prioritised which found no significant difference between 3 day courses and 5 to 10 day courses of antibiotics. Based on this evidence, the lack of direct evidence and their experience of the use of 3 day courses of nitrofurantoin in practice, the committee were able to extrapolate the data from other antibiotics to include a recommendation for 3 day courses of nitrofurantoin.
20	Scottish Antimicrobial Prescribing Group	Guideline	General	General	Needs to be more reference throughout about the CDI risk with cefalexin.	Thank you for your comment. The committee discussed, as outlined in the rationale, that, if an antibiotic is needed to treat an infection that is not life threatening, a narrow-spectrum antibiotic should generally be first choice. Indiscriminate use of broad-spectrum antibiotics creates a selective advantage for bacteria resistant even to these 'last-line' broad-spectrum agents, and also kills normal commensal flora leaving people susceptible to antibiotic-resistant harmful bacteria such as Clostridium difficile. For infections that are not life threatening, broad-spectrum antibiotics need to be reserved for second-choice treatment when narrow-spectrum antibiotics are ineffective. Cefalexin is only a second-choice antibiotic in pregnant women and children.
21	Scottish Antimicrobial Prescribing Group	Guideline	General	General	Each guideline refers to "Allergic reactions to penicillins occur in 1-10% of people and anaphylactic reactions occur in less than 0.05%. People with a history of atopic allergy (for example, asthma, eczema and hay fever) are at a higher risk of anaphylactic reactions to penicillins"	Thank you for your comment. The information on penicillin allergy has been updated to include information from the NICE guideline Drug allergy: diagnosis and management.

					This is at odds with the British Society of Allergy and Clinical Immunology (BSACI) guidelines (published in Clinical & Experimental Allergy 45;300-327). They state "The prevalence of penicillin hypersensitivity in the general population is unknown as there are no prospective studies evaluation sensitisation rates during treatment" "Atopy does not predispose to the development of allergic reactions to penicillin, but asthma can be a risk factor for life threatening reactions"	
22	Scottish Antimicrobial Prescribing Group	Guideline	General	General	Consider consistent reference to NEWS or a validated early warning score in the visual guidelines when assessing patients presenting with acute infection.	Thank you for your comment. The remit of this guidance is the management of common infections not diagnosis. Therefore, NEWS or other validated early warning scores for identifying acutely ill patients - including those with sepsis – are not referred to but the NICE guideline on sepsis is.
23	Scottish Antimicrobial Prescribing Group	Guideline	2-3		Poor choice of wording. Suggests only changing abx in resistant organisms only if no sign of improvement. Reference to only change antibiotics if symptoms are not improving – so don't change or stop antibiotics if the patient is improving, even if the MSSU shows resistance? (exception of pregnancy). This is contradicted in P18.	Thank you for your comment. The committee discussed the comment and made no changes to the recommendation. However more detail on the reason for the recommendation was added to the rationale. The committee agreed that for children and young people, men and non-pregnant women, it is appropriate to only change antibiotics according to susceptibility results if symptoms are not already improving. Often, susceptibility results may not be back for some days (when short courses may be completed), and because of differences between the in vitro and in vivo effectiveness of antibiotics, susceptibility results may not always be accurate. For some populations, where symptoms of the

						UTI are already improving, an additional course of antibiotics may be unnecessary treatment.
24	Scottish Antimicrobial Prescribing Group	Guideline	7		Table 1: Fosfomycin – dose repeated in treatment of male UTI Should fosfomycin be included as second choice? Not in line with PHE guidance. Dosing schedule is a single dose for women only, needs repeat dose for men. Fosfomycin is a really useful agent for ESBL so consider with-holding it as a treatment option unless it is the only oral option available.	Thank you for your comment. NICE are aware of the important role played by Public Health England and guidance on the treatment of lower UTI. We have worked closely with Public Health England to produce this guideline and the NICE antimicrobial prescribing guidelines will replace the PHE guidance as they are published. Based on evidence the committee recommended fosfomycin in non-pregnant women only. We did not identify evidence for men regarding use of fosfomycin, and fosfomycin is not recommended in men. The committee agree that fosfomycin should be a second-choice in non-pregnant women, not a first-choice, to reserve its use, for extended-spectrum beta-lactamases.
25	Scottish Antimicrobial Prescribing Group	Guideline	7		Table 2: Nitrofurantoin should not be used in 3rd trimester. Although this is referenced in the small print it would be safer to make it explicit in the text.	Thank you for your comment. The committee discussed the comment and added (avoid at term) to nitrofurantoin in the antibiotic table, in addition to the footnote which says 'Avoid at term in pregnancy; may produce neonatal haemolysis (BNF, June 2018)'
26	Scottish Antimicrobial Prescribing Group	Guideline	8		Antibiotics for men – the statement about second choice treatment "consider alternative diagnoses and follow recommendations in the NICE guideline on acute pyelonephritis or acute prostatitis"…is equally applicable before commencing antibiotic treatment.	Thank you for your comment. The committee agree that alternative diagnoses should always be considered in line with the recommendation, 'Reassess if symptoms worsen rapidly or significantly at any time, or do not

						start to improve within 48 hours of taking the antibiotic, taking account of: other possible diagnoses, any symptoms or signs suggesting a more serious illness or condition, such as pyelonephritis, previous antibiotic use, which may have led to resistant bacteria.'
27	Scottish Antimicrobial Prescribing Group	Guideline	9		Trimethoprim liquid is currently difficult to obtain, and it is unclear when this situation will resolve. Second choice antibiotics should be based on sensitivities where possible.	Thank you for your comment. The committee acknowledged the concern around availability of trimethoprim liquid and several antibiotics are always recommended to cover these situations. Susceptibility results are not always available at the time a second choice antibiotic is chosen in lower UTI, but the committee agreed that these would be used in the decision if these were available. The footnote says, 'Check any previous urine culture and susceptibility results and antibiotic prescribing and choose antibiotics accordingly.' The committee made no changes to the recommendation.
28	Scottish Antimicrobial Prescribing Group	Guideline	12		Quantify hydration – full hydration is not meaningful. Over hydration can reduce the bladder contact time of the antibiotics so adequate, rather than over-hydration is important (using urine colour as a sensible guide). Suggest inclusion of hydration urine chart.	Thank you for your comment. The wording has been changed to 'Advise people with lower UTI about drinking enough fluids to avoid dehydration'.
29	Scottish Antimicrobial Prescribing Group	Guideline	19		All antibiotic courses which are resistant should be changed to a sensitive agent for all population groups irrespective of improvement.	Thank you for your comment. The committee discussed the comment and made no changes to the recommendation. However more detail on the reason for the recommendation was added to the rationale. The committee agreed that for children and young people, men

						and non-pregnant women, it is appropriate to only change antibiotics according to susceptibility results if symptoms are not already improving. Often, susceptibility results may not be back for some days (when short courses may be completed), and because of differences between the in vitro and in vivo effectiveness of antibiotics, susceptibility results may not always be accurate. For some populations, where symptoms of the UTI are already improving, an additional course of antibiotics may be unnecessary treatment.
30	Scottish Antimicrobial Prescribing Group	Guideline	28		Should a test of cure be recommended where asymptomatic bacteriuria or UTI has been diagnosed in pregnant women to avoid any ongoing risk?	Thank you for your comment. The remit of this guidance is the management of common infections not diagnosis, and the diagnosis of asymptomatic bacteriuria or test of cure is out of scope.
31	Chronic Urinary Tract Infection Campaign	Evidence review	7	9-17	The Little et al study 2009 only refers to women with moderate to severe symptoms does the second UK study also refer to the same patient group? Women with more severe symptoms or chronic UTI are likely to have different outcomes.	Thank you for your comment. The study by Little et al. 2009 has been cited as background information. No further evidence has been included on severe UTI in the background section as the population described by Little et al. is believed to include the majority of people with UTI relevant to this guideline. However, any evidence identified that describes severe UTI has been included in the evidence review where available. The 'second UK study' has now been removed from the evidence review.
32	Chronic Urinary Tract Infection Campaign	Evidence review	13-19	Included studies - General comment	The included studies varied in their duration of patient follow up, some only lasting for 28 days, 6 or 7 weeks, while others were not reported, only the longest study lasted for a significant period, 968 days. To evaluate the	Thank you for your comment. The evidence review reports outcomes at various durations of follow-up as specified in the included studies. The

					effectiveness of length of antibiotic courses patients need to be assessed for longer than 28 days or 7 weeks to monitor a recurrence of infection. The duration of the study time needs to be assessed when evaluating and reporting the evidence, evidence from studies with a short duration or unrecorded duration need to be reported with caution. A relapse of infection can occur 2, 6 or 9 months after initial antibiotic treatment. There is a paucity of good quality longitudinal research evaluating the effectiveness of 3 day regimens of antibiotics. This should be noted in the evidence review and the guidelines.	committee agree that a relapse of infection can occur several months after treatment, but this long-term follow up is often not reported in trials. Detail on the duration of follow-up for all outcomes is given in the GRADE tables in appendix H of the evidence review. A systematic review (Milo et al. 2005) was included comparing 3 day antibiotics to longer courses. The length of follow up was considered by the committee, and noted in the summary of evidence. Based on the evidence available and their experience, the committee were able to make recommendations on 3 day courses of antibiotics.
33	Chronic Urinary Tract Infection Campaign	Evidence review	General		Also, given that 3 day courses of antibiotics have a failure rate of 25-35% and 25%-50% (NICE) as do 14 day courses, no acknowledgment or advice is given for those who fail treatment – some of these patients will fail treatment repeatedly – how should they be treated in primary care? 6. Foxman B. The epidemiology of urinary tract infection. Nature reviews Urology. 2010;7. doi: 10.1038/nrurol.2010.190. 7. Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2011;52(5):e103-20. doi: 10.1093/cid/ciq257. PubMed PMID: 21292654.	Thank you for your comment. For people who fail first-line antibiotic treatment, second-line antibiotics (to be used when there is no improvement in lower UTI symptoms on first choice taken for at least 48 hours, or when first choice not suitable) are given in the table. There is also a recommendation to reassess symptoms that worsen rapidly or significantly at any time, or do not start to improve within 48 hours of taking the antibiotic, taking account of: other possible diagnoses; any symptoms or signs suggesting a more serious illness or condition, such as pyelonephritis; previous antibiotic use, which may have led to resistant bacteria. And to send a urine sample for culture and susceptibility testing if

					8. Laupland KB, Ross T, Pitout JD, Church DL, Gregson DB. Community-onset urinary tract infections: a population-based assessment. Infection. 2007;35(3):150-3. Epub 2007/06/15. doi: 10.1007/s15010-007-6180-2. PubMed PMID: 17565455. 9. Pickard R, Chadwick T, Oluboyede Y, Brennand C, von Wilamowitz-Moellendorff A, McClurg D, et al. Continuous low-dose antibiotic prophylaxis to prevent urinary tract infection in adults who perform clean intermittent self-catheterisation: the AnTIC RCT. Health technology assessment (Winchester, England). 2018;22(24):1-102. Epub 2018/05/17. doi: 10.3310/hta22240. PubMed PMID: 29766842. 10. Jackson D, Higgins E, Bracken J, Yandell PM, Shull B, Foster RT, Sr. Antibiotic prophylaxis for urinary tract infection after midurethral sling: a randomized controlled trial. Female pelvic medicine & reconstructive surgery. 2013;19(3):137-41. Epub 2013/04/25. doi: 10.1097/SPV.0b013e318285ba53. PubMed PMID: 23611930. 11. Zhong YH, Fang Y, Zhou JZ, Tang Y, Gong SM, Ding XQ. Effectiveness and safety of patient initiated single-dose versus continuous low-dose antibiotic prophylaxis for recurrent urinary tract infections in postmenopausal women: a randomized controlled study. The Journal of international medical research. 2011;39(6):2335-43. Epub 2012/02/01. doi: 10.1177/147323001103900633. PubMed PMID: 22289552. 12. Ahmed H, Davies F, Francis N, Farewell D, Butler C, Paranjothy S. Long-term antibiotics for prevention of recurrent urinary tract infection in older adults: systematic review and meta-analysis of randomised trials. BMJ open. 2017;7(5):e015233. Epub 2017/05/31. doi: 10.1136/bmjopen-2016-015233. PubMed PMID: 28554926; PubMed Central PMCID: PMCPMC5729980. 13. Muller AE, Verhaegh EM, Harbarth S, Mouton JW, Huttner A. Nitrofurantoin's efficacy and safety as	this has not already been done and review treatment when results are available. The NICE antimicrobial prescribing guideline on recurrent UTI also recommends to: - Seek specialist advice for women aged 16 years and over with recurrent lower UTI if the underlying cause is unknown or requires further investigation - Refer men aged 16 years and over (taking an individualised approach that takes account of factors such as multimorbidity) for specialist urology assessment and investigations because there may be underlying anatomical or functional abnormalities: - Refer pregnant women (aged 16 years and over) to an obstetrician for specialist assessment and investigations if recurrent UTI is diagnosed during pregnancy. - Refer children and young people under 16 years with recurrent UTI to a paediatric specialist for assessment and investigations, in line with the NICE guideline on urinary tract infection in under 16s: diagnosis and management. In response to the articles submitted:

					prophylaxis for urinary tract infections: a systematic review of the literature and meta-analysis of controlled trials. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases. 2017;23(6):355-62. Epub 2016/08/21. doi: 10.1016/j.cmi.2016.08.003. PubMed PMID: 27542332. 14. Lee BS, Bhuta T, Simpson JM, Craig JC. Methenamine hippurate for preventing urinary tract infections. The Cochrane database of systematic reviews. 2012;10:Cd003265. Epub 2012/10/19. doi: 10.1002/14651858.CD003265.pub3. PubMed PMID: 23076896. 15. Schilling JD, Lorenz RG, Hultgren SJ. Effect of trimethoprim-sulfamethoxazole on recurrent bacteriuria and bacterial persistence in mice infected with uropathogenic Escherichia coli. Infect Immun. 2002;70(12):7042-9. Epub 2002/11/20. PubMed PMID: 12438384; PubMed Central PMCID: PMCPMC132990. 16. Huttner A, Kowalczyk A, Turjeman A, Babich T, Brossier C, Eliakim-Raz N, et al. Effect of 5-Day Nitrofurantoin vs Single-Dose Fosfomycin on Clinical Resolution of Uncomplicated Lower Urinary Tract Infection in Women: A Randomized Clinical Trial. Jama. 2018;319(17):1781-9. Epub 2018/05/02. doi: 10.1001/jama.2018.3627. PubMed PMID: 29710295.	• Foxman et al. 2010 does not meet the inclusion criteria on study type (epidemiology study) • Gupta et al. 2011 does not meet the inclusion criteria on study type (other guidance) • Laupland et al. 2007 does not meet the inclusion criteria based on study type (observational) • Pickard et al. 2018 does not meet the inclusion criteria on population (this guideline does not include people with catheters; catheter associated UTI is covered by another antimicrobial prescribing guideline, where the AnTIC trial has been included) • Jackson et al. 2013 does not meet the inclusion criteria based on intervention (prophylaxis not covered by this guideline) • Zhong et al. 2011 does not meet the inclusion criteria based on population (recurrent UTI is covered by another antimicrobial prescribing guideline, where Zhong et al. 2011 has been included) • Ahmed et al. 2017 does not meet the inclusion criteria on population (people with recurrent UTI, not acute lower UTI; this study was published following the search for the associated antimicrobial prescribing guideline on recurrent UTI, therefore was not identified. As this study draws the same conclusions on the effectiveness

						of D-mannose, oestrogen and probiotics compared with the same antibiotics, in the same population of postmenopausal women as the evidence previously considered by the committee, this study will not be included in the recurrent UTI guideline) • Muller et al. 2017 does not meet the inclusion criteria on population (recurrent UTI covered by another antimicrobial prescribing guideline, where Muller et al. 2017 is included) • Lee et al. 2017 does not meet the inclusion criteria on population (in either this guideline or the recurrent UTI guideline) • Schilling et al. 2002 does not meet the inclusion criteria based on date • Huttner et al. 2018 was published following the search cut-off date for this guideline and therefore was not identified. This study has been considered by NICE and has not been included as the conclusion that nitrofurantoin is more effective than fosfomycin would not impact the recommendation to offer nitrofurantoin as first line treatment for lower UTI.
34	Chronic Urinary Tract Infection Campaign	Evidence review	Page 28	Line 27-30	Milo et al 2005, You state there was no significant difference between antibiotics given for 3 days compared to antibiotics given for 5 to 10 days.	Thank you for your comment. The committee discussed your comment and made no changes to the recommendation. The guideline recommends 3-day courses of

			Page 28 Page 29	Line 45-48 Line 9-12	However this statement is contradicted later in the reporting of the Milo data when it is reported that 3 day quinolone antibiotic was associated with significantly more women experiencing short term bacteriological failure compared with 5 to 10 days. And again when comparing co-trimoxazole 3 day treatment was associated with significantly more short term bacteriological failure compared to longer treatment duration.	antibiotics for non-pregnant women based on the available evidence, that overall, 3-day courses of any antibiotic were not significantly different to longer courses (5 to 10 days) of any antibiotic in preventing short-term or long-term symptomatic failure, short-term bacteriological failure, or the development of pyelonephritis. The guideline now has additional wording added, 'However, long-term bacteriological failure (at 4 to 10 weeks) was significantly higher with 3 day courses of any antibiotic compared with longer courses of any antibiotic (low quality evidence).' The rationale has also been updated to say 'Based on evidence, the committee agreed that a 3-day course of antibiotics was as effective as a 5- to 10-day course of antibiotics in non-pregnant women with lower UTI, and resulted in significantly fewer adverse events. The committee agreed that a longer course may increase the likelihood of complete bacteriological eradication, which may be important for some women (for example, women with repeated lower UTIs). Please note that quinolones or co-trimoxazole are not included in the antibiotic choice table for these patient groups.
35	Chronic Urinary Tract Infection Campaign	Evidence review	Page 35 Page 36	Line 1-43 Line 1-40	Children and UTI – This evidence is based on 2 systematic reviews, with a total of less than 2,000 children across both reviews. In addition, the Michael et al study excludes children with recurrent UTI – excluding a significant proportion of children who suffer from UTI	Thank you for your comment. The committee discussed your comment and made no changes to the recommendation. The committee were aware of the limitations of the

					and seen in primary care. I would urge caution making recommendations for 3 day courses of antibiotics across the paediatric population based on evidence from only 2 reviews, with a small population size, excluding a significant portion of children who suffer from (recurrent) UTIs. More evidence, especially, is needed before advice can be given for treating an acute UTI in a child who suffers from recurrent infection.	evidence, including sample size and the exclusion of children with recurrent UTI in Michael et al., however were also aware that in the second systematic review by Fitzgerald et al. approximately 50% of children had recurrent UTI. Based on the process for NICE antimicrobial prescribing guidelines, subgroup analysis of children with recurrent UTI has not been performed. However, based on the evidence available of a mixed population, the consideration of antimicrobial stewardship and their experience, the committee were able to make a recommendation for 3 day antibiotic courses. This is also in line with the NICE guideline on urinary tract infection in under 16s: diagnosis and management. The NICE antimicrobial prescribing guideline on recurrent UTI also recommends to: Refer children and young people under 16 years with recurrent UTI to a paediatric specialist for assessment and investigations, in line with the NICE guideline on urinary tract infection in under 16s: diagnosis and management.
36	Chronic Urinary Tract Infection Campaign	Draft guideline	2	1.1.1 Line2-4	We have concern regarding the statement defining infection as usually being caused by bacteria from the gastrointestinal tract implying that the normal urinary tract is “sterile”. There is evidence that there are now strong signals of the existence of a ‘‘core’’ urinary microbiome for the human urinary tract, particularly emerging with ageing. This has implications not just for acute infection but for recurrence of infection with the same pathogens.	Thank you for your comment. The committee discussed your comment and made no changes to the recommendation. The recommendation explains that lower UTI is usually caused by bacteria from the gastrointestinal tract entering the urethra and travelling up to the bladder. It is appreciated that there

					We would ask that the guidelines reflect that infection causation is not solely by gastrointestinal pathogens. A case control study examining the bladder microbiome Natasha Curtiss, Aswini Balachandran, Louise Krska, Claire Peppiatt-Wildman, Scott Wildman, Jonathan Ducketta 2017 Does the Urinary Microbiome Play a Role in Urgency Urinary Incontinence and Its Severity Lisa Karstens , Mark Asquith, Sean Davin, Patrick Stauffer, Damien Fair W.Thomas Gregory, JamesT.Rosenbaum, Shannon K.McWeeney and Rahel Nardos 2016 Gram-Positive Uropathogens, Polymicrobial Urinary Tract Infection, and the Emerging Microbiota of the Urinary Tract: Kimberly A. Kline and Amanda L. Lewis 2016 Microbial metagenome of urinary tract infection Ahmed Moustafa, Harinder Singh, Weizhong Li, Kelvin J. Moncera, Manolito G. Torralba, Yanbao Yu, Oriol Manuel, William Biggs, J. Craig Venter, Karen E. Nelson, Rembert Pieper, Amalio Telenti 2017 The Urinary Microbiome and Its Contribution to LUTS: Marcus J. Drake, Nicola Morris, Apostolos Apostolidis, Mohammad S. Rahnama and Julian R. Marchesi 2015	may be other causes of lower UTI, however based on their experience, the committee included the most common cause to include in the recommendation, which cannot include all causes. In regard to the articles submitted: • Curtiss et al. 2017 does not meet the inclusion criteria based on study type (observational) • Karstens et al. 2016 does not meet the inclusion criteria based on study type (observational) • Kline and Lewis 2016 does not meet the inclusion criteria based on study type (narrative review) • Moustafa et al. 2017 does not meet the inclusion criteria based on study type (observational) • Drake et al. 2015 does not meet the inclusion criteria based on study type (narrative review)
37	Chronic Urinary Tract Infection Campaign	Draft guideline	2	1.1.3 Line 8-19	Delayed prescription is very different to refusing treatment - and this is important. Of the utmost significance here is the guide to consider severity of symptoms - studies of delayed prescription self-select those patients willing to consider this and are likely therefore only to be generalisable to those who have less severe symptoms. There is no mention here of the relevance of dipstick testing. We suggest the guidance here is important as we hear of GPs who refuse antibiotics on the basis of a	Thank you for your comment. Please note, the remit of this guidance is the management of common infections not diagnosis, therefore more detail on dipstick testing is out of scope. As outlined in the rationale, either a back-up antibiotic prescription or an immediate antibiotic prescription can be prescribed for non-pregnant women with a lower UTI, with

					negative dipstick test even though these are recognised to have poor accuracy especially if the urine sample is very dilute.	decisions individualised, taking account of the severity of symptoms, the risk of developing complications or having treatment failure. Further wording has been added to the recommendation that the evidence for back-up prescriptions is only in non-pregnant women with a lower UTI, where immediate antibiotic treatment was not necessary. Further wording has also been added to the rationale that women included in the study had a mean age of 39 to 45 years and had moderate symptoms on average.
38	Chronic Urinary Tract Infection Campaign	Draft guideline	General		No advice given in the guidelines for treating adults and children with a UTI, but with negative dipstick and culture results. Given the research shows a failure rate of up to 50% for these tests GPs need to be given advice on treating these patients. 1. Gill K, Kang R, Sathiananthamoorthy S, Khasriya R, Malone-Lee J. A blinded observational cohort study of the microbiological ecology associated with pyuria and overactive bladder symptoms. Int Urogynecol J. 2018. Epub 2018/02/20. doi: 10.1007/s00192-018-3558-x. PubMed PMID: 29455238. 2. Price et al. The Clinical Urine Culture: Enhanced Techniques Improve Detection of Clinically Relevant Microorganisms. Journal of Clinical Microbiology. May 2016 (54) 5 3. Khasriya and Malone-Lee. The Inadequacy of Urinary Dipstick and Microscopy as Surrogate Markers of Urinary Tract Infection in Urological Outpatients with Lower Urinary Tract Symptoms Without Acute Frequency and Dysuria. Journal of Urololgy. 2010 183(5): 1843–1847 4. Heytens et al. Women With Symptoms of a Urinary Tract Infection but a Negative Urine Culture: PCR-based	Thank you for your comment. Please note, the remit of this guidance is the management of common infections not diagnosis. This guidance focuses on the treatment of lower UTI once a diagnosis has been made, and more detail on dipstick testing and urine culture is out of scope. In reference to the articles submitted: • Gill et al. 2018 was published after the search was conducted for this guideline, however it would not have been included on study type (observational study) • Price et al. 2016 does not meet the inclusion criteria on intervention (diagnosis) • Khasriya and Malone-Lee 2010 does not meet the inclusion criteria on intervention (diagnosis)

					quantification of Escherichia coli suggests infection in most cases. Clinical Microbiology and Infection. 2017 5. Swerkersson et al. Urinary Tract Infection in Infants: The significance of low bacterial count. Paediatric Nephrology 2016. 31:239–245 6.. Stamm et al. Diagnosis of Coliform Infection in Acutely Dysuric Women. New England Journal of Medicine. 1982 307(8): 463-468	• Heytens et al. 2017 does not meet the inclusion criteria on intervention (diagnosis) • Swerkersson et al. 2016 does not meet the inclusion criteria on study type (observational) • Stamm et al. 1982 does not meet the inclusion criteria based on date
39	Chronic Urinary Tract Infection Campaign	Draft guideline	2	1.1.3 Line 7-19	This recommendation incorporates GPs considering previous urine culture and susceptibility. It makes an assumption that culture results are accurate. In all patients with acute symptoms, current medical practice involves initial urinary dipstick testing for leucocyte esterase and nitrites. If acute symptoms are typical, a mid-stream, clean catch urine sample may be sent for culture, despite negative dipstick results. If the symptoms are equivocal (commonly occurring in chronic, non-dysuric LUTS patients) and the initial urinary dipstick is negative, the sample may not be sent for culture at all. Urine culture also has substantial limitations. For largely historical reasons, the gold standard has long been defined as bacterial growth of a single organism at more than 105 CFU/ml, with epithelial cells indicating contamination from the perineum. The 105 CFU/ml threshold was set out by Kass in 1957, and is widely criticized, as his patients' urine samples were collected from only 74 women with acute kidney infections, with bacteria thriving in their urine. Since the late 1950's there have been reports that such a threshold is not sufficiently sensitive to pick up all urinary infections, but the concerns of numerous scholars have been largely ignored by the medical community. In early reports, Stamm and colleagues have demonstrated that the threshold set out by Kass can only pick up 50% of urinary tract infections. They proposed a more sensitive diagnostic criterion of 102 CFU/ml, which has been supported by many other recent studies. It should also be noted that "mixed	Thank you for your comment. The remit of this guidance is the management of common infections not diagnosis, therefore more detail on urine culture is out of scope. In reference to the submitted articles: • Heytens et al. 2017 does not meet the inclusion criteria on intervention (diagnosis) • Drake et al. 2017 does not meet the inclusion criteria on study type (narrative review) • Hilt et al. 2014 does not meet the inclusion criteria on intervention (diagnosis) • Price et al. 2016 does not meet the inclusion criteria on intervention (diagnosis) • Soto 2014 does not meet the inclusion criteria on study type (narrative review) • Khasriya and Malone-Lee 2010 does not meet the inclusion criteria on intervention (diagnosis)

					growth" culture with evidence of epithelial shedding, in the context of symptomatic, pyuric patients, point to a very significant pathological state, and should not be dismissed as "contaminated samples". Further, urinalysis, by dipstick within GP surgery only detects those bacteria which reduce nitrates to nitrites in the urine but several uropathogens do not reduce nitrate to nitrite, and therefore its utility is restricted to Enterobacteriaceae which give a positive test result. This makes the nitrite test considerably less useful. One study notes that dipstick tests were just 56% sensitive to leukocyte esterase and 10% sensitive to nitrites in a study of patients with chronic LUTS without dysuria. Meta-analyses of the use of urinary dipsticks in adults and in children have been reported concluding that dipsticks cannot exclude infection reliably in most clinical settings. There are serious shortcomings affecting the routine diagnostic tests health practitioners rely on to diagnose UTIs, with many health practitioners unaware of their frequent failures to detect or correctly identify pathogenic bacteria. We must also draw the committee's attention to the following noted in the European Association of Urology Guidelines on Urological Infections 2017 from which some of this guidance is drawn: In patients presenting with typical symptoms of an uncomplicated cystitis urine analysis (i.e. urine culture, dip stick testing, etc.) leads only to a minimal increase in diagnostic accuracy. However, if the diagnosis is unclear dipstick analysis can increase the likelihood of a uncomplicated cystitis diagnosis if leukocytes and nitrite are positive, only nitrite or nitrite and blood are positive or leukocytes and blood are positive. Taking a urine culture is recommended in patients with atypical symptoms, as	• Deville et al. 2004 does not meet the inclusion criteria on date • Hurlbut et al. 1991 does not meet the inclusion criteria on date • Gorelick et al. 1999 does not meet the inclusion criteria on date

					well as those who fail to respond to appropriate antimicrobial therapy. In patients presenting with symptoms of uncomplicated cystitis a colony count of 103 cfu/mL of uropathogens confirms microbiologically the diagnosis. Based on these notes and our previous comments, we would draw the committee's attention to the fact that most GPs would not have the knowledge to request a lower CFU count for a patient, particularly if the initial dipstick or urine analysis was unclear or negative. If these recommendations are being made by the EAU then it should be reflected in these guidelines. We thus recommend that signs and symptoms of infection should be equally weighted and GPs not just be guided by dipstick or culture results. Heytens et al. Women with Symptoms of a Urinary Tract Infection but a Negative Urine Culture: PCR-based quantification of Escherichia coli suggests infection in most cases. Clinical Microbiology and Infection. 2017 Drake et al. The Urinary Microbiome and Its Contribution to Lower Urinary Tract Symptoms. Neurology and Urodynamics. 2017 36:850–853 22. Hilt et al. Urine Is Not Sterile: Use of enhanced urine culture techniques to detect resident bacterial flora in the adult female bladder. Journal of Clinical Microbiology. 2014 52(3):871-6 Price et al. The Clinical Urine Culture: Enhanced Techniques Improve Detection of Clinically Relevant Microorganisms. Journal of Clinical Microbiology. May 2016 (54) 5 Soto. Importance of Biofilms in Urinary Tract Infections: New Therapeutic	

					Approaches. Advances in Biology 2014. Article ID 543974 Khasriya and Malone-Lee. The Inadequacy of Urinary Dipstick and Microscopy as Surrogate Markers of Urinary Tract Infection in Urological Outpatients with Lower Urinary Tract Symptoms Without Acute Frequency and Dysuria. Journal of Urololgy. 2010 183(5): 1843–1847 Deville WL, Yzermans JC, van Duijn NP et al: The urine dipstick test useful to rule out infections. A meta-analysis of the accuracy. BMC Urol 2004; 4: 4. Hurlbut TA 3rd and Littenberg B: The diagnostic accuracy of rapid dipstick tests to predict urinary tract infection. Am J Clin Pathol 1991; 96: 582. Gorelick MH and Shaw KN: Screening tests for urinary tract infection in children: a meta-analysis. Pediatrics 1999; 104: e54.	
40	Chronic Urinary Tract Infection Campaign	Draft guideline	2	1.1.4 Line 21-22	We are concerned to see this advice again considering severity of symptoms is imperative. Refusing/delaying treatment and allowing infection to worsen until cultures come through is very high risk and could cause significant clinical worsening of infection and increased risk of serious sequelae. It is also ethically unacceptable if the patient is in significant distress and discomfort. In addition given bacterial replication rates especially in the most common pathogen, e-coli, which is known to reproduce within 20 minutes, the patient could deteriorate significantly within a short duration. The efficacy of immediate versus delayed antibiotic administration on bacterial growth and biofilm production of selected strains of uropathogenic Escherichia coli and Pseudomonas aeruginosa	Thank you for your comment. The committee discussed the comment and this recommendation has been removed. In reference to the submitted articles: • Gandee et al 2015 does not meet the inclusion criteria on study type (in vitro study) • Anderson et al. does not meet the inclusion criteria on date

					Leah Gandee et al Int. Braz j urol. vol.41 no.1 Rio de Janeiro Jan./Feb. 2015 Role of Bacterial Growth Rates in the Epidemiology and Pathogenesis of Urinary Infections in Women J. D. Anderson et al J Clin Microbiol. 1979 Dec; 10(6): 766–771.	
41	Chronic Urinary Tract Infection Campaign	Draft guideline	2	1.1.5 Line 23-29	This guideline fails to address the most common challenge in treating UTI for clinicians - when the patient has clear clinically significant symptoms but the culture comes back with insufficient growth and/or mixed growth and/or as possibly contaminated. This is a significant omission. Guidance for how to treat in this situation must be included in this guideline as it is a common clinical scenario. We suggest that following recent research indicating that most patients with symptoms of a lower UTI do indeed have bacterial infection (For example Heytens et al 2017 Women with symptoms of a urinary tract infection but a negative urine culture: PCR-based quantification of Escherichia coli suggests infection in most cases. Clin Microbial Infect. 2017 39(9):647-652), GPs should treat on the basis of symptoms in the absence of a positive culture as well as taking into account recent research on the clinical significance of signs such as increased epithelial cells in samples as possible indicators of infection, not contamination.	Thank you for your comment. The remit of this guidance is the management of common infections not diagnosis, therefore more detail on what to do when people have UTI symptoms but negative urine culture is out of scope. In reference to the submitted article: • Heytens et al. 2017 does not meet the inclusion criteria on intervention (diagnosis)
42	Chronic Urinary Tract Infection Campaign	Draft guideline	3	1.1.10 Line 22-24	This guideline suddenly does mention dipstick testing for children - again this is recognised to be a very inaccurate test with a high rate of false negatives. The guideline does not state what to do if testing fails to identify infection when there are clear clinical symptoms.	Thank you for your comment. The committee discussed the comment and made no changes to the recommendation. The remit of this guidance is the management of common infections not diagnosis. However, there is a NICE guideline on UTI in children and young people under 16 years. This guideline covers diagnosis in children and young people and is therefore signposted.

43	Chronic Urinary Tract Infection Campaign	Draft guideline	4 5 5 5	1.1.14 Line 17-28 Line 1-2 1.1.15 Line 3-9 1.1.16 Line 10-20	Advice here is given to seek medical help if symptoms worsen rapidly or significantly, do not improve within 48 hours of taking the antibiotic or if the patient becomes systemically very unwell - but no guidance to GP/clinicians re what to do with a patient who does return. Samples taken then are likely to fail to culture due to antibiotic use and patients are often left with no alternative to treat worsening infection. Guidelines must indicate appropriate actions here when samples/cultures are unlikely to offer much help. Guidelines must make mention of the fact that negative culture does not mean there is no infection and offer guidance to GPs for how to treat in this situation - particularly if the patient has very severe symptoms and/or is systemically very unwell and/or is a child under 16.	Thank you for your comment. The committee discussed the comment and made no changes to the recommendation. The remit of this guidance is the management of common infections not diagnosis. At reassessment, the prescriber is advised to consider other possible diagnoses, any symptoms or signs suggesting a more serious illness or condition, such as pyelonephritis and previous antibiotic use, which may have led to resistant bacteria. Sending a urine sample for culture and susceptibility testing if this has not already been done and reviewing treatment when results are available is advised, and second-choice antibiotics are given in the table for treatment failure. Referral to hospital is also recommended for people aged 16 years and over with lower UTI if they have a severe systemic infection, or any of the high risk criteria for severe illness or death from the NICE guideline on sepsis. For children or young people with lower UTI, referral to hospital in line with the NICE guideline on urinary tract infection in under 16s: diagnosis and management is recommended.
44	Chronic Urinary Tract Infection Campaign	Draft guideline	5	1.1.16 Line 10-20	There is significant concern about the usage of further culture following antibiotic treatment as this implies over-reliance on testing rather than the patient symptoms. If the symptoms are equivocal (commonly occurring in chronic, non-dysuric LUTS patients) and the initial urinary dipstick is negative, the sample may not be sent for culture at all.	Thank you for your comment. The remit of this guidance is the management of common infections not diagnosis. At reassessment, sending a urine sample for culture and susceptibility testing if this has not already been done is

					Further low count bacterial growth is not considered and previous use of antibiotics will affect culture results as well as advice given to patients to keep hydrated which will dilute the urine. If the GP considers a retest, guidance should be provided to the patient so that a sample is not over dilute. This is not reflected in the guidelines. Additionally, as previously mentioned, standard culture collection and analysis is unreliable. The assumption of no infection in LUTS patients cannot be made based on negative results on routine or follow up diagnostic testing. Again, equal weighting must be given to patient symptoms. Kunin CM, White LV, Tong HH. A reassessment of the importance of `low-count' bacteriuria in young women with acute urinary symptoms. Ann Intern Med 1993; 119 : 454–460 Arav-Boger B, Leibovici L, Danon YL. Urinary tract infections with low and high colony counts in young women. Spontaneous remission and single-dose vs multiple-day treatment. Arch Intern Med 1994; 154: 300–304	recommended to enable further decisions on antibiotic treatment to be made. The guideline does not offer recommendations around diagnosis. In reference to the submitted articles: • Kunin et al. 1993 does not meet the inclusion criteria based on date • Arav-Boger et al. 1994 does not meet the inclusion criteria based on date
45	Chronic Urinary Tract Infection Campaign	Draft guideline	6	1.3.1 Line 17-22	Recent research suggests ibuprofen is a poor choice and may worsen symptoms. The recent study by Vik et al 2018 recommends that ibuprofen alone is not given as an initial treatment to women with uncomplicated UTI due to the risk of pyelonephritis. Therefore it is imperative women have a back prescription for antibiotics. Questions over ibuprofen use are indicated in the written comments (page 10/29, bullet 3) which note that women who received ibuprofen were significantly more likely to receive additional antibiotic prescription in the 12 months following. Although the authors questioned whether this effect was due to the group having a higher rate of UTI it is also a clinically significant outcome for many women	Thank you for your comment. Please note that NICE recommends analgesics (paracetamol or, if preferred and suitable, ibuprofen) for the management of pain within the self-care options. Analgesics are not recommended instead of antibiotics. The study by Vik et al. 2018 was published after the search cut-off date for this guideline and was therefore not included. NICE has reviewed this study following your comment, and as antibiotic treatment is recommended

					who do suffer repeated UTIs meaning the advice to take ibuprofen is unwise. Ibuprofen versus pivmecillinam for uncomplicated urinary tract infection in women—A double-blind, randomized non-inferiority trial Ingvild Vik et ak Published: May 15, 2018 PLoS Med 15(5): e1002569.	as well as ibuprofen (for the self-care management of pain), the conclusions from this study that pivmecillinam is more effective than ibuprofen are the same conclusions which had already been considered by the committee. Therefore it would not impact the current recommendations. For this reason, the study by Vik et al. 2018 has not been included in the evidence review.
46	Chronic Urinary Tract Infection Campaign	Draft guideline	7	Table 1	These prescription lengths are very short and likely to be the shortest clinically successful prescriptions. The guidelines need to state that for patients with a history of complex or recurring infections longer/repeated courses may be needed. We suggest the advice is for patients to return to GP if symptoms have not resolved within the 3 day course and that courses are extended if necessary until symptoms resolve, indicating that the infection has been eradicated. Failure to fully treat and eradicate infection increases the risk of resistance developing meaning that patients with more stubborn infections MUST receive adequate length prescriptions.	Thank you for your comment. The committee discussed your comment and made no change to the recommendation. This guideline is for the treatment of lower UTI. The tables and rationale state that if people with lower UTI have symptoms of pyelonephritis, or the person has a complicated UTI (associated with a structural or functional abnormality, or underlying disease, which increases the risk of a more serious outcome or treatment failure), the NICE guideline on acute pyelonephritis should be referred to for antibiotic choice. For lower UTI, the guideline recommends 3-day courses of antibiotics for non-pregnant women based on the available evidence, that overall, 3-day courses of any antibiotic were not significantly different to longer courses (5 to 10 days) of any antibiotic in preventing short-term or long-term symptomatic failure, short-term bacteriological

						failure, or the development of pyelonephritis. The guideline now has additional wording added, 'However, long-term bacteriological failure (at 4 to 10 weeks) was significantly higher with 3 day courses of any antibiotic compared with longer courses of any antibiotic (low quality evidence).' The rationale has also been updated to say 'Based on evidence, the committee agreed that a 3-day course of antibiotics was as effective as a 5- to 10-day course of antibiotics in non-pregnant women with lower UTI, and resulted in significantly fewer adverse events. The committee agreed that a longer course may increase the likelihood of complete bacteriological eradication, which may be important for some women (for example, women with repeated lower UTIs). However, it was not possible to analyse data separately for people with repeated lower UTIs. For people who fail first-line antibiotic treatment, second-line antibiotics (to be used when there is no improvement in lower UTI symptoms on first choice taken for at least 48 hours, or when first choice not suitable) are given in the table. There is also a recommendation to reassess symptoms that worsen rapidly or significantly at any time, or do not start to improve within 48 hours of taking the antibiotic, taking account of: other possible diagnoses; any symptoms or signs suggesting a more

						serious illness or condition, such as pyelonephritis; previous antibiotic use, which may have led to resistant bacteria. And to send a urine sample for culture and susceptibility testing if this has not already been done and review treatment when results are available.
47	Chronic Urinary Tract Infection Campaign	Draft guideline	8	Table 4	The same comments (above) apply to prescriptions for children.	Thank you for your comment. The committee discussed your comment and made no change to the recommendation. This guideline is for the treatment of lower UTI. The tables and rationale state that if children or young people with lower UTI have symptoms of pyelonephritis, or the person has a complicated UTI (associated with a structural or functional abnormality, or underlying disease, which increases the risk of a more serious outcome or treatment failure), the NICE guideline on acute pyelonephritis should be referred to for antibiotic choice. For lower UTI, the guideline recommends 3-day courses of antibiotics for children and young people based on the available evidence, that there was no significant difference between short-course (3 to 7 days) and long-course (10 to 14 days) antibiotics in the number of children with persistent bacteriuria or the rate of reinfection or recurrence; and there was no significant difference between short course (2 to 4 days) and long course

						(7 to 14 days) in the number of children with UTIs at the end of treatment, or the rate of recurrence of UTI. Three-day treatment is in line with the NICE guideline on urinary tract infection in under 16s: diagnosis and management. For people who fail first-line antibiotic treatment, second-line antibiotics (to be used when there is no improvement in lower UTI symptoms on first choice taken for at least 48 hours, or when first choice not suitable) are given in the table. There is also a recommendation to reassess symptoms that worsen rapidly or significantly at any time, or do not start to improve within 48 hours of taking the antibiotic, taking account of: other possible diagnoses; any symptoms or signs suggesting a more serious illness or condition, such as pyelonephritis; previous antibiotic use, which may have led to resistant bacteria. And to send a urine sample for culture and susceptibility testing if this has not already been done and review treatment when results are available.
48	Chronic Urinary Tract Infection Campaign	Draft guideline	General		The very recent study by Swamy et al 2018 suggests that longer courses of antibiotics are less likely to cause a recurrence in symptoms and also casts doubt on the suitability that short course antibiotics are appropriate to all.	Thank you for your comment. The committee base their recommendations on evidence and their experience. There is a recommendation which covers reassessment if symptoms worsen or do not start to improve.

					Swamy S, Barcella W, De Iorio M, Gill K, Kupelian A, Khasriya R, et al. Recalcitrant chronic bladder pain and recurrent cystitis but negative urinalysis – What should we do? International urogynecology journal. 2018;In press.	Please note that Swamy et al. 2018 was published after the search cut-off and is a retrospective case series rather than a randomised controlled trial, and as such would not have been included in the review.
49	Chronic Urinary Tract Infection Campaign	Draft guideline	7 8	Table 1 Table 4	Tables 1 & 4 show a discrepancy in antibiotic prescription length for men and women. In Women, prescription length is noted at 3 days where as men is noted at 7-day initial treatment. Whilst infection rates for men are lower, antibiotic failure rates of 3 day courses of between 25-30% are found in treatment of patients. An assumption is made that these courses work for 100% of patients and there is no consideration for those who fail and what should be done next by way of treatment. Foxman B. The epidemiology of urinary tract infection. Nature reviews Urology. 2010;7. doi: 10.1038/nrurol.2010.190. Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2011;52(5):e103-20. doi: 10.1093/cid/ciq257. PubMed PMID: 21292654.	Thank you for your comment. The committee discussed the comment and made no changes to the recommendation. The committee based their recommendations on evidence and experience as outlined in the rationale, that 3-day course of all the recommended antibiotics (apart from fosfomycin where a single dose is given) was sufficient to treat lower UTI in non-pregnant women. If women have a complicated UTI (associated with a structural or functional abnormality, or underlying disease, which increases the risk of a more serious outcome or treatment failure), antibiotics recommended in the NICE antimicrobial prescribing guideline on acute pyelonephritis should be prescribed. In men a 7-day course is required to ensure complete cure because men are more at risk of complications from UTIs than women due to anatomical differences and possible outflow obstruction. There is a recommendation which covers reassessment if symptoms worsen or do not start to improve. And second-choice antibiotics (for if

						there is no improvement in lower UTI symptoms on first choice taken for at least 48 hours, or when first choice not suitable) are given in the tables. Regarding the submitted articles: • Foxman et al. 2010 does not meet the inclusion criteria on study type (epidemiology study) • Gupta et al. 2011 does not meet the inclusion criteria on study type (other guidance)
50	Chronic Urinary Tract Infection Campaign	Draft guidelines	12	Line 26-30	We are concerned that this description may imply that a single causative pathogen is responsible for uncomplicated UTI. As per our answer for section 1.1.3, infections are now multi-pathogenic. Even with a positive initial urine sample, if the infection is not cleared based on culture results, consideration by the GP must include not only the same pathogen but other causative low growth pathogens. Tenke P, Koves B, Nagy K, Hultgren SJ, Mendling W, Wullt B, et al. Update on biofilm infections in the urinary tract. World JUrol. 2011. Blango MG, Mulvey MA. Persistence of uropathogenic Escherichia coli in the face of multiple antibiotics. AntimicrobAgents Chemother. 2010;54(5):1855-63. Hoiby N, Bjarnsholt T, Givskov M, Molin S, Ciofu O. Antibiotic resistance of bacterial biofilms. Int J Antimicrob Agents. 2010;35(4):322-32. doi: 10.1016/j.ijantimicag.2009.12.011. PubMed PMID: 20149602. Anderson GG, Dodson KW, Hooton TM, Hultgren SJ. Intracellular bacterial communities of uropathogenic	Thank you for your comment. The committee discussed your comment and made no changes to the recommendation. The committee acknowledged that multiple pathogens can cause UTI. The guideline states the most common isolates. It does not dispute the fact that more than one pathogen can cause UTI. In reference to the submitted articles: • Tenke et al. 2011 did not meet the inclusion criteria based on study type (narrative review) • Blango et al. did not meet the inclusion criteria based on study type (narrative review) • Hoiby et al. 2010 does not meet the inclusion criteria based on study type (narrative review) • Anderson et al. 2004 does not meet the inclusion criteria based on date

					Escherichia coli in urinary tract pathogenesis. Trends Microbiol. 2004;12(9):424-30. Anderson GG, Palermo JJ, Schilling JD, Roth R, Heuser J, Hultgren SJ. Intracellular bacterial biofilm-like pods in urinary tract infections. Science. 2003;301(5629):105-7. Epub 2003/07/05. doi: 10.1126/science.1084550. PubMed PMID: 12843396. Reid G. Biofilms in infectious disease and on medical devices. IntJAntimicrobAgents. 1999;11(3-4):223-6. Costerton JW, Cheng KJ, Geesey GG, Ladd TI, Nickel JC, Dasgupta M, et al. Bacterial biofilms in nature and disease. AnnuRevMicrobiol. 1987;41:435-64.	• Anderson et al. 2003 does not meet the inclusion criteria based on date • Reid et al. 1999 does not meet the inclusion criteria based on date • Costerton et al. 1987 does not meet the inclusion criteria based on date
51	Chronic Urinary Tract Infection Campaign	Draft guideline	13	Efficacy of Antibiotics Line 23-33	We are concerned that the study quoted Falagas et al 2009 noted treatment against placebo stating “complete symptom resolution” in 61.8% of patients. The committee has assumed that this indicates short course antibiotic treatment means that ALL acute UTI infections achieve resolution whereas 39% of patients did not achieve symptom resolution against placebo when on treatment. As the poor efficacy of initial/short course antibiotic treatment achieves only 61.8% with complete symptom resolution. This is an important clinical issue and one which is not addressed at all in this draft guideline. This is a significant omission which must be resolved. These guidelines must offer a clinical pathway to treat those patients who are not completely well after standard short courses of antibiotic, advising extending the treatment until symptoms completely resolve, changing antibiotic if symptoms worsen or are not improving and according to any susceptibility results from culture testing. Clear advice on duration of antibiotic treatment and how/when to extend from the short courses used as standard is as important as guidance on which antibiotic to use - but is currently absent in these guidelines.	Thank you for your comment. For lower UTI, the guideline recommends short courses of antibiotics for non-pregnant women, children and young people based on the available evidence. The rationale has been updated to say ‘Based on evidence, the committee agreed that a 3-day course of antibiotics was as effective as a 5- to 10-day course of antibiotics in non-pregnant women with lower UTI, and resulted in significantly fewer adverse events. The committee agreed that a longer course may increase the likelihood of complete bacteriological eradication, which may be important for some women (for example, women with repeated lower UTIs). However, it was not possible to analyse data separately for people with repeated lower UTIs.

					In addition, when a patient presents to the GP having failed initial treatment and urine analysis is negative, what are the next steps for the GP given the proven unreliability of testing? This is not addressed.	For people who fail first-line antibiotic treatment, second-line antibiotics (to be used when there is no improvement in lower UTI symptoms on first choice taken for at least 48 hours, or when first choice not suitable) are given in the table. There is also a recommendation to reassess symptoms that worsen rapidly or significantly at any time, or do not start to improve within 48 hours of taking the antibiotic, taking account of: other possible diagnoses; any symptoms or signs suggesting a more serious illness or condition, such as pyelonephritis; previous antibiotic use, which may have led to resistant bacteria. And to send a urine sample for culture and susceptibility testing if this has not already been done and review treatment when results are available.
52	Chronic Urinary Tract Infection Campaign	Draft guideline	16	Line 1-8	This study illustrates well the challenge of culturing and how few women who had a successful positive culture. Only 2/3 of women who did receive antibiotics had a positive culture. Significant research suggests this is due to the poor accuracy and sensitivity of current testing, not because only 2/3 had true infection. We suggest that to leave women with active infection without antibiotic treatment is both clinically unwise and ethically unacceptable.	Thank you for your comment. The remit of this guidance is the management of common infections not diagnosis, and further detail on urine culture is out of scope. As outlined in the rationale, either a back-up antibiotic prescription or an immediate antibiotic prescription can be prescribed for non-pregnant women with a lower UTI, or waiting until any microbiological results are available can also be considered. However, these decisions should be individualised, taking account of the severity of symptoms, the risk of developing complications or having

						treatment failure. The recommendations allow an immediate antibiotic to be given where the prescriber feels this is appropriate.
53	Chronic Urinary Tract Infection Campaign	Draft guideline	16	Line 22-25	Little et al 2010's findings that a delay of 48 hours in starting antibiotics was associated with a longer duration of moderately bad symptoms is concerning when advice in these guidelines is to issue delayed prescriptions. We suggest that the guidelines need to be clearer on which patient group this is appropriate advice for: only those with mild-moderate symptoms and no previous history of significant infections.	Thank you for your comment. As outlined in the rationale, either a back-up antibiotic prescription or an immediate antibiotic prescription can be prescribed for non-pregnant women with a lower UTI, or waiting until any microbiological results are available can also be considered. However, these decisions should be individualised, taking account of the severity of symptoms, the risk of developing complications or having treatment failure. The recommendations allow an immediate antibiotic to be given where the prescriber feels this is appropriate. The recommendation for back-up prescribing is to use this if symptoms do not start to improve within 48 hours or if they worsen rapidly or significantly at any time. Further wording has been added to the recommendation that the evidence for back-up prescriptions is only in non-pregnant women with a lower UTI, where immediate antibiotic treatment was not necessary. Women included in the study had a mean age of 39 to 45 years and had moderate symptoms on average. Recommendation 1.1.3 has been amended to reflect these points.

54	Chronic Urinary Tract Infection Campaign	Draft guideline	17	line 5/final line	We welcome the advice that non-pregnant women with lower UTI would receive either antibiotic prescription or a delayed prescription. However we hear of many women denied prescription because dipstick tests and/or cultures fail to accurately identify infection - this needs to be addressed and GPs encouraged to use clinical judgement and to prescribe based on symptoms, particularly if these are severe. We suggest however that a forward dated prescription is unwise and removes the element of control for the patient themself. This is essential in case symptoms begin to worsen suddenly or significantly meaning that treatment must be started before 48 hours and without the delay which would be incurred if patents have to remake contact with the GP because their only prescription is forward dated.	Thank you for your comment. The remit of this guidance is the management of common infections not diagnosis, therefore further details on dipstick testing is out of scope. NICE is exploring the development of an additional tool to explain the different approaches that can be taken when implementing a back-up prescribing approach. NICE will use these comments when considering the implementation plans for the guidelines.
55	Chronic Urinary Tract Infection Campaign	Draft guideline	25	Line 26-31	The study reported (Milo et al) found no difference n effectiveness of 3 day courses compared to 5-10 day courses of antibiotics. However this study is over a decade out of date. Recent data suggests that some patients, in particular those with more severe symptoms or a history of recurrent UTI may well benefit from longer courses.	Thank you for your comment. The committee were aware of the date of the systematic review by Milo et al. comparing 3 day courses compared with 5-10 day courses of antibiotics. However based on their experience in combination with the evidence identified and the consideration of antimicrobial stewardship, the committee were able to make a recommendation on the use of 3 day courses of antibiotics. Additional wording has also been added to the guideline, ‘However, long-term bacteriological failure (at 4 to 10 weeks) was significantly higher with 3 day courses of any antibiotic compared with longer courses of any antibiotic (low quality evidence).’ The rationale has been updated to say ‘Based on evidence, the committee agreed that a 3-day course of antibiotics was as effective as a 5- to 10-day course of antibiotics in non-

						pregnant women with lower UTI, and resulted in significantly fewer adverse events. The committee agreed that a longer course may increase the likelihood of complete bacteriological eradication, which may be important for some women (for example, women with repeated lower UTIs). However, it was not possible to analyse data separately for people with repeated lower UTIs. Based on the process for NICE antimicrobial prescribing guidelines, subgroup analysis of people with severe symptoms or history of recurrent UTI has not been performed.
56	Chronic Urinary Tract Infection Campaign	Draft guideline	25	Line 26-31	The discussion paper notes there is no difference between the efficacy of 3-day length courses to 5-10 day courses yet a subgroup paper shows bacteriological failure at 3 days. Nitrofurantoin appears to lose efficacy if given for only 3 days. In an open-label, randomized controlled trial, Hooton et al. compared 3 day regimens of high-dose nitrofurantoin (100 mg four-times daily), trimethoprim/sulfamethoxazole, cefadroxil and amoxicillin; 6 weeks post-therapy, nitrofurantoin's clinical efficacy was only 61%. Similarly, a 2002 trial by Christiaens et al. comparing 3 days of nitrofurantoin with placebo in young women with symptoms of UTI and pyuria found clinical cure rates of 70% versus 42%, respectively, 7 days after the start of therapy. We would also note that the ESPAUR report (2016) states that 86% of CCGs have resistance rates greater than 25%, highlighting that trimethoprim can no longer be advised as the first-line empiric antibiotic treatment for UTIs. This	Thank you for your comment. The committee discussed your comment. The guideline recommends 3-day courses of antibiotics for non-pregnant women based on the available evidence, that overall, 3-day courses of any antibiotic were not significantly different to longer courses (5 to 10 days) of any antibiotic in preventing short-term or long-term symptomatic failure, short-term bacteriological failure, or the development of pyelonephritis. Additional wording has been added to the guideline, 'However, long-term bacteriological failure (at 4 to 10 weeks) was significantly higher with 3 day courses of any antibiotic compared with longer courses of any antibiotic (low quality evidence).' The rationale has been updated to say

					would highlight an issue with short course prescription usage and failure of laboratory testing or retesting for an appropriate antibiotic and confirmation of infection. Further, published clinical research from this year notes that longer term antibiotic treatment is appropriate for patients who report failure on initial antibiotic treatment. This clinical research noted no antibiotic resistance. Antimicrobial stewardship: prescribing antibiotics Key therapeutic topic [KTT9] Published date: January 2015 Last updated: January 2017 National Institute for Health and Care Excellence. Hooton TM , Winter C, Tiu Fet al. . Randomized comparative trial and cost analysis of 3-day antimicrobial regimens for treatment of acute cystitis in women. JAMA 1995; 273: 41–5. Christiaens TC , De Meyere M, Verschraegen Get al. . Randomised controlled trial of nitrofurantoin versus placebo in the treatment of uncomplicated urinary tract infection in adult women. Br J Gen Pract 2002; 52: 729–34. Swamy S, Barcella W, De Iorio M, Gill K, Kupelian A, Khasriya R, et al. Recalcitrant chronic bladder pain and recurrent cystitis but negative urinalysis – What should we do? International urogynecology journal. 2018	'Based on evidence, the committee agreed that a 3-day course of antibiotics was as effective as a 5- to 10-day course of antibiotics in non-pregnant women with lower UTI, and resulted in significantly fewer adverse events. The committee agreed that a longer course may increase the likelihood of complete bacteriological eradication, which may be important for some women (for example, women with repeated lower UTIs). However, it was not possible to analyse data separately for people with repeated lower UTIs. Please note Hooton et al. 1995 and Christians 2002 were published before our search cut-off of 2006. However both of these studies were included in prioritised systematic reviews (Falagas et al. 2009 and Zalmanavoci-Trestioreanu et al. 2010), therefore the data has been considered by the committee. Swamy et al. 2018 was published after the search cut-off and is a retrospective case series rather than a randomised controlled trial, therefore would not have been included in the evidence review. Trimethoprim is only recommended if there is a low risk of resistance. The guideline recommends a lower risk of resistance may be more likely if not used in the past 3 months, previous urine culture suggests susceptibility (but this was not used), and in

						younger people in areas where local epidemiology data suggest resistance is low. A higher risk of resistance may be more likely with recent use and in older people in residential facilities. The guideline recommends taking account of local antimicrobial resistance data when prescribing antibiotic treatment for lower UTI.
57	Chronic Urinary Tract Infection Campaign	Draft guideline	26 27	Line 29-32 penultimate bullet Line 11-21	We have grave concerns about the suggestion here of single dose antibiotics - as mentioned, when said patients are more likely to develop persistent and resistant infections. Lutters et al 2008 also found single dose antibiotics associated with higher rates of persistent UTI in older women with UTI. Therefore we suggest that such short courses are unwise and the guidelines should make it clear that they are not to be used. If women's symptoms are significant and do need antibiotic treatment it is essential the course is long enough to effectively treat and eradicate the causative organism.	Thank you for your comment. The committee discussed your comment and made no changes to the recommendation. Based on evidence and experience, the only single-dose antibiotic recommended was fosfomycin for non-pregnant women as a second-choice antibiotic. This is the licensed dosing regimen for this antibiotic. Various single-dose antibiotics were included in Lutters et al. 2008, including sulfamethiazole, ciprofloxacin, fosfomycin, pefloxacin, trimethoprim and isepamicin.
58	Chronic Urinary Tract Infection Campaign	Draft guideline		General	It is noted that there is no mention of the quality of samples in order to have reasonable chance of accurate result. The original Kass criteria comment on the risk of false negatives when samples are very dilute and/or when frequency is very high meaning urine has not remain in the bladder for long. Guidelines should include advice on how to collect samples (including using first urine of day where possible) and warn of the risk of false negatives, particularly if sample is obviously very dilute and transparent. In this situation negative results (eg of dipstick tests, which rely on concentration) should be viewed with real caution and considered as part of the clinical picture, with greater emphasis on symptoms.	Thank you for your comment. The remit of this guidance is the management of common infections not diagnosis, and further details on diagnostic accuracy are out of scope. In reference to the submitted article: • Kass et al. 1957 does not meet the inclusion criteria based on date

					Kass EH. Bacteriuria and the Diagnosis of Infection in the Urinary Tract. Archives of Internal Medicine. 1957 100:709-714	
59	Chronic Urinary Tract Infection Campaign	Visual Summary		General	Initial advice makes no mention of severity of symptoms. It is importance this 'at a glance' guidance is as clear as the written guidelines that severity of symptoms is a significant factor in decision making regarding treatment. This is particularly the case in advice about delayed prescriptions. Advice to consider waiting for culture results before prescribing is unwise and fails to address the frequency of false negatives in culture. Patient symptoms MUST be taken into account particularly if they are severe.	Thank you for your comment. This wording of the visual summary has been amended following further discussion by the committee.
60	National Minor Illness Centre	Visual summary Guideline	1 3	Left blue box 24	For children, infection with non-E. coli organisms is an indication for imaging in the current NICE guidance. These children will not be identified at the time of their first infection if the dipstick test option is used alone without sending an MSU. UTI in children is not that common in primary care. Every GP sees cases occasionally, but nothing like the incidence of UTI in adults. Please review the criteria for sending a sample for culture in people under 16 years of age. Note that any child with even a single recurrence needs this – so wouldn't it be helpful to know what the infective organism was in the first episode too? There are multiple indications for culture in NICE 'Diagnosing urinary tract infection in under 16s'. Is this practical? It is easier for clinicians to try to remember that virtually all children need a sample for culture (including those who have a positive dipstick test for nitrite or leukocyte esterase, OR a negative dipstick test despite symptoms - so then it's not culture OR dipstick but BOTH) unless they are determined to be very unlikely to have a UTI at all (mild symptoms, no immunosuppression, no previous episodes, dipstick test	Thank you for your comment. The remit of this guidance is the management of common infections not diagnosis. The guideline signposts to the NICE guideline for UTI in children and young people under 16 years, which covers diagnosis in children and young people.

					negative and correlating with symptoms not thought to be indicating a UTI).	
61	National Minor Illness Centre	Visual summary	1	Left blue box	“Send midstream urine for culture and susceptibility for pregnant women and men before prescribing”. This could be misinterpreted as implying that there is a need to await the result. The problem is that the line above recommends an “immediate” antibiotic, and then this line says that something else has to happen beforehand. What actually matters is that the midstream sample is collected before the patient starts the antibiotic. In practice, what happens is that the patients presents with acute symptoms, the clinician arranges the sample collection and lab request, and prints the prescription all in the same consultation. A simple message like “test and treat” would cover this.	Thank you for your comment. The visual summary and the recommendation have been amended to reflect that the MSU should be taken before antibiotics are started.
62	National Minor Illness Centre	Visual summary	1	Col 3, top white box	“With a back-up prescription, advise: ….possible adverse effects include diarrhoea and nausea”. It needs to be clear that these are potential problems of the antibiotic, not the infection being untreated for 48 hours.	Thank you for your comment. The wording has been amended to reflect that adverse effects are of the antibiotic
63	National Minor Illness Centre	Visual summary Guideline	1 6, 12	Grey box 20, 17	Self-care advice includes “Advise an adequate intake of fluid”, but is there any evidence or rationale for this? Everyone should take ‘adequate’ fluid. By raising the issue under self-care, extra fluid is therefore implied. The problem is that extra fluid intake can exacerbate the frequency and associated dysuria. There could be issues with dilution of immunoglobulin / WBC in the urine. Without fever (which shouldn’t be present in cystitis) then there is no reason to suppose that there will be excess fluid loss that needs extra hydration to replace it. Would NICE ‘Advise an adequate intake of fluid’ for every infection? If not, then what is the reasoning to include it here? The recommendation is “based on experience” but without supporting evidence being cited.	Thank you for your comment. The wording has been changed to advise people with lower UTI about drinking enough fluids to avoid dehydration.
64	National Minor Illness Centre	Visual summary Guideline	1 6	Grey box 21	It would be more helpful to say “Explain no evidence to support the use of over-the-counter remedies”, as this would include the alkalinising agents that can impair the anti-bacterial activity of nitrofurantoin. This is more of a concern than the use of cranberry.	Thank you for your comment. The committee discussed the comment and amended the wording. It now reads: ‘Be aware that no evidence was found on cranberry products or

						urine alkalinizing agents to treat people with a lower UTI.'
65	National Minor Illness Centre	Visual summary Guideline	1 6	Grey box 1	It would be very helpful to add that asymptomatic bacteriuria should NOT be screened for pre-operatively (a common and pointless practice that encourages the use of inappropriate antibiotics). Martinez-Velez D, Gonzalez-Fernandez E, Esteban J, Cordero-Ampuero J. Prevalence of asymptomatic bacteriuria in knee arthroplasty patients and subsequent risk of prosthesis infection. EurN JN OrthopN SurgN TraumatolN 2016; 26(2):209-14 Nicolle LE. Asymptomatic bacteriuria. Curr Opin Infect Dis 2014; 27(1):90-6	Thank you for your comment. The committee discussed the comment and made no change to the recommendation. Screening for asymptomatic bacteriuria is outside the scope of this antimicrobial prescribing guideline. In reference to the submitted articles: • Martinez-Velez et al 2016 does not meet the inclusion criteria on population (not UTI) • Nicolle et al. 2014 does not meet the inclusion criteria based on study type (narrative review)
66	National Minor Illness Centre	Visual summary Guideline	2 7	Left table 6, 13, 31	Why include standard-release form when it is associated with a higher risk of adverse symptoms and costs more than the modified-release form? Drug tariff May 2018: 50mg cap (30) £15.42; 50mg tab (28) £11.36; mr cap (14) £9.50 Liu J, Chan SY, Ho PC. Polymer-coated microparticles for the sustained release of nitrofurantoin. J Pharm Pharmacol 2002; 54(9):1205-12 Ertan G, Karasulu E, Abou-Nada M, Tosun M, Ozer A. Sustained-release dosage form of nitrofurantoin. Part 2. In vivo urinary excretion in man. J Microencapsul 1994; 11(2):137-40 Maier-Lenz H, Ringwelski L, Windorfer A. Comparative pharmacokinetics and relative bioavailability for different preparations of nitrofurantoin. Arzneimittelforschung 1979; 29(12):1898-901	Thank you for your comment. The committee discussed the comment and made changes to the relevant tables. The committee agreed to remove immediate-release nitrofurantoin from the antibiotic choice tables and recommend the modified-release preparation only, based on the twice a day dosing and, in their experience, improved tolerability. In reference to the submitted articles: • Liu et al. 2002 does not meet the inclusion criteria based on date • Ertan et al. 1994 does not meet the inclusion criteria based on date

					There is clear incentive for a person to take medication for relief of unpleasant symptoms, so the normal concern that more than two doses daily increases the risk of missed doses is not so relevant, but there is still what is termed 'the burden of tablet taking'. Four doses daily, in addition to any other medications being taken long-term, adds to the burden for the patient. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance Clinical Therapeutics 2001; 23(8):1296-1310 If it is decided to keep immediate-release Nitrofurantoin in the guideline, then please could it be placed after the modified-release option to at least avoid giving prescribers a false impression of preference?	• Maier-Lenz et al. 1979 does not meet the inclusion criteria based on date • Claxton et al. 2001 does not meet the inclusion criteria based on date
67	National Minor Illness Centre	Visual summary Guideline	2 7	Left table 8	How does the prescriber know "if low risk of resistance"?	Thank you for your comment. The committee discussed your comment and made changes to the relevant tables. The tables now includes the following footnote: 'A lower risk of resistance may be more likely if not used in the past 3 months, previous urine culture suggests susceptibility (but this was not used), and in younger people in areas where local epidemiology data suggest resistance is low. A higher risk of resistance may be more likely with recent use and in older people in residential facilities'.
68	National Minor Illness Centre	Visual summary Guideline	2 7	Left table 16	The dose recommended for Pivmecillinam, which includes a higher first dose than subsequent ones, concurs with BNF and the PHE guideline. The committee will be aware that the dose differs from that stated in the SPC of the generic manufactured by Aurobindo Pharma - Milpharm Ltd, where all the doses are the same for the course. We have previously written to the manufacturerof Selexid (Leo), who do recommend a loading dose, to ask	Thank you for your comment. NICE uses the BNF for dosages when making recommendations. NICE will contact the BNF regarding this issue.

					why this might have an advantage, as the pharmacokinetics as found in the SPC do not indicate any particular requirement (the serum half-life is 1.2 hours). We had no reply. Perhaps it would be worth checking with the MHRA on the evidence for the loading dose?	
69	National Minor Illness Centre	Visual summary Guideline	2 9 29	Right table 9, 15 26	The resource implication mentioned at the end of the guideline that the price of Nitrofurantoin liquid for children is £446.95 for 300ml. This is such an implication for our CCG that the recommendation is unlikely to be accepted. Although the volume required for a course is less than 300ml, a community pharmacist is unlikely to be able to use the remainder and so the cost to the CCG is likely to be this high for one treatment. It may be the committee's view that this cost is justified on the grounds of the antibiotic being narrow-spectrum. A far less expensive alternative would be Pivmecillinam, which is licensed for children. Children over 40kg take the same dose as adults, those under 40kg can halve or quarter the tablets using a tablet cutter available from pharmacies for a cost of about £3. Children down to the age 6 years can usually swallow small divided tablets, and Bonnie Kaplan has shown that children down the age of 4 years can also swallow solid medication with simple instruction (and often they prefer it to the taste of liquid medicine). Kaplan BJ, Steiger RA, Pope J, Marsh A, Sharp M, Crawford SG (2010). Better than a spoonful of sugar: Successful treatment of pill swallowing difficulties with head posture practice. Paediatr Child Health, 15(5), e1-5. Leo Laboratories Ltd replied to our request about dosing for young children indicating that, if required, a tablet or part thereof could safely be crushed.	Thank you for your comment. The committee considered the resource implications of implementing the guideline when reviewing the evidence and producing recommendations. The committee acknowledged the current high cost of nitrofurantoin liquid and recommended that if 2 or more antibiotics are appropriate, the antibiotic with the lowest acquisition cost should be chosen. A footnote has also been added to the antibiotic choice table for children, to note that tablets can be given if the appropriate dose can be achieved and the child or young person is able to swallow tablets. In reference to the submitted article: • Kaplan et al 2010 does not meet the inclusion criteria based on intervention
70	National Minor Illness Centre	Visual summary Guideline	2 9	Right table 40	Would it be worth adding to footnote 2 that the dose calculated from a child's weight should not exceed the adult dose? We have experience of a child discharged from hospital taking 250mg trimethoprim twice daily because he weighed 62.5kg.	Thank you for your comment. NICE uses the BNF for dosages when making recommendations.
71	National Minor Illness Centre	Visual summary	2	Right table	To a new prescriber, it may appear odd that doses of Amoxicillin are quoted for 5-11 years and 12-17 years of	Thank you for your comment. The committee discussed your comment

		Guideline	9	30	age and that the dose is the same for both, and includes 17 when the table refers to young people under 16. An experienced prescriber may think nothing of this because that is how it appears in the BNFC (although in the BNFC there is a subtle difference between the two age ranges for high doses used in more serious infections). Consider simplifying the table and just say '5 to 16 years, 500 mg three times a day for 3 days'. If this is accepted, then the other dose ranges for children and young people should also be changed from a maximum of 17 to 16 to align with that table's title.	and made changes to the table to reflect your comment.
72	National Minor Illness Centre	Visual summary Guideline	3 8	Left table 3	Could the treatment options for asymptomatic bacteriuria be in the order of narrower-spectrum first? This would then mirror the order in the table.	Thank you for your comment. The committee discussed your comment and made changes to the wording to reflect your comment.
73	National Minor Illness Centre	Visual summary Guideline	3 8	Left table 11	Footnote 4 is important but does not appear linked to Nitrofurantoin in the table, but we feel that a footnote could easily get overlooked. Is there any way of making the point more prominent?	Thank you for your comment. We have amended the visual summary.
74	Profile Pharma	Draft Guideline & Visual summary	7	Table 1	The recommendations in this table differ significantly from the current Public Health England (PHE) 'Management and treatment of common infections. Antibiotic guidance for primary care: For consultation and local adaptation. Published October 2017 and last reviewed November 2017 (see page 6, UTI in adults (lower)). Specifically the PHE drug choice advice refers to 'first line' and 'if first line unsuitable' rather than suggesting first and second choice as in the draft NICE guideline. In addition PHE does not stipulate 'Second choice (no improvement in lower UTI symptoms on first choice taken for at least 48 hours, or when first choice not suitable)' as the draft NICE guideline does. It is our view that national guidelines for the treatment and management of the same condition produced by two national bodies should be congruent to avoid causing confusion for healthcare professionals which may create inequalities in care provided to patients as healthcare professionals will not know which guideline is the most appropriate to use. Please consider rewording the NICE guideline to be	Thank you for your comment. NICE is aware of the important role played by Public Health England on the treatment of lower UTI. We have worked closely with Public Health England to produce this guideline. NICE antimicrobial prescribing guidelines will replace the PHE guidance as they are published.

					aligned with the PHE guideline wording in relation to first line/if first line unsuitable.	
75	Profile Pharma	Draft Guideline & visual summary	7	Table 1	Please consider making a clear statement that current 'second choice' options recommended in the guideline may be prescribed empirically when first choice options are not suitable. The current wording of footnote 3 may lead healthcare professionals to think that second choice options are only available after susceptibility testing results are obtained	Thank you for your comment. The committee discussed your comment and made no changes to the recommendation. Table 1 subheading 'Second choice' states: 'Second choice (no improvement in lower UTI symptoms on first choice taken for at least 48 hours, or when first choice not suitable).'
76	Profile Pharma	Draft Guideline & visual summary	7	Table 1	In the guideline Public Health England (PHE) 'Management and treatment of common infections. Antibiotic guidance for primary care: For consultation and local adaptation. Published October 2017 and last reviewed November 2017 (see page 6, UTI in adults (lower)), PHE note that if fever is present then an alternative to nitrofurantoin should be used first line. The current NICE guideline does not include this advice and does not seem to have reviewed any evidence relating to this PHE recommendation. Please consider adding this recommendation to the guideline.	Thank you for your comment. NICE is aware of the important role played by Public Health England and on the treatment of lower UTI. We have worked closely with Public Health England to produce this guideline. NICE antimicrobial prescribing guidelines will replace the PHE guidance as they are published. PHE make their recommendation based on Christiaens et al. 2002. This study was published before the search cut-off for this guideline. Please note Christiaens excluded people with fever to avoid complicated UTI. The antibiotics recommended in table 1 are for lower UTI. This table has a footnote that 'if there are symptoms of pyelonephritis or the person has a complicated UTI (associated with a structural or functional abnormality, or underlying disease, which increases the risk of a more serious outcome or treatment failure), see the recommendations on

						choice of antibiotic in the NICE guideline on acute pyelonephritis.'
77	Profile Pharma	Draft Guideline & visual summary	7	Table 1	The drug choices in the NICE guideline are different to the drug choices in the Public Health England (PHE) 'Management and treatment of common infections. Antibiotic guidance for primary care: For consultation and local adaptation. Published October 2017 and last reviewed November 2017 (see page 6, UTI in adults (lower)) guideline. To avoid confusion for healthcare professionals please consider aligning the drug choices recommended between these guidelines.	Thank you for your comment. NICE is aware of the important role played by Public Health England on the treatment of lower UTI. We have worked closely with Public Health England to produce this guideline. NICE antimicrobial prescribing guidelines will replace the PHE guidance as they are published.
78	Profile Pharma	Draft guideline	22	18	Based on the evidence review which included Falagas 2010, please consider fosfomycin as a third alternative here. The conclusion drawn by the review committee regarding the Falagas 2010 study suggests fosfomycin is no more efficacious or safe than other antibiotics based on the results of this publication. This conclusion is based very narrowly purely in terms of efficacy and safety. No studies are powered to show differences in adverse events. There was no published discussion in the consultation draft or evidence review from the committee regarding other aspects of the drug which may be taken into account such as the ease of adherence to fosfomycin because of the single stat dose regimen and it is also a liquid formulation when taken which makes it easy to swallow. Also, fosfomycin has a well documented low propensity to cause resistance (please refer to ref 1. Heytens S, Boelens J, Claeys G et al (2016). Uropathogen distribution and antimicrobial susceptibility in uncomplicated cystitis in Belgium, a high antibiotics prescribing country: 20-year surveillance. European Journal of Clinical Microbiology & Infectious Diseases. DOI: 10.1007/s10096-016-2776-8. Ref 2. National Institute for Public Health and the Environment (2017). NethMap 2017: Consumption of antimicrobial agents and antimicrobial resistance among medically important bacteria in the Netherlands) despite considerable empirical prescribing in other European countries in line with other international guidelines.	Thank you for your comment. The committee discussed the comment and made no changes to the recommendation. The committee agreed that fosfomycin should be a second-choice in non-pregnant women, not a first-choice, to reserve its use, for extended-spectrum beta-lactamases, etc. In reference to the submitted articles: • Heytens et al. 2016 does not meet the inclusion criteria based on study type (observational) • National Institute for Public Health and the Environment (2017) does not meet the inclusion criteria based on study type (observational data)

	Profile Pharma	Draft guideline	29	26	Please consider adding fosfomycin to this bullet point as an alternative oral solution. Fosfomycin 3g granules in a sachet requires to be dissolved in water to make a solution before being taken by patients. The complete course of treatment is one 3g sachet stat. Therefore Fosfomycin should be considered an alternative oral solution which costs £4.86 per treatment course (Drug Tariff, May 2018). Nitrofurantoin has greater resource implications when an oral suspension is needed and trimethoprim oral suspension may not be a suitable alternative due to resistance thus making fosfomycin a suitable alternative from a resourcing point of view	Thank you for your comment. The committee discussed your comment and made no changes to the recommendation. The committee agreed that fosfomycin should be a second-choice in non-pregnant women, not a first-choice, to reserve its use, for extended-spectrum beta-lactamases etc.
79	Barking and Dagenham, Havering & Redbridge CCGs	Visual summary	2		It can be clinically difficult to distinguish lower from upper UTI, so first line recommendation of nitrofurantoin will be associated with failures - and I am seeing increasing numbers of such cases in secondary care. To make matters worse, EUCAST does not provide guidance on susceptibility of non-E.coli coliforms against nitrofurantoin.	Thank you for your comment. Your comment highlights a diagnostic issue. However, the remit of this guidance is the management of common infections not diagnosis. Antibiotic choices for upper UTI are given in the NICE antimicrobial prescribing guideline on acute pyelonephritis. The antibiotic prescribing tables for lower UTI include a footnote that ‘If there are symptoms of pyelonephritis or the person has a complicated UTI (associated with a structural or functional abnormality, or underlying disease, which increases the risk of a more serious outcome or treatment failure), see the recommendations on choice of antibiotic in the NICE guideline on acute pyelonephritis.’
80	Barking and Dagenham, Havering & Redbridge CCGs	Visual summary	2		I strongly support trimethoprim within first line guidance - we do not have sufficient lab data at national level to suggest that resistance is a problem, particularly in those who have had little exposure to antibiotics	Thank you for your comment.

81	Barking and Dagenham, Havering & Redbridge CCGs,	Visual summary	2		Given the widespread desire to use as narrow spectrum agents as possible, why recommend fosfomycin or pivmecillinam as second line rather than co-amoxiclav, which is almost universally effective. I am aware that it has been argued that co-amox has a greater selective pressure for resistant isolates than pivmecillinam. However, the risk of over-use reducing the effect of fosfo and pivmecillnam makes me feel that the case for co-aomox is nowhere strong enough. Furthermore, EUCAST do not provide guidance for clinical breakpoints for non E.coli/ Klebsiella / Proteus coliforms.	Thank you for your comment. The committee discussed your comment and made no changes to the recommendation. Based on evidence, experience and resistance data, the committee agreed to recommend pivmecillinam or fosfomycin at usual doses as second-choice antibiotics for use if lower UTI symptoms do not improve on a first-choice antibiotic taken for at least 48 hours. Co-amoxiclav was not recommended because there was limited evidence of its use in lower urinary tract infection and concerns over resistance.
82	The British Society for Antimicrobial Chemotherapy	Guideline	General		I think this document would be improved if it included diagnostic signs and symptoms of lower UTI.	Thank you for your comment. The remit of this guidance is the management of common infections not diagnosis. Providing further details on diagnostic signs and symptoms in the guideline is out of scope, but further background information on signs and symptoms is given in the evidence review.
83	The British Society for Antimicrobial Chemotherapy	Guideline	2	1.1.5	Although implied, I think it would be worth stating that antibiotic therapy does not need to be changed if the culture reports resistant bacteria and the patient's symptoms are improving.	Thank you for your comment. The committee discussed your comment and made no changes to the recommendation, which they felt was clear.
84	The British Society for Antimicrobial Chemotherapy	Guideline	3	1.1.9	Although implied, I think it would be worth stating that antibiotic therapy does not need to be changed if the culture reports resistant bacteria and the patient's symptoms are improving.	Thank you for your comment. The committee discussed your comment and made no changes to the recommendation, which they felt was clear.
85	The British Society for Antimicrobial Chemotherapy	Guideline	6	1.2.1	Change "is not routinely screened for, or treated" to "Must/should not be routinely screened for". I think stronger wording to discourage screening urine is warranted. If we could get this common practice changed	Thank you for your comment. The remit of this guidance is the management of common infections not diagnosis. Screening for

					it would have a significant impact on total antibiotic usage in primary and secondary care.	asymptomatic bacteriuria is outside the scope of this antimicrobial prescribing guideline.
86	The British Society for Antimicrobial Chemotherapy	Guideline	13	15	Asymptomatic bacteriuria is only treated in pregnancy and prior to urological instrumentation. It may be worth being explicit here. Stating that asymptomatic bacteriuria should be treated only if considered a risk factor in clearly defined situations without stating those situations leaves this open to interpretation. For example it could be argued that an immunosuppressed patient is at risk of UTI and therefore treated (which of course is not the case).	Thank you for your comment. This wording has been changed to 'Asymptomatic bacteriuria is not routinely screened for or treated, except if it is considered a risk factor, such as in pregnant women'
87	The British Society for Antimicrobial Chemotherapy	Guideline	General	General	General concern is the antibiotic choices make no reference to local resistance rates or for come choices national data (we have a high co-amoxiclav resistance rates as does the recent national E coli BSI dataset) plus advises high risk antibiotics for inpatient treatment from the C difficile point of view	Thank you for your comment. The committee discussed your comment and added a recommendation to: take account of local antimicrobial resistance data when prescribing antibiotic treatment.
88	Concordia International	Guideline	Page 7 Table 1	2-4	You state under "First choice" that "Nitrofurantoin – if eGFR <45ml/minute" We request you consider the full guidance on eGFR for these products, as stated in their Summary of Product Characteristics (SmPCs). The SmPCs for the relevant immediate or modified-release Nitrofurantoin, under section 4.3 or 4.4, further state that: "Nitrofurantoin may be used with caution as short-course therapy only for the treatment of uncomplicated lower urinary tract infection in individual cases with an eGFR between 30-44 ml/min to treat resistant pathogens, when the benefits are expected to outweigh the risks."	Thank you for your comment The committee discussed your comment and added a footnote on the relevant tables that nitrofurantoin may be used with caution if eGFR is 30–44 ml/minute to treat uncomplicated lower UTI caused by suspected or proven multidrug resistant bacteria and only if potential benefit outweighs risk (BNF, June 2018).
89	Concordia International	Guideline	Page 7 Table 1	3-4	We are concerned you have listed Nitrofurantoin 50 mg four times a day before Nitrofurantoin 100 mg modified-release, which is only taken twice daily. We believe that Nitrofurantoin 100 mg modified release (twice daily) should be listed first, and before the four times daily regimen, for the following reasons:	Thank you for your comment. The committee discussed the comment and changed the relevant tables. The committee agreed to remove immediate-release nitrofurantoin from the relevant antibiotic choice tables

					Improved patient compliance: Reducing the dosing from 4 times a day to 2 times a day has demonstrated that patient compliance improves. Reference: MeReC Bulletin Volume 11, Number 4, 2000) Reduced side effects: By reducing daily dosing it is a well-established fact that side effects are also reduced. Reference: https://www.sciencedirect.com/science/article/pii/S0048969712013927 A cost-effective option: Prices are currently Nitrofurantoin 50 mg (28) tablets £11.36 and Nitrofurantoin 100 mg modified-release 100 mg (14) capsules £9.50. Thus, the modified-release preparation is 16% cheaper.	and recommend the modified-release preparation only, based on its twice a day dosing and, in their experience, improved tolerability. In reference to the submitted article: • Daughton et al. 2013 does not meet the inclusion criteria based on study type (narrative review)
90	Concordia International	Guideline	Page 7 Table 1	8-9	You state “Second choice (no improvement in lower UTI symptoms on first choice taken for at least 48 hours, or when first choice not suitable)” We would like to highlight that the licensed treatment durations for immediate or modified-release Nitrofurantoin is 7 days. We believe that if there is no improvement after 48 hours on first choice treatment then the full licensed course should be considered i.e. 7 days for the Nitrofurantoin products. 48 hours could be considered a too short a time to assess whether a treatment has failed, especially when the licensed course is 7 days.	Thank you for your comment. The committee discussed your comment and made no changes to the recommendation. The committee agreed based on evidence, experience and resistance data, that a 3-day course of all the recommended antibiotics (apart from fosfomycin where a single dose is given) was sufficient to treat lower UTI in non-pregnant women. Additional wording has now been added to the rationale that a longer course may increase the likelihood of complete bacteriological eradication, which may be important for some women (for example, women with repeated lower UTIs). However, it was not possible to analyse data separately for people with repeated lower UTIs.

						The committee agreed that a second choice antibiotic is recommended if there is no improvement in lower UTI symptoms on first choice taken for at least 48 hours. There are serious complications of lower UTI if it does not respond to antibiotic treatment, include ascending infection leading to pyelonephritis, renal failure, and sepsis. The committee noted the licence for nitrofurantoin was for a treatment duration of 7 days but the BNF recommends 3 to 7 days treatment, and 3 days is usual practice for lower UTI in most non-pregnant women.
91	Concordia International		Page 7 Table 2		Same comments apply as Comments 1 and 3 above.	Thank you for your comment. The committee discussed your comment and added a footnote on the relevant tables that nitrofurantoin may be used with caution if eGFR is 30–44 ml/minute to treat uncomplicated lower UTI caused by suspected or proven multidrug resistant bacteria and only if potential benefit outweighs risk (BNF, June 2018). The committee agreed based on evidence, experience and resistance data, that a 3-day course of all the recommended antibiotics (apart from fosfomycin where a single dose is given) was sufficient to treat lower UTI in non-pregnant women. Additional wording has now been added to the rationale that a longer course may increase the likelihood of complete bacteriological eradication,

						which may be important for some women (for example, women with repeated lower UTIs). The committee agreed that a second choice antibiotic is recommended if there is no improvement in lower UTI symptoms on first choice taken for at least 48 hours. There are serious complications of lower UTI if it does not respond to antibiotic treatment, include ascending infection leading to pyelonephritis, renal failure, and sepsis. The committee noted the licence for nitrofurantoin was for a treatment duration of 7 days but the BNF recommends 3 to 7 days treatment, and 3 days is usual practice for lower UTI in most non-pregnant women.
92	Concordia International		Page 8/9 Table 4		Same comments apply as Comments 1 and 3 above.	Thank you for your comment. The committee discussed your comment and added a footnote on the relevant tables that nitrofurantoin may be used with caution if eGFR is 30–44 ml/minute to treat uncomplicated lower UTI caused by suspected or proven multidrug resistant bacteria and only if potential benefit outweighs risk (BNF, June 2018). The committee agreed based on evidence, experience and resistance data, that a 3-day course of all the recommended antibiotics (apart from fosfomycin where a single dose is given) was sufficient to treat lower UTI in non-pregnant women.

						Additional wording has now been added to the rationale that a longer course may increase the likelihood of complete bacteriological eradication, which may be important for some women (for example, women with repeated lower UTIs). However, it was not possible to analyse data separately for people with repeated lower UTIs. The committee agreed that a second choice antibiotic is recommended if there is no improvement in lower UTI symptoms on first choice taken for at least 48 hours. There are serious complications of lower UTI if it does not respond to antibiotic treatment, include ascending infection leading to pyelonephritis, renal failure, and sepsis. The committee noted the licence for nitrofurantoin was for a treatment duration of 7 days but the BNF recommends 3 to 7 days treatment, and 3 days is usual practice for lower UTI in most non-pregnant women.
93	Healthcare Infection Society	Antimicrobial prescribing: Urinary tract infections (lower)	3	1.1.10	1.1.10 Obtain a midstream urine sample from children and young people with lower UTI and dipstick test or send for culture Suggests that it's either dipstick or send for culture. Needs to indicate that dipsticking is optional, and culture is essential.	Thank you for your comment. The committee discussed the comment and made no changes to the recommendation. This recommendation reflects recommendations in the NICE guideline on urinary tract infection in under 16s: diagnosis and management, which is signposted.

94	Healthcare Infection Society	Antimicrobial prescribing: Urinary tract infections (lower)	6	1.2.2	1.2.2 Urine is pregnancy is commonly contaminated. A second sample should be obtained to confirm ASB before giving antibiotics. UTI in adults is not a homogeneous entity. There should be a separate section on identification and management of UTI in the elderly emphasising: the lack of clinical and prognostic significance of ASB or pyuria; that dipstick screening is unhelpful; that positive urine culture is meaningless unless there are clear LUT symptoms; that attributing a positive culture as a cause of non-specific symptoms will lead to an erroneous diagnosis of UTI – and then to recurrent UTI as the organism will inevitably recur. Apart from pregnant women, there should be a statement about NOT screening for “clearance” after an antibiotic treatment course. This practice leads to repeated courses of antibiotics for so-called “treatment failure”, or leads to a label of “recurrent UTI”.	Thank you for your comment. The remit of this guidance is the management of common infections not diagnosis, and further details on diagnosis is out of scope.
95	Royal College of General Practitioners	Draft lower UTI		1.1.3	This needs to start with symptoms and signs and whether to test at all or take history or to undertake urinalysis. At present as a GP this leads to delayed or actual antibiotic treatment and MSUs. This is not usual practice in UK which revolves around urinary dipstick testing first line and MSU in failure to cure. The guidance needs to consistent with the Public Health England (PHE) Diagnosis of urinary tract infections (UTIs) 2017	Thank you for your comment. The remit of this guidance is the management of common infections not diagnosis, and further details on diagnosis is out of scope.
96	Royal College of General Practitioners	Guideline		1.1.4	Public Health England advises not to send urine microscopy in suspected UTIs in women under 65 years of age if it is severe or > 3 symptoms of UTI dysuria, frequency, suprapubic tenderness, urgency, polyuria and or haematuria	Thank you for your comment. The remit of this guidance is the management of common infections not diagnosis, and further details on diagnosis is out of scope. Please note that this recommendation has now been removed.

97	Royal College of General Practitioners	Guideline		1.1.8	Can this over pregnant women also add the caution of trimethoprim 1st and nitrofurantoin 3rd trimester to improve information giving as says prescribe using a narrow spectrum antibiotic at present. This could blend into the PHE antimicrobial guidelines for primary care and talk about a 7 day course in men and pregnant women at this point - it is discussed further down.	Thank you for your comment. The committee discussed the comment and made no changes to the recommendation. Table 2 lists the choice of antibiotics for pregnant women. Table 2 also includes the safety warning on nitrofurantoin. The committee did not recommend trimethoprim for pregnant women because it is contraindicated in pregnancy.
98	Royal College of General Practitioners		7	Table 1	GPs have never previously used pivmecillinam or fosfomycin; these are new to UK GP formularies and if going to be introduced require UK wide GP and their HCP education on these medications including any interactions and pitfalls, and pharmacies to stock the medication. There is an educational need to have a training available to ensure the workforce get it if a guideline is to be effective?	Thank you for your comment. Access to training is outside the scope of this guideline. However, the rationale has been updated to say 'The committee acknowledged that prescribers may be less familiar with these antibiotics, but they are often used in other European countries.' And the table now says pivmecillinam (a penicillin).
99	Royal College of General Practitioners	overall			How does this guideline relate to PHE antimicrobial guidelines which come down to CCGs? How does this guideline relate to PHE UKSMI template on UK standards for microbiological investigation; urine tests in which some cystitis is diagnosed by symptoms and 2 symptoms requires urinalysis but neither require MSU? It is currently confusing – could align more to other national guidance. Whilst the guidance is on treatment it would be enhanced by looking at symptoms and investigation for basic non pregnant women at least which is most cases in primary care	Thank you for your comment. NICE is aware of the important role played by Public Health guidance on the treatment of lower UTI. We have worked closely with Public Health England to produce this guideline and the NICE antimicrobial prescribing guidelines will replace the PHE guidance as they are published. The remit of this guidance is the management of common infections not diagnosis, and further detail on diagnostic signs and symptoms and urine testing is out of scope. More background information on signs and symptoms is given in the evidence review.

100	Royal College of General Practitioners			General	Local resistance patterns are not mentioned nor is there are commendation that PHLS publishes these on a frequent basis but the evidence from Cardiff is that this works in using an antibiotic that works	Thank you for your comment. The committee discussed your comment and added a recommendation to: take account of local antimicrobial resistance data when prescribing antibiotic treatment.
101	Royal College of General Practitioners			General	Nitrofurantoin when no egfr available- to use or not in the elderly? In reality little harm is apparent and trimethoprim can cause acute kidney injury in this group quite commonly with sharp rises in potassium should it be measured	Thank you for your comment. NICE uses the BNF for appropriate use and dosing in specific populations, for example renal impairment, and their advice is given.
102	Royal College of General Practitioners			General	Nitrofurantoin liquid is extremely expensive	Thank you for your comment. The committee acknowledged the current high cost of nitrofurantoin liquid and recommended that if 2 or more antibiotics are appropriate, the antibiotic with the lowest acquisition cost should be chosen. A footnote has been added to the antibiotic choice table for children, to note that tablets can be given if the appropriate dose can be achieved and the child or young person is able to swallow tablets.
103	Royal College of General Practitioners			General	It is getting increasingly common to get hospital discharge letters with a diagnosis of urospesis when little evidence of true septic shock and no laboratory evidence of any urinary tract infection.	Thank you for your comment. The remit of this guidance is the management of common infections not diagnosis, and further details on the diagnosis of urosepsis is out of scope.
104	Royal College of Pathologists	Guideline	General	General	All five guidelines have insufficient discussion on the diagnosis of urinary tract infections. All five guidelines start with an assumption that a correct clinical diagnosis of UTI has been made. In practice, this aspect of UTI management is probably the most problematic.	Thank you for your comment. The remit of this guidance is the management of common infections not diagnosis, and further details on diagnosis is out of scope. The guidelines start from the point that a diagnosis has been made.
105	Royal College of Pathologists	Guideline	4	1.1.14 1.1.15	Advice to patients should include advice on recognising allergic reactions and the advice that resistance may	Thank you for your comment. The committee discussed the comment

					develop as a consequence of antibiotic use that could compromise the effectiveness of future treatment	and made no changes to the recommendation. The safety section includes advice on allergic reactions, and non-penicillin options, for example, are given in the antibiotic choice tables. Resistance has been considered by the committee when recommendations were made.
106	Royal College of Pathologists	Guideline	7	Table 1	The reference to choosing trimethoprim if there is a low risk of resistance is practically difficult to interpret. “Low” is not quantified, and even if it was, it is virtually impossible for prescribers to guess the probability that a particular urine isolate will be trimethoprim sensitive	Thank you for your comment. The committee discussed your comment and made changes to the relevant tables. The tables now include the following footnote: ‘A lower risk of resistance may be more likely if not used in the past 3 months, previous urine culture suggests susceptibility (but this was not used), and in younger people in areas where local epidemiology data suggest resistance is low. A higher risk of resistance may be more likely with recent use and in older people in residential facilities.’