NICE National Institute for Health and Care Excellence

2020 surveillance of urinary tract infection in under 16s: diagnosis and management (NICE guideline CG54)

Surveillance proposal

We propose to update the guideline on urinary tract infection in under 16s: diagnosis and management. The update will focus on symptoms and signs to aid clinical diagnosis of urinary tract infection (UTI).

Reasons for the proposal

We found new evidence covering all sections of the guideline.

Evidence from current surveillance indicates a potential update of the section of the guideline on symptoms and signs to aid clinical diagnosis of UTI. The DUTY study (Hay et al, 2016b) and its associated Health Technology Assessment (HTA: Hay et al, 2016a; Hollingworth et al, 2017) provides important new evidence to indicate which pre-school children should be tested for UTI in primary care, based on symptoms and signs. This evidence suggests potentially important differences from tabulated common signs and symptoms in the current guideline.

The new evidence could potentially underpin a more rigorous and cost-effective approach to indicate which children should undergo urine testing, helping to improve prompt diagnosis and treatment. In developing the current guideline, the committee noted this as a key strategy to prevent renal scarring, chronic kidney disease (CKD) and End-stage Renal Disease (ERD), particularly in infants and young children, in whom the diagnosis can easily be missed.

No update is suggested for other areas of the guideline, relating to: diagnosis; acute management of UTI and prevention of recurrence; imaging tests; surgical intervention; follow-up; and information and advice. Despite some apparent promise for biomarkers in a range of applications, insufficient evidence was found to impact on the recommendations relating to diagnosis. Most of the section on acute management of UTI and prevention of recurrence is now covered by the NICE antimicrobial prescribing guidelines. Insufficient evidence was found to impact on the recommendations on imaging strategy and testing. Evidence appeared broadly supportive of the recommendation against routine surgical intervention. Insufficient evidence was found to impact on the recommendations relating to follow-up. Minimal evidence found on providing information and advice appeared supportive of the current guideline.

For further details and a summary of all evidence identified in surveillance, see appendix A below.

Overview of 2020 surveillance methods

NICE's surveillance team checked whether recommendations in urinary tract infection in under 16s: diagnosis and management (NICE guideline CG54) remain up to date.

The surveillance process consisted of:

- Feedback from topic experts via a questionnaire.
- A search for new or updated Cochrane reviews and national policy.
- Consideration of evidence from previous surveillance.
- Examining related NICE guidance and quality standards and NIHR signals.
- A search for ongoing research.
- Examining the NICE event tracker for relevant ongoing and published events.
- Literature searches to identify relevant evidence.
- Assessing the new evidence against current recommendations to determine whether or not to update sections of the guideline, or the whole guideline.
- Consulting on the proposal with stakeholders (this document).

For further details about the process and the possible update decisions that are available, see ensuring that published guidelines are current and accurate in developing NICE guidelines: the manual.

Evidence considered in surveillance

Search and selection strategy

We searched for new evidence related to the whole guideline, through separate searches for diagnosis of UTI, management, and follow-up.

We found 84 included studies in a search for suitable evidence in each area as specified below, published between 3 Dec 2015 and 31 Aug 2019. The following study types were included:

- Sections on diagnosis: diagnostic accuracy studies, randomised controlled trials (RCTs) and systematic reviews;
- Management sections: RCTs and Cochrane systematic reviews;
- Sections on follow-up: cross-sectional and cohort studies;

We also included:

- 3 relevant studies identified by topic experts;
- 37 studies identified by search in previous surveillance in 2010, 2013 and 2016.

From all sources, we considered 125 studies to be relevant to the guideline.

See appendix A below for details of all evidence considered, and references.

Selecting relevant studies

Studies were selected in accordance with criteria used for the guideline. Studies on biomarkers as an alternative to imaging for detection of vesicoureteric reflux (VUR) or late renal scarring were included as new areas not currently covered by the guideline.

Ongoing research

Relevant ongoing research was identified including a study investigating probiotic prophylaxis to prevent recurrence of UTI. We will monitor this research and consider results for impact on the guideline when available.

Intelligence gathered during surveillance

Views of topic experts

We considered the views of topic experts who were recruited to the NICE Centre for Guidelines Expert Advisers Panel to represent their specialty. For this surveillance review, topic experts completed a questionnaire about developments in evidence, policy and services related to the guideline.

We sent questionnaires to 10 topic experts and received 6 responses. Responding topic experts included a professor of paediatric nephrology, a consultant neonatologist, microbiologist and paediatric nephrologists, and a general practitioner with special interest in infections.

Four topic experts thought the guideline should be updated, one that it should not be updated, and one did not comment on the need to update. Suggested reasons for update included a general comment that new evidence has been produced in this area; and specific pointers to evidence on UTI symptoms, a Cochrane review on interventions for children with VUR and related RCTs.

Key points highlighted in topic expert feedback included:

- Evidence was highlighted from the DUTY study on symptoms and signs of UTI, including that fever may not be as important a sign as previously thought, and that malodorous urine is more important. This evidence has informed a surveillance proposal to update the relevant section of the guideline.
- An observation that, for teams that have not moved to primary boric acid containers for collection, many urines will grow bacteria due to contamination and delay in transit. This could result in overdiagnosis and potentially drive poor antibiotic stewardship and antimicrobial resistance. Surveillance considered this was an implementation issue outside the scope of the NICE guideline.

- A suggestion that laboratory and clinician interpretation of urine culture results and their accompanying notes, e.g. on method of urine collection, should be detailed in the current guideline. Whilst this may be helpful, surveillance considered this was an implementation issue outside the scope of the NICE guideline.
- Concerns over false positive UTI diagnoses, including from urine dipstick testing, leading to unnecessary antibiotic prescriptions, possibly increasing antimicrobial resistance. This was considered as useful intelligence input particularly to the sections on UTI diagnosis.
- New evidence from a Cochrane review on alternative imaging modalities for detecting VUR. This review informed part of the section on imaging following UTI; no update was ultimately proposed for this section based on the available evidence.
- New evidence from an updated Cochrane review on interventions for VUR. This review informed the section on surgical intervention; however, no update was ultimately proposed for this section based on the available evidence.
- A suggestion that the paediatric nephrology community considers that long-term follow up should be carried out for children with even minor unilateral renal scarring following UTI, especially to monitor for potential hypertension. This led to a focused evidence search; no update was ultimately proposed for this section based on the available evidence.

Other sources of information

We considered all other correspondence received since the previous surveillance review.

External correspondence was received from stakeholders including professionals implementing the current guideline, and parents of children affected by UTI:

- A Trust in North East England has conducted an audit suggesting that the NICE imaging schedule following UTI in children misses potentially important clinical issues, compared with the regional schedule used in the North East (based on Guidelines for the Management of Acute Urinary Tract Infection in Childhood - Report of a Working Group of the Royal College of Physicians, 1991). The imaging schedule has been considered as part of the current surveillance, and the Trust's input is considered as part of intelligence discussed in section 1.3 of Appendix A.
- Personal letters were received regarding concerns, mainly from parents, over diagnosis and treatment of children with chronic/recurrent UTI. This has been considered in surveillance, informing the sections on UTI diagnosis, and communication with children and their carers.
- Topic experts highlighted, during the previous surveillance review, ongoing research on the value of C-reactive protein (CRP) and procalcitonin (PCT) in diagnosing acute febrile UTI. Evidence on CRP, PCT and other biomarkers has been considered in the current surveillance review, for localising UTI as upper or lower, as well as in other applications.

Views of stakeholders

Stakeholders are consulted on all surveillance reviews except if the whole guideline will be updated and replaced. Because this surveillance proposal is to update a single section of the guideline, we are consulting with stakeholders.

See ensuring that published guidelines are current and accurate in developing NICE guidelines: the manual for more details on our consultation processes.

Equalities

No equalities issues were identified during the surveillance process.

Overall surveillance proposal

After considering all evidence and other intelligence and the impact on current recommendations, we propose that an update is necessary.

Appendix A: Summary of evidence from surveillance

2020 surveillance of urinary tract infection in under 16s: diagnosis and management (2007) NICE guideline CG54

Summary of evidence from surveillance

Studies identified in searches are summarised from the information presented in their abstracts.

Studies focusing on antibiotic treatment of urinary tract infection (UTI) were excluded, since these now fall under the remit of 3 antimicrobial prescribing guidelines (APGs) for UTI. These are: NICE guideline NG109 on Urinary tract infection (lower): antimicrobial prescribing; NICE guideline NG111 on Pyelonephritis (acute): antimicrobial prescribing; and NICE guideline NG112 on Urinary tract infection (recurrent): antimicrobial prescribing.

Feedback from topic experts was considered alongside the evidence to reach a view on the need to update each section of the guideline.

For diagnostic test accuracy studies, numerical values are provided in the summaries for any or all of: sensitivity, specificity, area under the curve (AUC), and positive or negative likelihood ratios (LR+ / LR-), together with their 95% confidence intervals - where available from the study abstracts. In the impact statements, which examine usefulness of the tests including their potential addition to or substitution for currently recommended tests, diagnostic test parameters are described based on the most relevant abstract information. Sensitivity and/or specificity are described as either high, moderate or low. Descriptions may also be based on the level of diagnostic evidence provided, based on some combination of sensitivity and specificity, AUC or LR +/LR-. Tests may be described as very useful, moderately useful or not useful. Where applicable, diagnostic accuracy of the test under consideration is compared with that of the currently recommended test.

1.1 Diagnosis

Symptoms and signs

Surveillance proposal

This section of the guideline should be updated.

Previous surveillance summary

Previous surveillance identified 2 studies focusing on symptoms and signs to inform a decision about whether the next step to take is diagnosis, evaluating: UTI risk factors in

general (Finnell et al, 2011); and association of malodorous urine with UTI (Gauthier et al, 2012).

A technical report (Finnell et al, 2011) for the American Academy of Pediatrics (AAP) UTI guideline for children aged 2 to 24 months suggested that risk factors among children with fever may differ slightly between boys and girls, and that risk of UTI appears to increase with number of risk factors present. Risk factors identified by the report (fever lasting >24 hours, temperature >38°C) were considered consistent with those listed within NICE guideline CG54.

A Canadian prospective, consecutive cohort study (Gauthier et al, 2012) (n=396) examined association of parental reporting of malodorous urine with UTI, in children aged between 1 and 36 months (median age 12 months). Included were children presenting to the emergency department of a paediatric hospital suspected of UTI, based on unexplained fever, irritability or vomiting. Parents completed a standardised symptoms questionnaire, including on vomiting, gastrointestinal symptoms, pain on urination, and strength and offensiveness of urine smell. Of 331 children in the final analysis, 51 (15%) had a UTI. Malodorous urine was reported in 57% of children with UTI / 32% without. Logistic regression analysis indicated malodorous urine was associated with UTI: OR=2.83 (95%CI = 1.54 to 5.20). For detecting UTI, parental report of malodorous urine had sensitivity 0.57 (95%CI = 0.42 to 0.70), specificity 0.68 (95%CI = 0.62 to 0.74).

This evidence suggests that parental reporting of malodorous urine may increase probability of UTI among young children being assessed for suspected UTI; however, low sensitivity and specificity prevent firm diagnosis. These results were considered consistent with current NICE guideline CG54 recommendations, which recognises offensive urine as one of the less common signs and symptoms of UTI. However, a much higher proportion (57%) of children having malodorous/offensive urine was found in Gauthier et al (2012) than in the evidence for the current guideline: for which all studies found a proportion <20%.

Previous surveillance reviews concluded that the new evidence was unlikely to impact on current recommendations.

2020 surveillance summary

Two studies with 3 relevant publications were identified through the current surveillance review relating to signs and symptoms of UTI: a UK primary care multi-centre prospective diagnostic cohort study (the DUTY study: Hay et al, 2016b); and a related Health Technology Assessment (HTA: Hay et al, 2016a; Hollingworth et al, 2017).

The DUTY study (Hay et al, 2016b) (n=7,163 children aged under 5 years, presenting as unwell in NHS primary care, of whom 2,740 provided a cultured clean-catch urine sample) developed symptom-/sign-based algorithms to identify those children with higher likelihood of UTI for further diagnostic testing. The comparator was clinical judgement.

Other data from the DUTY study informed the 2017 partial guideline update on urine dipstick testing for children aged under 3 years. In addition to symptoms and signs, the DUTY

study assessed urine dipstick testing as an intermediate diagnosis step to inform antibiotic treatment, compared with requesting a urine culture directly, for children considered at intermediate risk of UTI based on the clinical algorithms.

From 2,740 clean-catch samples for which urine culture was available, 60 (2.2%) were UTI positive. Seven symptoms and signs were found to be independently associated with UTI: previous UTI; increasing pain/crying on passing urine; increasingly smelly urine; absence of severe cough; increasing clinician impression of severe illness; abdominal tenderness on examination; and normal findings on ear examination. These informed algorithms to predict UTI likelihood and inform subsequent testing: a coefficient-based algorithm using all 7 symptoms and signs; and a simplified points-based algorithm using the first 5 only. Validated AUC for the coefficient- and points-based algorithms for detecting UTI were 0.87 and 0.86, respectively; compared with 0.77 for clinical diagnosis, with sensitivity 46.6%. Adding dipstick nitrites, leukocytes, and blood increased both the coefficient- and points-based algorithm AUCs to 0.90.

The related Health Technology Assessment (HTA) (Hay et al, 2016a; Hollingworth et al, 2017) synthesised results from the DUTY study with the wider literature. Based on the developed algorithms from the DUTY study, the HTA modelled and assessed cost-effectiveness of different scenarios for selecting young children presenting in primary care for UTI diagnostic testing and potential antibiotic treatment. For 7 diagnostic strategies using different levels of sensitivity versus specificity, the HTA estimated short-term and lifetime costs and healthcare outcomes: symptomatic days, recurrent UTI, and QALYs.

GP's clinical judgement was compared with 3 diagnostic strategies based on a 'coefficient score' combining all 7 (parent-reported) symptoms and (clinical) signs, and with 4 strategies based on weighted scores using the first 5 symptoms and signs. The 'DUTY 5%' strategy, sampling approximately 5% of children based on 7 symptoms/signs, had the highest specificity of the coefficient-based approaches. The 'DUTY≥3' strategy, sampling children presenting with 3 or more points based on 5 symptoms/signs, had the highest sensitivity of the weighted score-based approach.

DUTY study GPs reported a working diagnosis of UTI in 9.1% of children using clinical judgement, with sensitivity 56.4% to detect children with culture confirmed UTI. Using the modelled strategies enabled increased specificity or sensitivity compared with clinical judgement, depending on which strategy was chosen. Using the 'DUTY 5%' strategy, urine sampling could be approximately halved, to sample 4.8% of children, while maintaining sensitivity at 58.2%. The more sensitive 'DUTY 10%' strategy samples a similar proportion (9.6%) of children as clinical judgment, with sensitivity 70.9%. The most sensitive DUTY clinical rules ('DUTY 20%' and 'DUTY≥3') achieved sensitivities in excess of 80%, though with large increases in urine sampling (19.9% and 26.4%, respectively). Sensitivity of each strategy was reduced by laboratory culture, due to imperfect diagnostic accuracy of NHS laboratories.

Sampling, culture and antibiotic costs were lowest in the high-specificity DUTY strategies (£1.08 for 'DUTY≥6' and £1.22 for 'DUTY 5%') compared to clinical judgement (£1.99). Outcomes were very similar across all diagnostic strategies. To estimate cost-effectiveness,

the authors used Incremental Net Monetary Benefit (iNMB) as an alternative to Incremental Cost-Effectiveness Ratio (ICER): positive iNMB indicates an intervention is cost-effective compared with an alternative at a given willingness-to-pay threshold (in this case £20,000/QALY). High-specificity DUTY strategies were more cost-effective than clinical judgement in both the short- (iNMB = £0.78 for 'DUTY 5%' and £0.84 for 'DUTY≥6') and long-term (iNMB = £2.31 for 'DUTY 5%' and £2.50 for 'DUTY≥6').

Intelligence gathering

During the stakeholder consultation for the 2017 partial guideline update focusing on urine dipstick testing for children aged under 3 years, a consultee commented that the main issue faced by GPs is deciding which children need to have a urine sample taken, and that this remained unclear in the guideline. Relating with this, some children with UTI may be missed through not obtaining a urine sample, perhaps because UTI was not suspected due to non-specific symptoms and signs. The consultee asked whether the consequences of these missed diagnoses had been considered. The guideline developer confirmed that children not suspected of having a UTI (and therefore not tested) fell outside the scope of the partial update, whilst also acknowledging urine samples not being obtained due to non-specific symptoms and signs as an important issue.

A topic expert, during current surveillance, suggested to review the DUTY study publications for their findings on UTI symptoms in pre-school children, noting a move away from fever toward offensive urine as a predictor of UTI. Previous surveillance had identified the DUTY study as important ongoing research which might affect guideline recommendations when published, potentially addressing a research recommendation: 'Combined population-based studies in primary and secondary care, with larger sample sizes, are needed to evaluate the association between symptoms and signs and UTI.'

We identified external guidance developed by Public Health England covering UTI diagnosis in primary care (PHE, 2019b). During stakeholder consultation on the draft guidance, a consultee noted that the DUTY algorithm for UTI diagnosis in primary care may improve management compared with usual care, though it has not been externally validated. In their response, PHE reinforced the need to follow NICE guideline CG54.

Some parental feedback was also received, indicating potential long-term harm in children proceeding to recurrent/chronic UTI through not receiving timely diagnosis and treatment. This may relate to poor recognition of signs and symptoms, as well as potentially false negative urine dipstick testing, both leading to missed diagnoses. Management of asymptomatic/recurrent infections is covered in the related APG on recurrent UTI.

Impact statement

A large multi-centre prospective diagnostic cohort study focusing on pre-school children in NHS primary care (DUTY study) found that clinical rules developed from the study data may have higher predictive power than clinical judgement alone, to indicate which children presenting in primary care should undergo urine testing, based on symptoms and signs. The clinical rules can be varied depending on preference for high sensitivity or specificity, with

high specificity strategies being more cost-effective than clinical judgement in both the short- and long-term.

The current guideline is based on evidence from case series studies in secondary/tertiary care, on observed frequency of various symptoms and signs in children with UTI.

A topic expert indicated that the DUTY study provides important results for assessing UTI based on symptoms and signs for the pre-school age group, including that fever may not be as important as previously thought; and that other symptoms/signs thought to be less consequential (such as offensive urine) may be more predictive of UTI. The DUTY study provides additional evidence on symptoms and signs for UTI, to help address the research recommendation posed in the current guideline.

Evidence from previous surveillance also suggests that offensive urine may be a better predictor than was considered when the guideline was originally developed. However, in isolation it can provide only low diagnostic accuracy for UTI.

Whilst data from the DUTY study has informed the current guideline through the 2017 partial guideline update, the update focused on urine testing for children aged <3 years, with other aspects including UTI symptoms and signs being out of scope.

The current guideline focuses on frequency of various symptoms and signs for children with UTI as an aid to clinical judgement, listing them from most to least common for three different age groups. The full guideline notes that this approach is based on limited evidence, with low predictive power for UTI, and makes a research recommendation to address this evidence gap.

In developing the current guideline, the committee further noted that the most important strategy to prevent renal scarring, chronic kidney disease (CKD) and End-stage Renal Disease (ERD) is prompt diagnosis and treatment of UTI, particularly in infants and young children, in whom the diagnosis can easily be missed. The new surveillance evidence indicating which symptoms and signs are predictive of UTI, particularly for pre-school children presenting in primary care, could potentially provide a more rigorous and cost-effective approach to indicate which children should undergo urine testing.

A potential limitation of the current surveillance evidence is lack of external validation of the developed clinical rules. However, this must be balanced against the very limited nature of evidence informing the current guideline. Another potential limitation is the relatively low numbers of positive urine cultures (n=60), which is reflective of the relatively low prevalence of UTI for children presenting in primary care. The authors discussed potential bias of clinicians toward higher index of suspicion for UTI in the study, suggesting this would, if anything, have tended to reduce superiority of the developed symptoms-/signs-based algorithms as a diagnostic tool compared with clinical judgment.

Further evidence from current surveillance, on symptoms and signs to assess likelihood of UTI and indicate further testing, may help improve prompt diagnosis and treatment. The new evidence may impact on recommendations.

New evidence identified that may change current recommendations.

Assessment of risk of serious illness

Surveillance proposal

This section of the guideline should not be updated.

Previous surveillance summary

No relevant evidence was identified.

2020 surveillance summary

A single study (Urbane et al, 2019) was found of relevance to NICE guideline NG143 on Fever in under 5s: assessment and initial management, to which the current guideline now cross-refers. This study will be considered at the next surveillance review of NG143.

Intelligence gathering

NICE guideline CG54 recommends that, for children presenting with a fever, illness level should be assessed in line with the NICE guideline on Fever in under 5s: assessment and initial management (NG143).

A query was received on how Fever in under 5s: assessment and initial management should be interpreted, in deciding whether a child has 'atypical UTI' due to being 'seriously ill' for the purpose of commencing the imaging schedule in section 1.3 of NICE guideline CG54. The enquirer noted two potential challenges in judging whether a child is considered 'seriously ill': the risk-based 'traffic-light' approach to assessing whether a child is seriously ill does not include definitive thresholds; and, since NICE guideline NG143 applies specifically to children aged under 5, symptoms and signs of serious illness may be different for older children. An element of clinical judgment is therefore required in making the assessment.

Impact statement

The recommendation in this section has been superseded by NICE guideline NG143 on Fever in under 5s: assessment and initial management, to which it fully cross-refers. No impact on the current recommendation is therefore anticipated from this surveillance review.

This section of the guideline should not be updated.

Urine collection

Surveillance proposal

This section of the guideline should not be updated.

Previous surveillance summary

Previous surveillance identified 13 studies focusing on urine collection to inform initial and confirmatory UTI diagnosis. Studies covered: related practices including pre-cleansing; contamination and diagnostic accuracy; patient impact; success, and technicality of using different urine collection methods.

Pre-cleansing before sampling

2 studies investigated pre-cleansing of the child (perineal/genital cleaning) as a potential way to reduce sample contamination:

An RCT (Vaillancourt et al, 2007) (n=350 toilet-trained children aged 2 to 18 years presenting in the emergency department of a tertiary care paediatric centre in Quebec, Canada) evaluated the effect on sample contamination of pre-cleansing of the child's perineal/genital region before mid-stream urine (MSU) collection, versus no pre-cleansing. Pre-cleansing reduced both contamination rates and the likelihood of a positive urinalysis.

Al-Farsi et al (2009) compared sterile water with povidone-iodine for cleaning the periurethral area prior to catheterisation, finding no significant difference in urine positive cultures between the alternative cleansing agents.

Contamination and diagnostic accuracy

Eight studies compared contamination rates and/or diagnostic accuracy for various sampling methods, including a technical report from the American Academy of Pediatrics (AAP) UTI guideline for children aged 2 to 24 months, and a report supporting WHO recommendations for paediatric urine sampling in less-developed countries.

A single study (Karacan et al, 2010) evaluated urine collection methods for UTI diagnosis in children, finding that suprapubic aspiration (SPA) had the lowest contamination rate; urine bag the highest. A technical report (Finnell et al, 2011) from the AAP UTI guideline for children aged 2 to 24 months discussed methods of urine collection, recommending that urine specimens for culture should only be obtained via catheterisation or suprapubic aspiration. Consideration was given to specificity, sensitivity, and difficulty in collecting samples. Cost-effectiveness was not analysed.

Three studies focused on clean-catch sampling. A retrospective observational cohort study (Tosif et al, 2012) (n=599 children aged <2 years) found higher contamination rates for clean-catch urine (CCU) samples compared with catheter specimen urine (CSU) and suprapubic aspiration (SPA): clean catch urine (CCU) 26%; catheter specimen urine (CSU) 12% (OR: 0.4 [95%CI = 0.2 to 0.8]); suprapubic aspiration (SPA) 1% (OR: 0.03 [95%CI = 0.0 to 0.3]. Lau et al (2007) compared clean void technique with catheterisation, finding both prone to contamination, with a high false positive rate. Long and Vince (2007) reviewed evidence for the WHO urine collection guidelines for less-developed countries, which recommend clean-catch urine (CCU).

Three studies focused on urine bag collection (which NICE guideline CG54 advises against using). Etoubleau et al (2009) compared bag with catheterised cultures, concluding that bag

positives should be confirmed with a more reliable method before treatment. Hosseini et al (2009) compared bag with SPA, finding higher contamination rates with bag. Perlhagen et al (2007) assessed specificity of a new type of urine bag, concluding that further study was required.

Success and patient impact

Two studies compared catheterisation and suprapubic aspiration (SPA). Tosif et al (2012) indicated that urine sampling via catheterisation may be associated with a higher success rate, and less pain, than SPA. El-Naggar et al (2010) compared infant pain responses for SPA and catheterisation in an RCT, finding that SPA was more painful.

Ultrasonography to aid invasive urine collection

Two studies examined volumetric bladder ultrasonography as an aid to catheterisation. Baumann et al (2007), studying caregiver and health care provider satisfaction, found this method was preferred compared with conventional catheterisation. Baumann et al (2008) found significantly improved success in obtaining a urine sample with this method, although there was a time delay.

No information was available from previous surveillance on cost-effectiveness of different urine collection methods.

None of the evidence identified from previous surveillance was considered to impact on the recommendations.

2020 surveillance summary

Seven studies were identified on urine collection methods, and ancillary aspects, to inform initial and confirmatory UTI diagnosis:

Pre-cleansing before sampling

A prospective study (Marzuillo et al, 2018) (n=612 children attending a nephrourological outpatient clinic, age not stated) evaluated the impact of cleaning the genital area with plain water on urine dipstick false positive rates, together with factors associated with false positive findings. Both toilet-trained and non-toilet-trained children were included. Samples were collected via urine bag. The reference test was a (second) urine dipstick test following cleaning with water, with each child acting as their own control. Each child had a first urine dipstick test, before cleaning with water and taking a second sample. The first test was considered a false positive if it was positive, but the second (reference) test was negative.

False positive urine dipstick samples were found in 22.9% of non-toilet-trained children, and 26.6% of toilet-trained children (p=0.37, average 25.5%). Factors leading to significantly increased risk of false positive were non-retractable foreskin, and female gender.

Clean-catch sampling method

A prospective observational study (Tosif et al, 2017) (n=247 clean-catch urine sampling attempts, in 217 pre-continent children aged 2 to 48 months in an emergency department)

aimed to determine the time taken for clean-catch urine (CCU) collection attempts, and the 'success' of this collection method in diagnosing/excluding UTI (reference test urine culture). For first CCU collection attempt, median collecting time taken to urine collection was 30.5 min (IQR = 11 to 66 min). Outcome was 'successful' (voided and caught) for 64% of attempts (95% CI = 58 to 70%), 'missed' (voided not caught) for 16% (95% CI = 11 to 20%), and 'stopped' for 20% (95% CI = 15 to 26%). Median time for 'successful' attempts (n=160 children, of which 129 sent for culture) was 25 min (IQR = 7 to 46.5min); for 'missed' 27 min (IQR = 11.6 to 59 mins); and 71 min (IQR = 42.5 to 93min) when 'stopped'. Of the 129 cultures, 50 (39%) were contaminated. The authors estimated that, if all urine specimens caught were sent for culture, estimated yield of an uncontaminated urine specimen would be 45%.

Techniques to assist in obtaining clean-catch samples

An RCT (Kaufman et al, 2017) (n=354 infants aged 1 to 12 months in an Australian tertiary paediatric hospital emergency department requiring urine sample) assessed a technique of gentle suprapubic cutaneous stimulation with a cold moist gauze ('Quick-Wee' method) to obtain a clean-catch sample. Infants were randomised to either Quick-Wee (n=174) or standard clean-catch urine (n=170) for 5 minutes, measuring voiding within 5 minutes, successful urine sample collection, contamination rate, and patient and clinician satisfaction.

Quick-Wee resulted in: higher rate of voiding within five minutes compared with standard clean catch urine (31% vs 12%, 95% CI for difference = 11% to 28%, P<0.001); higher rate of successful urine sample collection (30% v 9%, P<0.001); greater parental and clinician satisfaction (median 2 vs 3 on 5 point Likert scale, P<0.001). Difference in contamination between Quick-Wee and standard clean catch urine was not significant (27% vs 45%, P=0.29). Number needed to treat was 4.7 (95% CI = 3.4 to 7.7) to successfully collect one additional urine sample within five minutes using Quick-Wee compared with standard clean catch urine.

A diagnostic accuracy study (Herreros et al, 2018) (n=60 pairs of matched samples from infants <90 days old with unexplained fever in a Madrid hospital emergency room) evaluated the clean-catch method versus bladder catheterisation. For clean-catch samples obtained using standardised stimulation technique, leukocyte esterase (LE) and/or nitrites combined had sensitivity 86% and specificity 80% for diagnosing UTI (reference test urine culture). For samples obtained by catheterisation, sensitivity for LE and/or nitrites combined was not significantly different to the clean-catch samples (p=0.59). Specificity was not reported in the abstract.

A cross-sectional study (Tran et al, 2016) (n=142 infants under walking age who required a urine sample, in the emergency department of a children's hospital in France) assessed a technique based on bladder stimulation and lumbar stimulation manoeuvres to obtain a clean-catch urine sample in infants. At least two attempts were made; success rate and time to obtain urine sample within 3 minutes were evaluated. Discomfort (EVENDOL score ≥4/15) was measured, and risk factors in the failure of the technique were evaluated using a multivariate logistic regression model. Midstream clean-catch urine samples were obtained in

55.6% of infants, median time 52.0s. Success rate decreased with age from 88.9% (new-born) to 28.6% (>1 year) (p=0.0001); and with weight, from 85.7% (<4kg) to 28.6% (>10kg) (p=0.0004). Success rate was 60.8% for infants without discomfort (p<0.0001). Heavy weight and discomfort were associated with failure to obtain a sample, with adjusted ORs of 1.47 [1.04 to 2.31] and 6.65 [2.85 to 15.54], respectively.

Nappy pad sampling method

A publication from the DUTY study (Butler et al, 2016) (n=2,277 children aged <5 years, presenting acutely unwell to 233 UK primary care sites, for whom urine culture results were available: n=30 with UTI) focused on sampling using the nappy pad method as part of developing a clinical prediction rule to diagnose UTI. Nappy pad samples were compared with clean-catch samples, and with GP's 'working diagnosis' of UTI, using logistic regression to identify independent associations of symptoms, signs, and urine dipstick test results with UTI. Contamination rates were compared between nappy pad and clean-catch sampling. Female sex, smelly urine, darker urine, and absence of nappy rash were independently associated with UTI, with internally validated, coefficient model Area Under the Curve (AUC) 0.81 for nappy pad samples, compared with 0.87 for clean catch. Adding dipstick results, AUC for nappy pad samples was 0.87, compared with 0.90 for clean catch. In comparison, GPs' 'working diagnosis' of UTI had AUC 0.63 (95% CI = 0.53 to 0.72). In total 12.2% of nappy pad and 1.8% of clean-catch samples were 'frankly contaminated' (risk ratio 6.66; 95% CI = 4.95 to 8.96; P<0.001).

Cost-effectiveness of different urine collection methods

A cost-effectiveness study (Kaufman et al, 2019) (febrile children aged 0 to 24 months requiring urine sample to diagnose/exclude UTI, in an Australian paediatric emergency department) compared cost-effectiveness of both non-invasive (urine bag, clean catch and 5 min voiding stimulation for clean catch – Quick-Wee method as described in Kaufman et al, 2017) and invasive (catheterisation and SPA) urine collection methods. Costs included equipment, staff time and hospital bed occupancy. If initial collection attempts were unsuccessful, subsequent collection using catheterisation was assumed. The final outcome was a 'definitive sample' incorporating progressive dipstick, culture and contamination results.

A cost-effectiveness model was developed, based on RCT-level evidence from a literature review, combined with resource costs collected specifically for this study. Average costs and outcomes were calculated for both initial collection attempts and obtaining a definitive sample. One-way and probabilistic sensitivity analyses were performed. The authors found that, for initial collection attempts, catheterisation had the lowest cost per successful collection (£25.98) compared with SPA (£37.80), voiding stimulation (£41.32), clean catch (£52.84) and urine bag (£92.60). For definitive collection (meaning that sufficient sampling and testing had been done for definitive diagnosis), catheterisation had the lowest average cost per definitive sample (£49.39) compared with SPA (£51.84), voiding stimulation (£52.25), clean catch (£64.82) and urine bag (£112.28). Time occupying a hospital bed was the most significant determinant of cost.

A simulation run 1,000 times, based on variability in the published data used to inform the cost-effectiveness model, obtained average costs per definitive sample: catheterisation £48.60 (95% CI = £33.54 to £131.71); SPA £50.67 (95% CI = £39.72 to £97.93); voiding stimulation (using 'Quick-Wee' method) £51.21 (95% CI = £40.97 to £105.95); clean catch £65.03 (95% CI = £30.27 to £313.48); urine bag £126.43 (£59.92 to £323.38).

Intelligence gathering

Whilst topic experts did not comment specifically on urine collection, a topic expert was concerned about false positive UTI diagnoses, based on testing, leading to potentially unnecessary antibiotic prescribing. Parental concern was also expressed over false negative tests potentially leading to missed UTI diagnoses, though this possibly related more with asymptomatic/recurrent infections.

PHE published guidance on UTI diagnosis in primary care in January 2019 (PHE, 2019b), which is endorsed by NICE, and links with and refers to NICE guideline CG54 where relevant. The public consultation on the PHE guidance included the following feedback which appears may also be relevant for NICE guideline CG54:

- Querying the advice in PHE's Standards for Microbiological Investigations (UK SMI) B41 on Investigation of urine (PHE, 2019a) - that peri-urethral cleaning should be carried out before sampling. It was unclear to which age group the query applied; it may have related mainly with older adults in care homes. In the revised SMI, PHE have maintained a recommendation for pre-cleansing before clean-catch sampling (as would be suitable for precontinent infants and children), whilst removing a similar recommendation for mid-stream urine sampling (as would be suitable for toilet-trained children and most adults)
- Referencing the DUTY study (Butler et al, 2016 and other publications) around nappy pad sampling. In response, PHE have advised use of clean catch urine sampling in infants/toddlers, noting that nappy pads cause more contamination (PHE, 2019b).
- Referencing the 'Quick-Wee' method (Kaufman et al, 2017) to obtain clean-catch urine. In response, PHE have now included a statement in their flowchart for diagnosing UTI in children, recommending suprapubic cutaneous stimulation (as per the Quick-Wee method).

Impact statement

Pre-cleansing before sampling

Current surveillance identified a recent Italian study investigating the effect on contamination of pre-cleansing (of the periurethral area) in pre-continent children. However, this study used urine bag sampling, as recommended as standard practice in continental Europe – which the current guideline advises against.

Evidence from previous surveillance included a Canadian RCT focusing on toilet-trained children. The Canadian RCT is also cited in a systematic review of pre-analytic practices for

urine testing (LaRocco et al, 2016), which forms the basis of American laboratory guidelines. PHE cite this systematic review in advising periurethral cleaning before clean-catch urine collection as part of good laboratory practice in Standards for Microbiology Investigations (SMI) B41 (PHE, 2019a).

No evidence on pre-cleansing was identified in the current guideline and therefore, NICE guideline CG54 does not address pre-cleansing to potentially reduce contamination rates.

Pre-cleansing may be considered to form ancillary technical information to support sampling methods recommended in the current guideline. For this purpose, guidance such as UTI diagnosis in primary care (PHE, 2019b) and Standards for Microbiology Investigations (SMI) B41 (PHE, 2019a) can provide a suitable medium.

The new and cumulative evidence is therefore not expected to impact on recommendations.

New evidence is unlikely to change guideline recommendations.

Clean-catch sampling method

From current surveillance, a large UK multi-centre prospective diagnostic study (DUTY study) found that clean-catch urine collection had lower contamination rates and was more diagnostically accurate than nappy pad sampling for pre-school children presenting in primary care, and appeared likely to be more cost-effective when integrated into diagnostic strategies.

Limited evidence was found on cost-effectiveness of clean-catch urine collection for infants aged <1 year, from an Australian study in secondary care. Clean catch, especially when used with a voiding stimulation technique ('Quick-Wee'), cost less per sample than urine bag sampling in this setting. Clean catch collection, especially when used with the voiding stimulation technique, was estimated to cost only slightly more per sample than either of the invasive methods, suprapubic aspiration (SPA) or catheterisation (which had the lowest cost/sample). The higher cost was due to additional hospital bed time required for unsuccessful clean-catch attempts. However, predicted cost per sample was uncertain for all methods, with transferability of results to a UK setting also unclear. Furthermore, the child's quality of life and pain experienced, and parental preference, together with possible harms from invasive sampling methods, were not explicitly considered.

An Australian emergency department study indicated that, for pre-continent children, clean-catch sampling may lead to high rates of contamination, be time-consuming, and be frequently unsuccessful in obtaining a sample. A Spanish emergency department study indicated moderately useful UTI diagnostic accuracy for clean-catch sampling (using a voiding stimulation technique) when paired with urine dipstick testing for young infants aged <3 months, with sensitivity comparable to (invasive) catheterisation.

Previous surveillance evidence indicated that clean-catch urine (CCU) samples had higher contamination rates compared with invasive catheter specimen urine (CSU) and SPA samples. The current guideline included evidence from a study on caregiver preferences for collecting

urine from pre-continent children at home. Most caregivers found the clean-catch method time-consuming and often messy, with some giving up after prolonged attempts.

No specific intelligence was received on clean-catch sampling, although stakeholder response to the PHE guidance on UTI diagnosis in primary care (PHE, 2019b) mentioned higher contamination rates of nappy pad sampling compared with clean-catch.

Whilst the current guideline recommends clean catch urine sampling as the first-choice method for urine collection, or suitable alternative non-invasive methods if clean-catch is unobtainable, it provides flexibility to choose invasive urine collection methods, recommending catheter samples or suprapubic aspiration (SPA) if non-invasive methods are not possible or practical. This would normally be in a secondary (or tertiary) care setting, where a child would tend to present as more unwell, and where required equipment and expertise is available. Limited evidence was identified for clean-catch sampling combined with dipstick testing in ruling out UTI in infants aged <3 months, before potentially using more invasive collection methods and/or urine culture.

Cumulative evidence from current and previous surveillance suggests that clean-catch sampling remains the most accurate non-invasive method for urine collection. The evidence appears consistent with current guideline recommendations, and no impact is expected on recommendations.

New evidence is unlikely to change guideline recommendations.

Techniques to assist in obtaining clean-catch samples

An Australian emergency department study, augmented by a cost-effectiveness study, found that a voiding stimulation technique ('Quick-Wee') improved success rate, cost-effectiveness and patient/caregiver satisfaction for clean-catch sampling in infants aged <1 year. This technique requires a single operator such as a health care professional, or a caregiver with suitable instruction.

Emergency department studies from France and Spain assessed a different voiding stimulation technique intended to help obtain clean-catch samples for infants aged <3 months. The technique, which requires three trained operators, was less successful in obtaining a sample with increasing infant age.

No evidence on techniques to enhance clean-catch urine collection was identified as part of the current guideline, and no evidence was found in previous surveillance.

PHE now recommend the 'Quick-Wee' technique to aid clean-catch sampling within their guidance on UTI diagnosis in primary care (PHE, 2019b).

The current guideline does not address potential techniques to inform or enhance clean-catch urine collection. Such techniques may be considered to form ancillary technical information to support sampling methods recommended in the current guideline. For this purpose, guidance such as UTI diagnosis in primary care (PHE, 2019b) can provide a suitable medium, adding useful operational detail to complement the current guideline.

The new and cumulative evidence is not therefore expected to impact on recommendations.

New evidence is unlikely to change guideline recommendations.

Nappy pad sampling method

Evidence from current surveillance indicated that nappy pad sampling has higher contamination rates and lower diagnostic accuracy compared with clean-catch urine collection, while describing it as remaining a 'clinically-useful' sampling method. Evidence from previous surveillance supports the finding that clean-catch sampling is diagnostically superior to nappy pad sampling.

The current guideline included evidence from a study on caregiver preferences for collecting urine from pre-continent children at home. Caregivers preferred urine pads (and to a lesser extent urine bags), finding them comfortable and easy to use, though some found extracting urine from the pad awkward.

Consultation feedback on PHE's guidance on UTI diagnosis in primary care (PHE, 2019b) suggested that nappy pad sampling is insufficiently accurate, citing the DUTY study. In response, PHE advise using clean catch urine sampling in infants/toddlers and note that nappy pads cause more contamination (PHE, 2019b).

For pre-continent children, the current guideline recommends urine collection pad (nappy pad) sampling as the second line urine collection method after clean-catch sampling, emphasising that manufacturer's instructions must be followed.

Nappy pad sampling, whilst less accurate than clean-catch due to higher contamination rates, may still provide a practicable second-line method more accurate than urine bag collection. This appears consistent with current guideline recommendations.

New evidence is unlikely to change guideline recommendations.

Urine preservation

Surveillance proposal

This section of the guideline should not be updated.

Previous surveillance summary

No relevant evidence was identified.

2020 surveillance summary

No relevant evidence was identified.

Intelligence gathering

A topic expert commented that, for teams which have not moved to primary boric acid containers for collection, urine samples may grow bacteria due to contamination and delay in transit. The topic expert noted that this may contribute to overdiagnosis, which could drive poor antibiotic stewardship and antimicrobial resistance.

Impact statement

No new evidence was found for urine preservation.

The current guideline identified evidence on chemical preservation and refrigeration of urine samples, and the effect of time and temperature on bacterial growth, leading to the current recommendations that samples should immediately be either refrigerated or preserved with boric acid, if they cannot be cultured within 4 hours of collection and noting that manufacturer's instructions should be followed if using boric acid. The guideline also noted that: 'When analysis of urine samples is requested, there is often inadequate explanation of the collection procedure. Various studies have reported that this is a problem in primary care.'

A topic expert drew attention to potential inadequate use of primary boric acid containers for collecting urine, potentially leading to increased false positive results and overdiagnosis.

The topic expert's comment appears consistent with the guideline recommendation which includes use of boric acid as a urine preservative. This would appear to be an operational/implementation issue for the NHS and primary care practices.

No impact is thus anticipated on current recommendations.

New information is unlikely to change guideline recommendations.

Urine testing

Surveillance proposal

This section of the guideline should not be updated.

Previous surveillance summary

The 2016 surveillance review decision was to partially update the guideline, focusing on the subsection on urine testing. This was based on advice from topic experts, together with evidence indicating sufficient accuracy for urine dipstick testing to now be used routinely as an initial diagnostic test for UTI in younger, as well as older, age groups. As a result, new recommendations were published in 2017 for urine dipstick testing as a key initial diagnostic test for UTI in infants aged >3 months and <3 years.

Previous surveillance also identified studies examining other options for urine testing for initial and confirmatory UTI diagnosis. These included: assessment of automated microscopy;

utility of repeat urine cultures; biomarkers including procalcitonin (PCT), C-reactive protein (CRP) and novel biomarkers including IL-8; and bacterial concentration thresholds for diagnosing UTI.

Previous surveillance reviews concluded from these studies that no further changes to recommendations on urine testing would be indicated at this point.

2020 surveillance summary

A total of 18 new studies were identified on urine testing for diagnosing UTI: 17 primary research studies, and one secondary analysis of a prospective study (for point-of-care testing [Tzimenatos et al, 2018]).

Urinalysis, including dipstick testing, point-of-care testing and automated flow cytometry

Urine concentration effects on urinalysis accuracy

A retrospective cross-sectional study (Chaudhari et al, 2017) (n=14,971 children aged <13 years, median age 1.5 years in an emergency department) assessed whether urinalysis performance for detecting UTI varies with urine concentration, measured by specific gravity. Urinalysis results were based on presence of leukocyte esterase (LE) by urine dipstick, together with microscopic pyuria. The reference test was urine culture. With increasing specific gravity (i.e. moving from most dilute to most concentrated urine), positive likelihood ratios for urinalysis decreased, from 12.1 to 4.2, and negative likelihood ratios increased (data not given) indicating that urinalysis test performance is affected by urine concentration and improves as urine becomes more dilute.

Urinalysis in young infants comparing different definitions of a positive UTI culture

A secondary analysis from a prospective study (Tzimenatos et al, 2018) (n=4,147 febrile infants aged <=60 days at 26 emergency departments) evaluated test characteristics of urinalysis for diagnosing UTIs, with and without associated bacteraemia. Two definitions of UTI were used: growth of >=50,000 or >=10,000 colony-forming units (CFUs)/mL of a uropathogen. Positive urinalysis was defined by presence of any leukocyte esterase, nitrite, or pyuria (>5 white blood cells per high-power field).

For UTIs with colony counts >=50,000 CFUs/mL (n=289, including 27 with bacteraemia) urinalysis had sensitivity: overall 0.94 (95%CIs: 0.91-0.97); 1.00 (95%CIs: 0.87-1.00) with bacteraemia; 0.94 (95%CIs: 0.90-0.96) without bacteraemia. Specificity was 0.91 (95%CIs: 0.90-0.91) for all groups.

For UTIs with colony counts >=10,000 CFUs/mL, urinalysis had sensitivity 0.87 (95%CIs: 0.83-0.90) and specificity 0.91 (95% CIs: 0.90-0.92).

Urine dipstick testing

Children under 16

A retrospective review (Maduemem et al, 2019) (n=262 children aged under 16, median age 0.79 years [range 0.02 to 15.95 years], with positive urine culture) evaluated sensitivity of dipstick urinalysis and microscopy for diagnosing UTI. Reference test was urine culture.

Nitrite, blood, and leukocyte esterase (LE) had sensitivities of 0.54 (95%CIs = 0.46 to 0.62), 0.74 (95%CIs = 0.68 to 0.80), and 0.86 (95%CIs = 0.82 to 0.91), respectively. Pyuria, based on >=100 cells/mm3, had sensitivity of 0.92 (95%CIs = 0.89 to 0.95). Using presence of any of the three dipstick parameters increased sensitivity to 0.97 (95% CIs = 0.95 to 0.99). Lowest sensitivity was 0.49 (95% CIs = 0.40 to 0.58), for combined positive LE and nitrite. There was a significant association between positive LE dipstick test and pyuria (P = 0.000004). Specificity and AUC were not reported.

Younger infants

A study (Herreros et al, 2018) (n=60 pairs of matched samples from infants <90 days old with unexplained fever in a Madrid hospital emergency room) evaluated the clean-catch method versus bladder catheterisation. For clean-catch samples obtained using standardised stimulation technique, leukocyte esterase (LE) and/or nitrites combined had sensitivity 86% and specificity 80% for diagnosing UTI (reference test urine culture). For samples obtained by catheterisation, sensitivity for LE and/or nitrites combined was not significantly different to the clean-catch samples (p=0.592).

Point-of-care dip testing, and automated flow cytometry

Children aged under 18 years

A retrospective chart review (Malia et al, 2017) (n=334 children aged under 18 presenting to a paediatric emergency department) assessed whether point-of-care (POC) dip testing is as accurate as laboratory urinalysis (UA) in UTI diagnosis. Urine culture was the reference test. A positive POC dip was defined as having positive leukocyte esterase (LE) or presence of nitrites. A positive lab urinalysis (lab UA) was defined as having positive LE, nitrites, or >10 white blood cells/high power field. The POC dip had sensitivity 91.4% (95%CI = 76.9% to 98.2%) and specificity 63.9% (95%CI = 57.2% to 69.3%). The lab UA had sensitivity 91.4% (95%CI = 76.9% to 98.2%) and specificity 63.9% (95%CI = 58.2% to 69.3%). The lab dip had sensitivity 88.6% (95%CI = 73.3% to 96.8%) and specificity 65.6% (95%CI = 59.9% to 70.9%).

A prospective cross-sectional study (Duong et al, 2016) (n=1,106 children, age not stated, n=1,247 febrile episodes) compared predictive values of flow cytometry and dipstick testing as initial UTI diagnostic tests. Urine culture was the reference test. At optimal cut-off point >=35 WBC/ml of urine, flow cytometry had sensitivity 99.5% and specificity 80.6%, AUC 0.99 (95% CI = 0.98 to 0.99). Urinary WBC counts had significantly higher AUC than for LE dipstick (0.92 [95% CI, 0.90 to 0.94]), nitrite dipstick (0.83 [95% CI, 0.80 to 0.87]), or the combination of positive LE and/or nitrite dipstick (0.91 [95% CI, 0.89 to 0.93]) test (P<0.001). The authors calculated that using the optimal cut-off point would have reduced the number of samples sent to laboratory for culture by 67%. Increasing the cut-off point for flow cytometry to 100 WBC/µl of urine raised specificity to 97%, and reduced sensitivity to 89%.

Children aged under 13 years

A prospective study (Broeren et al, 2019) (n=412 samples from children aged under 13 years, with suspected UTI) investigated test parameters for a specific urine flow cytometry technology (Sysmex UF1000i) in diagnosing UTI, compared to conventional diagnostic

techniques. The reference test was urine culture. Using a cut-off value of 250 bacterial/mul in presence of leukocyturia, flow cytometry had sensitivity 0.97 (NPV 97%), specificity 0.91 (PPV 90%). AUC was 0.97 (95%CI = 0.93 to 1.00) for bacterial count.

Children aged under 2 years

A retrospective cross-sectional study (Chaudhari et al, 2018) (n=2,554 children aged <2 years, median age 6.1 months, tested for UTI in a single large emergency department) evaluated the test performance of microscopic bacteriuria by automated urinalysis, compared with microscopic pyuria, for presumptive UTI in young children. The reference test was urine culture (19% of children tested positive). Automated microscopic bacteriuria >=1+ had LR+ 4.5 (95%CI = 3.9 to 5.2), LR- 0.52 (95%CI = 0.47 to 0.57). Pyuria alone (>=5 WBC/high-power field) had LR+ 4.5 (95%CI = 4.1 to 5.0), LR- 0.14 (95%CI = 0.11 to 0.18). With addition of automated microscopic bacteriuria >=1+, LR+ was 16.3 (95%CI = 12.6 to 21.1), LR- 0.51 (95%CI = 0.47 to 0.56). Automated microscopic bacteriuria had AUC 0.73 (95%CI = 0.70 to 0.76) compared with pyuria AUC 0.92 (95%CI = 0.90 to 0.93).

A retrospective cross-sectional study (Chaudhari et al, 2016) (n=27,000 infants, median age 1.7 months, tested for UTI in emergency department) determined optimal urine white blood cell (WBC) threshold for UTI in young infants when using automated urinalysis, stratified by urine concentration. Reference test was urine culture, with UTI defined as >=50,000 colony-forming units/mL from catheterised specimens (UTI prevalence 7.8%). Test characteristics for automated microscopic urinalysis were calculated across a range of WBC and leukocyte esterase (LE) cut-off points, dichotomized into specific gravity groups (dilute urine sg <1.015; concentrated urine sg >=1.015). WBC had different optimal cut-off points depending on urine concentration: for dilute urine, at cut-off point 3 WBC/high-power field (HPF), LR+ was 9.9, LR- 0.15. For concentrated urine, at cut-off point 6 WBC/HPF, LR+ was 10.1, LR- 0.17. For dipstick analysis, positive LE had: LR+ 22.1, LR- 0.12 in dilute urine; LR+ 31.6, LR- 0.22 in concentrated urine.

Biomarkers for UTI diagnosis

Seven studies were found evaluating novel biomarkers for diagnosing UTI.

Serum/urine neutrophil gelatinase-associated lipocalin (sNGAL/uNGAL) test

A prospective observational study (Krzemien et al, 2018) (n=84 infants, 66 with first UTI episode, 18 healthy controls, age not stated) assessed usefulness of both serum and urinary neutrophil gelatinase-associated lipocalin (sNGAL and uNGAL) to diagnose UTI in febrile and non-febrile infants. On enrolment, sNGAL, uNGAL, urinalysis, urine culture, white blood cell count (WBC), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), procalcitonin (PCT), and serum creatinine (sCr) were assessed. On average, both sNGAL and uNGAL levels were significantly higher in febrile UTI, compared to non-febrile UTI and controls (no data given). Mean sNGAL level, but not uNGAL, was significantly higher in the non-febrile UTI group compared to controls (no data given). sNGAL positively correlated with WBC, CRP, ESR and PCT, and uNGAL with CRP and leukocyturia. For diagnosing febrile UTI, sNGAL with optimum cut-off level 76.2 ng/ml had sensitivity 92.9%, specificity 94.4% (AUC 0.98); uNGAL with cut-off level 42.2 ng/ml had sensitivity 73.8%, specificity 72.2%, and AUC of 0.76. For

diagnosing non-febrile UTI, sNGAL with optimum cut-off level 39.0 ng/ml had sensitivity 83.3%, specificity 55.6% (AUC 0.70); no data provided for uNGAL.

A retrospective study (Jung et al, 2018) (n=422 infants aged <3 months, mean age 56 days, admitted for fever) evaluated diagnostic accuracy of urinary neutrophil gelatinase-associated lipocalin (uNGAL) and beta-2 microglobulin (uB2MG), in early detection of UTI in infants aged <3 months with fever. uNGAL and uB2MG levels were compared between groups with UTI (n=102) and without UTI at time of admission. The reference test was urine culture. Levels of uNGAL were higher in the UTI group than in the non-UTI group (366.6 ng/mL vs. 26.9 ng/mL, P<0.001). Levels of uB2MG were not different between the 2 groups. Multivariate analysis showed uNGAL as an independent predictive factor for UTI (P=0.033). For detecting UTI, uNGAL had sensitivity 90.2%, specificity 92.5%, and accuracy 91.9% (AUC=0.942). uB2MG had sensitivity 48.0%, specificity 43.8%, and accuracy 44.8% (AUC=0.407).

A prospective cross-sectional study (Lubell et al, 2017) (n=260 infants and children aged <=24 months) assessed the accuracy of urinary neutrophil gelatinase-associated lipocalin (uNGAL) to diagnose UTI in febrile infants and young children. uNGAL levels, urinalysis, Gram-stain and culture were obtained, with UTI defined by colony counts (reference test). For uNGAL, AUC was 0.978. At threshold uNGAL level 39.1 ng/mL, sensitivity was 97.1% and specificity 95.6%. LE or nitrite combination had sensitivity 74.3%, specificity 97.3%. Gram-stain had sensitivity 74.3%, specificity 100.0%.

A study (Valdimarsson et al, 2017) (n=185, age not stated; 108 with UTI, controls 64 febrile children without UTI and 13 healthy children) evaluated usefulness of neutrophil gelatinase-associated lipocalin (uNGAL) and 7 other urine biomarkers to diagnose UTI in infants. Logistic regression and ROC curves were performed for UTI patients versus febrile controls for all biomarkers. Urine NGAL (uNGAL) in absolute concentration had sensitivity 93% and specificity 95%, at cut-off level 38 ng/mL. Adjusted for creatinine, uNGAL had sensitivity 96%, specificity 100% for diagnosing UTI, at cut-off level 233 ng/mg.

Serum STREM-1 test

A prospective cross-sectional study (Ehsanipour et al, 2017) (n=61 children, mean age 3.6 years, 24 with upper UTI, 12 with lower UTI, 25 without UTI in a hospital in Tehran) evaluated serum STREM-1 for both diagnosing UTI and differentiating upper from lower UTI. Urinary analysis and culture were performed for all UTI cases; only positive cultured cases with the same microorganism were enrolled in the study. STREM-1 level was significantly different in UTI cases compared with controls overall. With cut-off point 111.5 pg/ml, STREM-1 had sensitivity 83.3%, specificity 60% to distinguish UTI from control.

HD5 and HNP

A prospective study (Watson et al, 2016) (n=199 paediatric Emergency Department or Urgent Care patients evaluated for a UTI, age not stated) assessed diagnostic accuracy of antimicrobial peptides (AMPs): human alpha-defensin 5 (HD5), and human neutrophil peptides (HNP) 1-3, as novel UTI biomarkers in children. Urine culture was the reference standard. Sensitivities and specificities of leukocyte esterase (LE), HD5, HNP1-3, and test

combinations were compared. For predicting positive urine culture, HD5 had AUC 0.86 (95%CIs = 0.81 to 0.92), and HNP1-3 had AUC 0.88 (95%CIs = 0.82 to 0.93). Compared to LE >= trace, the combination test "LE and HD5" increased specificity by 6% (95%CIs = 3 to 10%) without decreasing sensitivity (absolute figures not given). In a subgroup with urine collected by clean-catch, combination tests "LE and HD5" and "HD5 and HNP1-3" increased specificity by >10% compared to LE alone (absolute figures not given).

uHSP70

A study (Yilmaz et al, 2016) (n=121 children, age not stated) assessed the 70-kDa family of heat shock proteins (HSPs): HSP70s, for diagnosing UTI in children. Children were divided into four groups: symptomatic UTI (reference test not stated; n=30); healthy children (control group; n=30); asymptomatic patients with proven bacterial contamination in urine culture (contamination group; n=21); fever caused by other infections (non-UTI infection group; n=30). Urine HSP70 levels and creatinine (Cr) were measured at time of presentation and after treatment. Mean urine HSP70:Cr ratio (uHSP70/Cr) prior to treatment was significantly higher in the UTI group than in control, contamination and non-UTI infection groups, and was highest in patients with clinical pyelonephritis, defined as axillary fever >=39°C, leucocytosis, and positivity for C-reactive protein. Mean uHSP70/Cr after treatment decreased in the UTI group. For predicting UTI, with cut-off level 158 pg/mg, uHSP70/Cr had sensitivity 100%, specificity 100%, AUC=1.

Polymerase chain reaction (PCR) and recombinase polymerase amplification (RPA)

A prospective cohort study (Felt et al, 2017) (n=193 urine samples from children aged <36 months) assessed utility of PCR as a rapid diagnostic tool for children undergoing evaluation for UTI in the emergency department. *Escherichia coli* positive samples were identified with sensitivity 100% (95%CI = 71.5% to 100%) and specificity 99.5% (95%CI = 97.9 to 99.5%), using a quantification cycle (Cq) threshold of 26.15. With a Cq threshold of 19.03, E.coli infections >100,000 colony-forming units/mL were identified with sensitivity 100% (95%CI = 72.2% to 100%) and specificity 100% (95%CI = 98.6% to 100%).

A retrospective study (Raja et al, 2017) (n=50 samples) evaluated performance of a panel of isothermal real-time recombinase polymerase amplification (RPA) assays to detect common bacterial UTI pathogens: E.coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa and Enterococcus faecalis. The panel had specificity 100% (95%CI = 78 to 100%), sensitivity 89% (95%CI = 75 to 96%) for UTI detection. Reference test was urine culture. All five RPAs required reaction times of under 12 min to reach their lower limit of detection of 100 genomes per reaction or less; and did not cross-react with high concentrations of nontarget bacterial genomic DNA.

Intelligence gathering

The importance of clinical judgement for diagnosing UTI (of any type) was emphasised by topic experts, in the absence of sufficiently accurate tests.

At least one topic expert highlighted the importance of UTI diagnosis based on clinical judgement, fully considering clinical signs and symptoms in conjunction with the results of

urine dipstick testing (see subsection on symptoms and signs). A topic expert noted a study by Okarska-Napierala et al (2017) to support their view about the importance of clinical judgment when interpreting the results of diagnostic tests.

Post-publication feedback was also received from parents of children who had developed recurrent UTI after being initially diagnosed as not having UTI, following urine dipstick testing. Parents suggested dipstick testing was insufficiently accurate as a test, leading to false negatives and subsequent longer-term issues for their children.

Conversely, a topic expert (microbiologist) expressed concern at the rate of false positives from urine dipstick testing, leading to unnecessary antibiotic treatment and potentially increasing the risk of antimicrobial resistance. The topic expert suggested that clinical judgement may be equally as important for ensuring inappropriate antibiotic treatment is not provided.

In 2017, a topic expert suggested to check evidence on rapid point-of-care urinalysis as part of this surveillance review, based on a 2016 NIHR horizon scanning report. This suggestion was also supported by a consultee comment during the stakeholder consultation for PHE's guidance on UTI diagnosis in primary care (PHE, 2019b).

The DUTY study (Hay et al, 2016a, b) was highlighted by topic experts, albeit more for its evidence on symptoms and signs, rather than urine testing, for diagnosing UTI. The DUTY study provides additional health economic evidence around urine dipstick testing - for which data has already been incorporated in the 2017 partial guideline update.

Impact statement

Urinalysis, including dipstick testing, point-of-care testing and automated flow cytometry

Urine concentration effects on urinalysis accuracy

From the current surveillance, a single large study found that urinalysis performance, measuring dipstick leukocyte esterase (LE) and microscopic pyuria, varies with urine concentration, with LR+ increasing by a factor of nearly 3 from most concentrated to most dilute urine.

No evidence was identified from previous surveillance, or in the current guideline, on the effect of urine concentration on UTI diagnostic test performance; urine concentration is not mentioned in the current guideline. Urine dipstick testing using LE/nitrite combination is recommended by the current guideline, which is different from the LE- and microscopic pyuria-based urinalysis from the study identified in current surveillance.

If test performance does vary with urine concentration, health care professionals should be aware of this when making clinical decisions incorporating test results. Further research may be helpful on whether and how potential variation in test performance with urine concentration may translate to the current guideline recommendations, before considering any impact on the guideline.

New evidence is unlikely to change guideline recommendations.

Urinalysis in young infants comparing different definitions of a positive UTI culture

From the current surveillance, a single large study was identified on urinalysis for febrile infants aged <60 days in emergency department, using microscopy to test for pyuria, with bacteraemia if applicable, as well as LE/nitrite. It found that reducing the threshold colony count for a positive urine culture from 50,000 CFUs/mL to 10,000 CFUs/mL would slightly reduce sensitivity of urinalysis (i.e. its ability to detect a true UTI) in this age group, with specificity remaining constant. It was unclear whether automated or manual testing was used.

No evidence was identified from previous surveillance, or in the current guideline, on the effect of varying colony count threshold on UTI diagnostic test performance. The current guideline mentions the possibility of a child having an infection with a lower colony count, and that colony count cannot be considered the only criterion in diagnosing a UTI. For this age group, the current guideline recommends urine culture, together with referral to a paediatric specialist; this differs from the method for the study identified in current surveillance.

Further research on potential variation in test performance with differing threshold colony counts urine concentration may be helpful before considering any impact on the guideline.

New evidence is unlikely to change guideline recommendations.

Urine dipstick testing

Children under 16

A single retrospective study of children aged under 16 evaluated sensitivity of various parameters for dipstick urinalysis and microscopy, including nitrite, LE, blood and pyuria – both singly and in combination. LE or nitrite positive on urine dipstick, as per the current guideline recommendation, was found to have high sensitivity to detect UTI. Highest sensitivity to detect UTI was based on any positive result from the three dipstick parameters: nitrite, blood or LE. However, as the study was unable to measure specificity, clinical utility of the addition of blood as a dipstick parameter is unclear.

The current guideline recommends urine dipstick testing with LE/nitrite for children aged >3 months with suspected UTI. The new evidence is consistent with the guideline recommendation based on high sensitivity found for LE and/or nitrite in combination. Blood as an additional dipstick parameter may further increase sensitivity; however, further confirmatory research on overall clinical utility of this combination is required, with no impact expected on recommendations.

New evidence is unlikely to change guideline recommendations.

Younger infants

A single small study of febrile infants aged <60 days found that, for clean-catch samples obtained using a voiding stimulation technique, LE and/or nitrites combined had moderate sensitivity and specificity for diagnosing UTI. This is consistent with the evidence for infants aged <3 months which informed the 2017 partial update to the current guideline.

For this youngest age group, the current guideline recommends urine culture, together with referral to a paediatric specialist. Since there was no change in the recommendations for urine testing in this age group, based on evidence informing the 2017 partial update, no impact of the new evidence is anticipated on recommendations.

New evidence is unlikely to change guideline recommendations.

Point of care testing and automated flow cytometry

A study evaluated automated POC dip testing for UTI diagnosis in children aged under 18 years in emergency department, using LE and/or nitrite combination. POC testing had near-identical high sensitivity and moderate specificity to laboratory urinalysis; for which a positive result was defined as either positive LE or nitrites, or >10 white blood cells/high power field on microscopy. Though reported sensitivity was higher than that reported for urine dipstick testing in the 2017 partial update to the current guideline, the study did not directly compare POC dip testing with urine dipstick testing.

A study evaluated automated flow cytometry (Sysmex UF1000i) for UTI diagnosis for children aged under 13 years, finding it to have useful diagnostic accuracy with high sensitivity and specificity. Diagnostic parameters reported for flow cytometry in this study compare favourably with those based on evidence identified for urine dipstick testing in the 2017 partial update to the current guideline.

Another study compared predictive values of flow cytometry versus urine dipstick testing to detect UTI in febrile children (age range not stated). It found flow cytometry had higher AUC than dipstick testing, including either very high sensitivity or specificity (depending on the cut-off point). The authors calculated that using automated flow cytometry as a targeted screen indicating urine culture could have reduced samples for culture by 67%, compared with urine dipstick testing.

A large study evaluated automated urinalysis using microscopic bacteriuria versus pyuria, for UTI diagnosis in children aged <2 years. It found pyuria alone to be the most accurate test overall, with high AUC. LR+ (and specificity) could be increased at the expense of LR- (and sensitivity) by adding automated microscopic bacteriuria.

A large study determined optimum White Blood Cell (WBC) threshold for diagnosing UTI in infants using automated urinalysis. Optimum cut-off point and LR+/- varied with urine concentration. Dipstick analysis using positive LE obtained higher LRs making the test appear very useful for both dilute or concentrated urine. These LRs were slightly better than those

calculated for the 2017 partial update to the current guideline, for children aged between 3 months and 3 years using urine dipstick testing.

No evidence was identified in the current guideline on automated urinalysis for diagnosing UTI in any age group. Any evidence from previous surveillance has now been superseded by the 2017 partial update to the subsection on urine testing in the current guideline. Whilst automated urinalysis is not mentioned in the current guideline, it has been indicated as an emerging area based on an NIHR horizon scanning report. The current guideline recommends an LE/nitrite-based protocol for urine dipstick testing, for children aged >3 months.

The current surveillance provides some evidence that automated flow cytometry (Sysmex UF100) POC testing has moderate sensitivity for targeted screening for UTI prior to urine culture, for children aged up to 16; however, with low specificity. Overall diagnostic test parameters were slightly higher than for dipstick testing, though specificity was not reported for urine dipstick. However, the effect of including only febrile children in one of the two studies is unclear; this may have improved reported test parameters for flow cytometry.

The study identified in current surveillance for children aged under 13 years did not directly compare automated flow cytometry with dipstick testing; neither did the 2 studies for infants aged under 2 years. Therefore, it is unclear whether results from these studies are directly comparable with the protocol in the current guideline. One of the studies in infants aged under 2 years suggests that dipstick LE+ in automated urinalysis may have very useful LR+ and LR- for detecting UTI in infants, which varies with urine concentration. However, no direct comparison was made with the currently recommended LE/nitrite-based protocol.

Evidence from current surveillance appears to provide promising initial results for automated urinalysis to detect UTI in children aged under 16 years; including for the subgroups of children aged under 13 years and infants under 2 years. However, due to the limitations and uncertainties outlined above, further confirmatory research would be required, and no impact is anticipated on recommendations during the current surveillance.

New evidence is unlikely to change guideline recommendations.

Biomarkers for UTI diagnosis

Eight studies were found in the current surveillance evaluating novel biomarkers for diagnosing UTI.

Serum neutrophil gelatinase-associated lipocalin (sNGAL) test

A single study in the current surveillance found serum neutrophil gelatinase-associated lipocalin (sNGAL) to have moderately useful diagnostic accuracy for febrile UTI, and much lower diagnostic accuracy (though moderate sensitivity) for diagnosing non-febrile UTI.

Urine neutrophil gelatinase associated lipocalin (uNGAL) test

Four studies identified from current surveillance evaluated urine neutrophil gelatinase associated lipocalin (uNGAL) for diagnosing UTI, using similar cut-off levels in 3 studies for which this was reported. Sensitivity, specificity and overall diagnostic accuracy ranged from

low to high across the 4 studies. Observed variation may relate with study designs, sampling methods, and the role of chance in smaller studies. One of the studies compared uNGAL with automated urinalysis, finding uNGAL to have superior diagnostic accuracy. Diagnostic parameters for urinalysis appeared broadly similar to parameters from evidence informing the 2017 partial update to the current guideline, for urine dipstick testing.

Serum STREM-1 test

A single study in the current surveillance found the serum biomarker STREM-1 to have moderate sensitivity and limited specificity to detect UTI. No direct comparison was made with urine dipstick testing.

HD5 and HNP

A single study in the current surveillance found the biomarkers HD5 and HNP to have moderately high AUCs for predicting positive urine culture. Combining leukocyte esterase (LE) with HD5 was reported to increase specificity compared with LE alone, without decreasing sensitivity. HD5 and HNP1-3 in combination were also reported to increase specificity compared with LE alone. Clinical significance of these findings was unclear, and no direct comparison was made of these biomarkers with urine dipstick testing.

uHSP70

A single study in the current surveillance reported extremely high test accuracy for uHSP70/Cr in diagnosing UTI. Study design was unclear and may have been prospective case-control with multiple groups. Therefore, spectrum bias, due to use of healthier controls less representative of healthcare practice, may have elevated observed diagnostic accuracy. There was no direct comparison with urine dipstick testing.

IL-8 and TGF-beta1

A single study in the current surveillance found that the biomarker IL-8 had very high specificity, though limited sensitivity, for diagnosing UTI; TGF-beta1 have moderate specificity with lower sensitivity.

No evidence was identified for the current guideline on biomarkers for diagnosing UTI, or from previous surveillance on biomarkers for UTI diagnosis, although evidence had been previously identified on biomarkers for localising UTI (see later section).

No specific intelligence was received for this surveillance review on the use of novel biomarkers for UTI diagnosis. A topic expert in previous surveillance had indicated relevant evidence on biomarkers.

The current guideline recommends urine dipstick testing based on LE and/or nitrite for children aged >3 months, followed by urine culture for positive results. Urine culture with referral to a paediatric specialist is recommended for all children aged <3 months with suspected UTI.

Evidence from the current surveillance appears to provide promising results for diagnosing UTI for several biomarkers including uNGAL and sNGAL, potentially with better diagnostic

test parameters than for currently recommended urine dipstick testing. However, the experimental nature of the studies, potential limitations in study design, and heterogeneity of results for the 4 studies involving uNGAL, mean that for all promising biomarkers, further confirmatory research would be required. No impact is therefore expected on recommendations.

New evidence is unlikely to change guideline recommendations.

Polymerase chain reaction (PCR) and recombinase polymerase amplification (RPA)

Two studies evaluated nucleic acid amplification methods for diagnosing UTI: polymerase chain reaction (PCR) and recombinase polymerase amplification (RPA).

A single study found that polymerase chain reaction (PCR) had high sensitivity and specificity as a rapid diagnostic tool for children undergoing UTI evaluation in emergency department. A second single retrospective clinical study found that recombinase polymerase amplification (RPA) had high sensitivity and specificity for UTI detection.

No evidence was identified for the current guideline, or from previous surveillance, on nucleic acid amplification methods for diagnosing UTI. No specific intelligence was received on use of PCR or RPA. PCR requires complex laboratory testing, whereas RPA is simpler and may be used outside of a laboratory.

The current guideline recommends urine dipstick testing based on LE and/or nitrite for children aged >3 months, followed by urine culture for positive results. Urine culture with referral to a paediatric specialist is recommended for all children aged <3 months with suspected UTI.

Evidence from the current surveillance may provide promising initial results for the nucleic acid amplification methods, PCR and RPA, for diagnosing UTI. Use of PCR may be more relevant for laboratories as a potential alternative to urine culture for confirming UTI, while RPA might be considered as a potential rapid point-of-care test. The RPA study in the current surveillance was small, and due to its study design may not fully represent results achievable in practice. Neither study directly compared the index test with urine dipstick testing which is recommended by the current guideline. It is therefore unclear whether sampling/setting or case presentation may have contributed to improved diagnostic accuracy of PCR and/or RPA relative to urine dipstick testing.

The commercial stage which these tests have reached is also unclear; though, as a proof-of-concept, the RPA test especially appears promising. Further confirmatory research would be required on these novel methods for diagnosing UTI, and no impact is expected on recommendations.

New evidence is unlikely to change guideline recommendations.

History and examination on confirmed UTI

Surveillance proposal

No new information was identified at any surveillance review.

This section of the guideline should not be updated.

This section of the guideline should not be updated.

Clinical differentiation between acute pyelonephritis (APN) and lower UTI

Surveillance proposal

No new information was identified at any surveillance review.

This section of the guideline should not be updated.

This section of the guideline should not be updated.

Laboratory tests for localising UTI

Surveillance proposal

This section of the guideline should not be updated.

Previous surveillance summary

Previous surveillance in 2013 identified a single systematic review and meta-analysis (Leroy et al, 2013) focusing on laboratory tests for localising UTI. This study assessed procalcitonin (PCT), C-reactive protein (CRP) and white blood cell count (WBC) as predictors of both acute pyelonephritis (APN) and renal scarring in children with a febrile UTI. The 2013 surveillance review concluded that PCT may have some value in ruling out APN during early stages of UTI, and that overall predictive abilities for PCT are not substantially greater than other available biomarkers, particularly for late renal scarring (noting that this would relate more with later testing under '1.3 Imaging', rather than with this section on localising of UTI).

2020 surveillance summary

A total of 15 studies were identified on laboratory tests for localising UTI: 2 meta-analyses (including one Cochrane review) and 13 primary studies, covering a range of different biomarkers:

Procalcitonin (PCT), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) tests

A Cochrane review (Shaikh et al, 2016) (n=24 studies, children aged U-18 with a culture-confirmed UTI episode; number of children reported separately for each biomarker)

investigated whether procalcitonin (PCT), C-reactive protein (CRP), or erythrocyte sedimentation rate (ESR) tests could replace acute DMSA scan in diagnostic evaluation of children with UTI, particularly to differentiate APN from lower UTI. It also assessed influence of patient and study characteristics on diagnostic accuracy; and compared performance of these three biomarker tests with each other.

For PCT (n=6 studies, 434 children, using cut-off value 0.5 ng/mL), summary estimates were: sensitivity 0.86 (95%CIs = 0.72 to 0.93); specificity 0.74 (95%CIs = 0.55 to 0.87). For CRP (n=13 studies, 1,638 children, using cut-off value 20 mg/L), summary estimates were: sensitivity 0.94 (95%CIs = 0.85 to 0.97); specificity 0.39 (95%CIs = 0.23 to 0.58). For ESR (n=6 studies, 1,737 children, using cut-off value 30 mm/h), summary estimates were: sensitivity 0.87 (95%CIs = 0.77 to 0.93); specificity 0.48 (95%CIs = 0.33 to 0.64).

CRP test

A diagnostic test accuracy meta-analysis (Zhang et al, 2018) (n=21 studies, number of children not stated) assessed whether CRP level can discriminate between APN and lower UTI in children with fever. Pooled results from the 21 included studies suggested that CRP had sensitivity 0.826 (95%CIs = 0.744 to 0.886) and specificity 0.669 (95%CIs = 0.582 to 0.747) in differentiating APN from UTI; AUSROC was 0.81 (95%CIs = 0.77 to 0.84).

PCT test

A retrospective study (Banuelos-Andrio et al, 2017) (n=101 children with first UTI episode) assessed PCT and other analytical parameters (white blood cell count [WBC], CRP) as markers of acute renal damage in children after a first febrile or afebrile UTI. DSMA scan was the reference test. Mean WBC, CRP and PCT values were significantly higher in patients with APN (n=64) compared with normal acute DMSA (n=37). For localising APN, AUCs were: 0.862 for CRP, 0.774 for WBC, 0.731 for PCT. At optimum statistical cut-off value 0.285ng/ml, PCT had sensitivity 71.4%, specificity 75%.

ESR test

A prospective study (Naseri et al, 2017) (n=20 children, age not stated, admitted with febrile UTI) assessed traditional inflammatory serologic parameters, urine analysis indexes, kidney ultrasonography and fever, in children with febrile UTI, for predicting APN using DMSA scan as reference test. Detailed parameters assessed included: body temperature >= 39C, white blood cell count >= 15000 cell/micro L, positive CRP, ESR (first hour) >= 30 mm/h, presence of proteinuria, severe pyuria or bacteriuria on urine analysis, urine specific gravity <= 1010, and renal ultrasonography. Of these parameters, ESR had (highest) sensitivity 100%, PPV 100%, at cut-off point >=30mm/h (specificity/AUC not stated). Urine specific gravity had (highest) specificity 75%, PPV 85.7%, at cut-off point <1,010.

Neutrophil gelatinase-associated lipocalin (NGAL)

Serum neutrophil gelatinase-associated lipocalin (sNGAL) test

A prospective study (Krzemien et al, 2019) (n=46 infants with first UTI episode, 23 with APN, 23 with lower UTI; age not stated) compared sNGAL with other inflammatory markers for predicting APN in infants with UTI. DMSA scan was used as a reference test. Significantly

elevated levels of sNGAL, PCT, CRP, and ESR were observed in infants with APN compared to those with lower UTI (data not given). Higher sNGAL, CRP, and ESR values, together with presence of fever, and longer duration of fever before antibiotic treatment, were associated with APN (no data on significance provided). AUC for predicting APN was 0.808 for sNGAL, 0.819 for PCT, and 0.841 for CRP; significantly better than for ESR (AUC 0.750) With cut-off value 100.8 ng/ml, sNGAL had sensitivity and specificity 82.6%. PCT and CRP were reported as having the same sensitivity and specificity as sNGAL, with cut-off values 0.15 ng/ml, and 5.3 mg/dl respectively. ESR had sensitivity 78.3%, specificity 60.9%, with cut-off value 40 mm/h.

Plasma neutrophil gelatinase-associated lipocalin (pNGAL) test

A retrospective review study (Kim et al, 2017) (n=138 children with febrile UTIs: 59 APN, 79 lower UTI) compared diagnostic accuracy of pNGAL) with PCT, CRP, and white blood cells (WBCs), for predicting APN in children with febrile UTIs. Levels of pNGAL, PCT, CRP, and WBCs in blood were measured on admission. pNGAL level was the only independent predictor of APN (P = 0.006), after multivariate analysis. At optimal cut-off value 117 ng/ml, pNGAL had sensitivity 86%, specificity 85%, PPV 81 %, NPV 89%, positive likelihood ratio 5.69 (95%CIs = 3.56 to 8.78), negative likelihood ratio 0.16 (95%CIs = 0.08 to 0.29) for identifying APN. pNGAL was more accurate than serum PCT, CRP, and WBCs for APN diagnosis (data not provided for other biomarkers).

Urine neutrophil gelatinase associated lipocalin (uNGAL) test

A prospective study (Nickavar et al, 2016) (n=63 children: 37 with acute pyelonephritis, mean age 39 months, 26 controls, mean age 43.6 months) assessed whether uNGAL is a reliable biomarker to diagnose APN, and monitor treatment. uNGAL was measured both before and 5 to 7 days after antibiotic treatment in the UTI group; and compared with the control group admitted for other bacterial infections. Median uNGAL level was significantly higher in patients with APN than the other subjects (0.48 vs. 0.065, P=0.001), and decreased significantly after antibiotic treatment (P=0.002). Using a cut-off of 0.20 ng/mL, sensitivity and specificity of uNGAL were 76% and 77% for prediction of APN, respectively: with AUC 0.75 (CI= 0.61-0.88).

A case-control study (Arambasic et al, 2016) (n=134 children, median age 2.5 years, admitted to a hospital paediatric clinic in Croatia; 80 with APN, 54 controls with non-APN febrile state including lower UTI) assessed uNGAL as a diagnostic biomarker of APN. uNGAL, white blood cells, C-reactive protein, urinalysis, urine culture, kidney ultrasound and DMSA scan were carried out for each child. uNGAL values were significantly higher in children with APN compared to the control groups (113.6 ng/mL vs. 10.2 ng/mL, p<0.001). With cut-off value 29.4 ng/mL, uNGAL had sensitivity 92.5% and specificity 90.7%; AUC=0.952 for detecting/differentiating APN. The authors reported that, using cut-off value 38.5 ng/mL, uNGAL can also differentiate APN from cystitis; and, using cut-off value 20.4 ng/mL, can differentiate lower UTI from febrile states with aetiology other than UTI.

A descriptive, cross-sectional study (Jellouli et al, 2016) (n=89 children aged 2 months to 14 years, mean age 3 years, diagnosed with UTI and admitted to a hospital in Iran) assessed

urinary neutrophil gelatinase-associated lipocalin (uNGAL) for detecting renal parenchymal involvement in children with APN. Urine samples were taken for uNGAL tests, urine cultures, and urinalyses. Some blood samples were collected for leukocyte count, CRP and ESR tests. DMSA scan was the reference test. At cut-off point >5 mg/l, for detecting renal parenchymal involvement, uNGAL had sensitivity 67.4%, specificity 97.8%, PPV 96.7%, NPV 76.3%. There was significant increase in uNGAL level, increase in CRP level, and higher DMSA scan grades ($p<0.001$).

Other biomarker tests, including combination biomarkers

Serum STREM-1 test

A prospective cross-sectional study (Ehsanipour et al, 2017) (n=61 children, mean age 3.6 years, 24 with upper UTI, 12 with lower UTI, 25 without UTI in a hospital in Tehran) evaluated serum STREM-1 for both diagnosing UTI and differentiating upper from lower UTI. Urinary analysis and culture were performed for all UTI cases; only positive cultured cases with the same microorganism were enrolled in the study. Upper and lower UTI were differentiated both clinically and through laboratory tests, confirmed by imaging studies (ultrasonography or DMSA scan). With cut-off point 132 pg/ml, STREM-1 had sensitivity 83.3%, specificity 60% to distinguish upper UTI from lower UTI.

Delta neutrophil index (DNI) test

A study (Kim et al, 2017) (n=288 young infants, age not stated) evaluated DNI for predicting APN, as well as VUR (see section 1.3 below). DNI was measured, together with conventional inflammatory markers: white blood cell (WBC) count, ESR, CRP. WBC, CRP, ESR and DNI levels were all higher for APN than for lower UTI ($p<0.01$, no other data provided). Multiple logistic-regression analyses showed DNI was also a predictive factor for areas of lack of uptake on DMSA scans, indicating APN ($P<0.01$). For predicting DMSA defects, AUC for DNI was 0.62 (95%CIs 0.558 to 0.687; $P<0.01$); AUC for CRP was 0.73, (95%CIs 0.673 to 0.789; $P<0.01$).

Mean platelet volume (MPV) test

A prospective study (Tekin et al, 2015) (n=94 children, age not stated) studied mean platelet volume (MPV) as a predictor of APN in children with UTI. The reference test for APN was DMSA scan; there were 43 patients in the APN group and 51 patients with lower UTI. MPV was associated with APN ($p<0.001$), with sensitivity 81.4% and specificity 86.3% for diagnosing APN (CIs not given), using optimal MPV cut-off value of 8.2fl (AUC = 0.906). MPV was also significantly associated with late renal scar formation ($p<0.001$). Other inflammation markers: white blood cell (WBC) count, ESR, and serum CRP, were also measured and compared. While all these inflammatory markers had higher values in the APN group compared with the lower UTI group ($p<0.05$), the authors reported that sensitivity and specificity of MPV for diagnosing APN were higher than for the other markers.

Pro-inflammatory urine interleukin (IL)-6, IL-8, anti-inflammatory transforming growth factor beta 1 (TGF-beta1) tests

A study (Krzemien et al, 2016) (n=35 children, mean age 6.1 months) assessed pro-inflammatory urine interleukin (IL)-6 and IL-8 concentrations, and anti-inflammatory transforming growth factor beta1 (TGF-beta1) level as biomarkers in infants with febrile UTI, non-febrile UTI and asymptomatic bacteriuria (ABU), including for detecting APN. Children were divided into three groups: group I - febrile UTI (n=13); group 2 - non-febrile UTI (n=13); group 3 - ABU (n=9). Urine IL-6, IL-8, TGF-beta1, serum C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and white blood cell count (WBC) were measured at enrolment. Renal ultrasound was performed in all children, and DMSA scan and micturating cystourethrogram (MCUG) performed in children with UTI. For detecting inflammatory changes in DMSA scan indicating APN (66.6% of children with UTI): at cut-off value 120 pg/mg creatinine (Cr), IL-8 had sensitivity 58.3%, specificity 100%; at cut-off value 40 pg/mg Cr, TGF-beta1 had sensitivity 66.7%, specificity 83.7%.

Multiple biomarker tests used in combination

A study (Jung and Lee, 2016) (n=250 infants admitted to hospital, age not stated: 150 with first febrile UTI, 100 controls with other febrile illnesses) assessed CRP, urine protein-creatinine ratio (uProt/Cr), and urine electrolytes, for discriminating APN from other febrile illnesses, and/or discriminating presence of cortical defect on DMSA scan (true APN) from its absence in infants with febrile UTI. Blood (CRP, electrolytes, Cr) and urine tests [uProt/Cr, electrolytes, and sodium-potassium ratio (uNa/K)] were performed upon admission; all infants with UTI underwent DMSA scans during admission. Data were compared between infants with UTI and controls, and between infants with and without a cortical defect on DMSA scan. Ability to predict true APN was analysed using multiple logistic regression analysis. CRP levels and uProt/Cr were significantly higher in infants with true APN than in controls; uNa levels and uNa/K were significantly lower in infants with true APN than in controls. CRP levels and uNa/K were relevant factors for predicting true APN. For predicting true APN, using CRP levels, u-Prot/Cr, u-Na levels, and uNa/K had sensitivity 94%, specificity 65%, PPV 60%, NPV 95%.

Intelligence gathering

The importance of clinical judgement for diagnosing UTI (of any type) was emphasised by topic experts, in the absence of sufficiently accurate tests. No specific intelligence was received on use of laboratory testing, including biomarkers, for localising UTI.

The current guideline included a research recommendation, stating: ‘Further research is needed to evaluate the effectiveness of procalcitonin and other inflammatory markers in localising UTI.’

Impact statement

Procalcitonin (PCT)

In the current surveillance, a Cochrane review together with a single study found PCT to have moderate sensitivity with low specificity to detect APN – with heterogeneous results in included studies. Previous surveillance identified a systematic review and meta-analysis of biomarkers including PCT for identifying APN and renal scarring in children with UTI, concluding that PCT may have some value in ruling out APN during early stages of UTI, with higher AUC than CRP.

The current guideline identified evidence on PCT for localising UTI from 4 studies, noting its variable diagnostic performance, the small number of studies and diverse cut-off points used.

It made a research recommendation to evaluate the effectiveness of PCT and other inflammatory markers in localising UTI. Fever >38.0°C is the key clinical criterion for diagnosing APN, and biomarkers including CRP or potentially PCT may be used in addition (though not on their own).

Evidence on PCT from cumulative surveillance appears consistent with the current guideline, in that PCT may potentially be used to assist in localising UTI, together with clinical signs and symptoms; however no specific recommendation is made to do so. Therefore, no impact is expected on recommendations.

New evidence is unlikely to change guideline recommendations.

C-reactive protein (CRP)

In the current surveillance, 2 review studies - a Cochrane review and a subsequent diagnostic meta-analysis - found CRP to have high sensitivity but low specificity to detect APN – with heterogeneous results in included studies. Previous surveillance identified a systematic review and meta-analysis of biomarkers, including CRP, for predicting APN and renal scarring in children with UTI: CRP was found to have some diagnostic capability for APN, though with lower AUC than PCT.

The current guideline recommendation on CRP is based on evidence from 12 studies; results were heterogeneous, and variable diagnostic performance was noted, partly due to diverse cut-off levels being used.

The current guideline recommends that CRP should not be used on its own to differentiate upper from lower UTI.

Evidence on CRP from cumulative surveillance appears consistent with the current guideline, in that CRP may potentially be used to assist in localising UTI, together with clinical signs and symptoms; however no specific recommendation is made to do so. Therefore, no impact is expected on recommendations.

New evidence is unlikely to change guideline recommendations.

Erythrocyte sedimentation rate (ESR) tests

In the current surveillance, a Cochrane review together with a single small study found ESR to have moderate sensitivity but low specificity to detect APN – with heterogeneous results in included studies. No evidence was identified from previous surveillance on ESR for localising UTI.

The current guideline identified evidence on ESR for localising UTI from 2 studies, with limited diagnostic performance for localising UTI.

Research recommendations in the current guideline include further research to evaluate the effectiveness of procalcitonin and other inflammatory markers in localising UTI.

The current guideline does not mention ESR as a potential biomarker to assist in localising UTI. Fever >38.0°C is the key clinical criterion for diagnosing APN.

Evidence on ESR from cumulative surveillance appears consistent with the current guideline, in that ESR may potentially be used to assist in localising UTI, together with clinical signs and symptoms; however no specific recommendation is made to do so. Therefore, no impact is expected on recommendations.

New evidence is unlikely to change guideline recommendations.

Neutrophil gelatinase-associated lipocalin (NGAL)

Current surveillance identified 5 studies in total assessing serum, plasma and urine NGAL for detecting APN. Serum (s)NGAL was found in a single study to have both moderately high sensitivity and specificity for detecting APN, on a par with both PCT and CRP, and superior to ESR. Plasma (p)NGAL was found in a single study to have both moderately high sensitivity and specificity for detecting APN, with greater diagnostic accuracy than PCT, CRP and WBCs. Three studies assessed urine (u)NGAL for detecting APN, mainly in young children (mean age <3 years): results were heterogeneous, with both sensitivity and specificity ranging from being limited to very good.

No evidence was identified either in the current guideline or from previous surveillance on NGAL (in any of its variants) for localising UTI.

The current guideline does not mention NGAL in any of its variants as a potential biomarker to assist in localising UTI.

Evidence from several small studies in the current surveillance suggests that sNGAL pNGAL and uNGAL have moderate sensitivity and specificity for localising UTI. Further confirmatory research is required on these biomarkers, including as potential alternatives to CRP (or PCT). No impact on recommendations is expected.

New evidence is unlikely to change guideline recommendations.

Other biomarker tests, including biomarkers in combination

Current surveillance identified 5 studies in total assessing various other biomarkers, including multiple biomarkers in combination, for detecting APN.

For detecting APN, serum STREM-1 had moderate sensitivity, though low specificity. DNI was not as accurate as CRP. MPV had moderately useful diagnostic accuracy including relatively high specificity. IL-8 had moderately useful diagnostic accuracy including high specificity; TGF-beta1 had moderate specificity, though inferior overall diagnostic accuracy to other markers. A combination of CRP, u-Prot/Cr, u-Na and uNa/K had moderately useful diagnostic accuracy including high sensitivity.

Previous surveillance had highlighted IL-6 and IL-8 as biomarkers of potential interest for further research, together with CRP and PCT. Evidence on IL-6 was included in a single study in the current guideline; IL-6 had moderately useful diagnostic accuracy for localising UTI, including greater specificity than sensitivity. No evidence was included in the current guideline for any of the other biomarkers in this section.

Evidence from several small studies in the current surveillance suggests that MPV, IL-8, and a combination of multiple biomarkers, may provide moderately useful diagnostic accuracy to aid in localising UTI, with high specificity for both MPV and IL-8, and high sensitivity for the biomarkers in combination. Further confirmatory research is required on these biomarkers, including as potential alternatives to CRP (or PCT). No impact on recommendations is expected.

New evidence is unlikely to change guideline recommendations.

Imaging tests for localising UTI

Surveillance proposal

This section of the guideline should not be updated.

Previous surveillance summary

No new evidence on imaging tests for localising UTI was found in previous surveillance.

2020 surveillance summary

Diffusion-weighted magnetic resonance imaging (DW-MRI) for detecting APN

A prospective study (Bosakova et al, 2018) (n=31 children [30 girls] aged 3 to 18 years with first episode of febrile UTI, with no previously-detected congenital malformation of the urinary tract) assessed whether DW-MRI was comparable with DMSA (reference test) to demonstrate acute renal parenchymal lesions in children with febrile UTI. DMSA and DW-MRI were both performed first within 5 days of UTI diagnosis, then at 6 months to detect late lesions. DW-MRI confirmed acute inflammatory changes of the renal parenchyma (mostly unilateral) in all 31 patients (100%), while DMSA detected inflammatory lesions in 22

children (71%; p = 0.002). Lesions were multiple in 26/31 children (84%) on DW-MRI, and in 9/22 (40%) on DMSA. At the 6-month control examination, scarring of the renal parenchyma was found equally by DW-MRI and DMSA-SRS in five patients (16%), three of whom were the same patients. Overall concordance of positive and negative late findings occurred in 87% of patients, with correspondence in anatomical location of acute and late lesions.

Aoyagi et al (2018) (n=7 children, age not stated, with temperature ≥38°C and positive urine culture) evaluated non-enhanced MRI with whole-body diffusion-weighted imaging (DWI) for detecting APN, with DMSA scan as reference test. Both tests were carried out ≤7 days from fever onset. For detecting APN lesions diagnosed by DMSA scan, MRI had sensitivity 80%, specificity 100%.

Intelligence gathering

The importance of clinical judgement for diagnosing UTI (of any type) was emphasised by topic experts, in the absence of sufficiently accurate tests. No specific intelligence was received on use of imaging for localising UTI.

Impact statement

Diffusion-weighted magnetic resonance imaging (DW-MRI) for detecting APN

The current surveillance identified 2 studies which assessed diffusion-weighted magnetic resonance imaging (DW-MRI) for diagnosing APN. One study considered DW-MRI to have higher sensitivity than DMSA scan (current gold standard) for detecting acute renal inflammatory lesions and multifocal lesions – whilst acknowledging that clinical significance of acute and late parenchymal findings on DWI-MRI is currently unclear. A small study found that DW-MRI had very useful diagnostic accuracy for diagnosing APN, with particularly high sensitivity.

No evidence was found from previous surveillance. Evidence informing the current guideline included a single study on gadolinium-enhanced MRI for localising UTI, which found high sensitivity but low specificity. This evidence was insufficient for any recommendation on MRI. The guideline committee suggested that, for most infants and children with UTI who respond promptly to treatment, localisation of UTI by imaging would be unnecessary and a poor use of NHS resources. Evidence was also identified for the current guideline from 2 studies on power Doppler ultrasonography, suggesting its diagnostic accuracy as sufficient for when imaging is deemed necessary to localise UTI, although this is not routinely recommended.

The current guideline recommends not to routinely use imaging for localising a UTI. Fever >38.0°C is the key clinical criterion for diagnosing APN, and if a biomarker (such as CRP) is used, it should not be on its own. If use of imaging is considered clinically important, power Doppler ultrasound is recommended or, if this is unavailable or diagnosis cannot be confirmed, a DMSA scintigraphy scan.

Evidence from 2 small studies in the current surveillance suggests that DW-MRI may have very useful diagnostic accuracy for detecting APN, possibly on a par with DMSA, and superior to gadolinium-enhanced MRI from evidence informing the current guideline.

However, the evidence from these studies remains limited, and further confirmatory research is required; therefore, no impact is anticipated on recommendations. The current guideline does not in any case recommend routine imaging for localising UTI.

New evidence is unlikely to change guideline recommendations.

1.2 Acute management of UTI

Surveillance proposal

This section of the guideline should not be updated.

Several recommendations (1.2.1.3 – 1.2.17) in this section have been superseded by the following NICE antimicrobial prescribing guidelines:

- NICE guideline NG109 on Urinary tract infection (lower): antimicrobial prescribing
- NICE guideline NG111 on Pyelonephritis (acute): antimicrobial prescribing
- NICE guideline NG112 on Urinary tract infection (recurrent): antimicrobial prescribing

The remaining recommendations (1.2.1.1 – 1.2.1.3 and 1.2.1.8-1.2.1.9) were considered as part of the surveillance review but no new evidence or intelligence was identified.

This section of the guideline should not be updated.

1.2.2 Prevention of recurrence

Surveillance proposal

This section of the guideline should not be updated.

Previous surveillance summary

Previous surveillance identified several studies which included probiotics or cranberry products as alternative prophylaxis to antibiotics.

It is unclear, from an assessment of the abstracts, how many of these studies specifically assessed the effectiveness of prophylaxis after first UTI to prevent recurrence. Recommendations on prophylaxis for children already experiencing recurrent UTI have been superseded by the APG on recurrent UTI; therefore, any evidence in this area would now be included in future surveillance reviews of the APG.

One RCT (Ferrara et al, 2009), one Cochrane review (Jepson et al, 2013) and another systematic review (Williams et al, 2013) examined cranberry products for preventing UTI recurrence.

Jepson et al analysed RCTs and quasi-RCTs of cranberry juice or other cranberry products for preventing UTIs. One RCT compared cranberry syrup with trimethoprim for prophylaxis of repeat symptomatic UTI (192 children aged 1 month to 13 years with recurrent UTI, VUR of any degree, or renal pelvic dilatation associated with a UTI). Compared with control (placebo, water or no treatment), cranberry products did not reduce symptomatic UTI across all susceptible populations with one or more UTI at follow-up, nor in a subgroup of children with recurrent UTI. This Cochrane review included 27 studies of which only 5 included children; hence, generalisability of the meta-analysis results to the guideline population is unclear.

Williams et al identified 3 relevant RCTs (394 children) and suggested there may be a role for cranberry concentrate.

Ferrara et al compared the effect of daily cranberry juice versus a Lactobacillus drink over 6 months in children with recurrent UTI, concluded there was a beneficial effect from daily consumption of concentrated cranberry juice.

The evidence on cranberry products for preventing UTI recurrence was mixed; but suggested overall that cranberry products do not appear to prevent recurrence of UTIs; therefore, there was no impact on guideline recommendations from previous surveillance.

A single study was identified on the effectiveness of probiotics for preventing UTI recurrence (Lee et al, 2007). Comparing the effect of probiotics prophylaxis (Lactobacillus acidophilus) with antibiotic prophylaxis using cotrimoxazole, the incidence of recurrent UTI did not differ significantly between the two groups. This suggests that probiotics may be equivalent to cotrimoxazole for prophylaxis against recurrent UTI.

2020 surveillance summary

The current surveillance identified a single RCT assessing the effectiveness of probiotic prophylaxis after first UTI to prevent recurrence:

Probiotic prophylaxis

An RCT (Sadeghi-Bojd et al, 2019) (n=181 children, aged 4 months to 5 years) investigated probiotic prophylaxis versus placebo for preventing recurrent UTI, for children with normal urinary tracts, after recovery from their first febrile UTI. The intervention was a probiotic mixture of Lactobacillus acidophilus, Lactobacillus rhamnosus, Bifidobacterium bifidum, and Bifidobacterium lactis, for total 18 months therapy. Primary outcome was UTI-free survival ('composite cure') at 18 months, and secondary endpoint was median time to first UTI recurrence. Composite cure (reduction in the risk of recurrent UTI) was significantly higher for the probiotics group compared with placebo after 18 months. Median time to first incidence of UTI recurrence was significantly lower for the probiotic group. No specific adverse events were found among participants in the probiotic group during therapy.

Intelligence gathering

No topic expert feedback was relevant to this section. We are monitoring an ongoing Polish trial in this area: Effectiveness of Probiotics Prophylaxis of Urinary Tract Infections in Children.

Impact statement

A single RCT found a probiotic mixture given as prophylaxis to be more effective than placebo in reducing recurrence following first time UTI in children aged 4 months to 5 years.

No evidence on probiotics for preventing UTI recurrence after first infection was identified for the current guideline. One RCT was identified from previous surveillance, which found no difference between probiotics and cotrimoxazole for preventing UTI recurrence. It is unclear whether this study specifically assessed the effectiveness of prophylaxis after first UTI to prevent recurrence. No topic expert feedback was received on this area.

The current guideline states that antibiotic prophylaxis should not be routinely recommended in infants and children following first-time UTI.

Evidence from previous surveillance on cranberry products suggests they do not appear to prevent recurrence of UTIs.

A single trial in the current surveillance suggests that a probiotic mixture may be effective for reducing UTI recurrence following first infection. An RCT from previous surveillance found that probiotics may be equivalent to cotrimoxazole for reducing recurrent UTI, although applicability to the current guideline was unclear. Results from the RCT in the current surveillance would need further confirmatory research; therefore, no impact is currently anticipated on recommendations.

New evidence is unlikely to change guideline recommendations.

1.2.3 Antibiotic prophylaxis

Previous surveillance summary

Previous surveillance identified multiple studies focusing on antibiotic prophylaxis to prevent UTI recurrence.

It is unclear, from an assessment of the abstracts, how many of these studies specifically assessed the effectiveness of prophylaxis after first UTI to prevent recurrence. Recommendations on prophylaxis for children already experiencing recurrent UTI have been superseded by the APG on recurrent UTI; therefore, any evidence in this area would no longer be eligible for this surveillance review.

2020 surveillance summary

No relevant evidence was identified.

Intelligence gathering

No topic expert feedback was relevant to this section.

Impact statement

This section of the guideline should not be updated.

This section of the guideline should not be updated.

1.3 Imaging tests

Surveillance proposal

This section of the guideline should not be updated.

Identifying structural and functional abnormalities of the urinary tract, including vesicoureteral reflux (VUR)

Contrast-enhanced voiding urosonography (ceVUS)

Previous surveillance summary

No evidence was identified from previous surveillance specifically on contrast-enhanced voiding urosonography (ceVUS) for detecting vesicoureteric reflux (VUR). However, other evidence from previous surveillance suggested that, overall, the current guideline imaging protocol appears to have high specificity but low sensitivity for detecting VUR (as well as renal scarring); and that, whilst relatively low cost, the current guideline imaging protocol may be associated with more radiation exposure than other guidelines (Routh et al, 2012; La Scola et al, 2013). The evidence from previous surveillance was considered to have no impact on current recommendations.

2020 surveillance summary

Two studies were identified, with 3 publications in total, assessing diagnostic accuracy of ceVUS: one review study, published as both a broader literature review (Chua et al, 2019b) and a meta-analysis focusing on a subset of studies using 2nd generation contrast agent (Chua et al, 2019a); and one study which retrospectively reviewed patient records (Tang et al, 2019).

A literature review (Chua et al, 2019b) (45 studies) assessed diagnostic accuracy of ceVUS compared with MCUG (reference test), for detecting and evaluating VUR. Due to heterogeneity of the available literature, reported diagnostic accuracy was summarised across the 45 included studies using descriptive statistics of median and interquartile range (IQR). Two generations of ultrasound contrast agent were identified in the available studies: 1st

generation (Levovist) and 2nd generation (SonoVue). No serious adverse events were reported in any of the studies. For detecting VUR, 1st generation contrast agent had sensitivity 90.25 (IQR 83.25 to 97), specificity 93 (IQR 91.3 to 95.25), regardless of ultrasound mode. Additionally, 2nd generation contrast agent had sensitivity 86.26 (IQR 81.13 to 97), specificity 90.99 (IQR 84 to 98).

A comparative diagnostic accuracy meta-analysis (Chua et al, 2019a) (12 studies, n=953 patients, 1,917 ureteral units) assessed diagnostic accuracy of ceVUS using 2nd generation contrast with harmonic imaging (CEVUS-HI) compared with MCUG (reference test), for diagnosing VUR in children. Following a systematic literature search, QUADAS-2 was used to appraise comparative studies from multiple databases, with heterogeneity and inter-study variability determined, together with diagnostic accuracy parameters, and AUC using bivariate model meta-regression. 12 studies with low to high risk of bias were included in meta-analysis. Heterogeneity with interstudy variability was noted ($p < 0.0001$, I-squared > 70%). No serious adverse events were reported associated with CEVUS-HI. Pooled diagnostic accuracy of CEVUS-HI for detecting VUR amongst children was: sensitivity 90.43 (95% CI=90.36 to 90.50), specificity 92.82 (95% CI=92.76 to 92.87), LR+ 12.59 (95% CI=12.49 to 12.68), LR- 0.103 (95% CI=0.102 to 0.104), extrapolated pooled diagnostic odds-ratio 122.12 (95% CI=120.75 to 123.49), AUC 0.965.

A study which retrospectively reviewed patient records (Tang et al, 2019) (n=22 infants aged 19 days to 24 months, 44 pelviureteric units [PUUs]) assessed ceVUS for diagnosing VUR (reference test MCUG); and evaluated the safety profile of ceVUS and the relevant imaging findings. All patients tolerated procedures well with no significant complications. For detecting VUR irrespective of severity (4 of 44 PUUs), ceVUS had sensitivity 100%, specificity 100%. Except for one PUU which showed grade 2 VUR on ceVUS but grade 1 VUR on MCUG, all other PUUs showed concordant findings on both examinations. ceVUS also detected: hydronephrosis (n=10), ureterocoele (n=1), multicystic dysplastic kidney (n=1), renal cysts (n=3), and urethral diverticulum (n=1).

Intelligence gathering

No intelligence was received on ceVUS during the current surveillance.

Impact statement

Evidence from a systematic review and its related meta-analysis using a subset of studies assessing the current (2nd generation) contrast agent, together with a study which retrospectively reviewed patient records, indicates that ceVUS has very useful diagnostic accuracy to detect VUR, including both high sensitivity and specificity. Accuracy of ceVUS may be comparable with MCUG, which is recommended within the current guideline imaging schedule for detecting VUR and is the current gold standard for this purpose.

The current guideline considered evidence from an HTA including 14 studies of ceVUS together with 2 additional primary studies, concluding that MCUG and ceVUS (using its older name 'cystosonography') were the most sensitive tests for VUR, and that ceVUS may have diagnostic accuracy for VUR comparable with MCUG, albeit with some heterogeneity in

study results. Limited data suggested that ceVUS and MCUG also have similar cost/scan. However, without further evidence on treatment outcomes following imaging of the bladder and kidneys, relative cost-effectiveness could not be assessed. Whilst the committee suggested that ceVUS might be used as an alternative to MCUG for diagnosing VUR, this did not appear as a formal recommendation.

Previous surveillance noted evidence indicating that radiation exposure through the current guideline imaging protocol may be high compared with other guidelines. Both MCUG (for detecting VUR) and DMSA tests (for detecting renal scarring) contribute to this radiation burden, which would ideally be reduced in line with the 'As Low As Reasonably Practicable' (ALARP) principle.

No specific topic expert input was received on ceVUS for detecting VUR. CEVUS-HI (Chua et al, 2019a; Tang et al, 2019) is a relatively recent technology; the 2nd generation contrast enhancement agent appears to have been widely available since 2016.

The current guideline recommends not routinely imaging infants and children who have had a UTI, except in specific circumstances: MCUG is recommended for infants aged under 6 months with atypical or recurrent UTI, and MCUG should be considered for children aged between 6 months and 3 years with atypical or recurrent UTI if the following features are present: dilatation on ultrasound; poor urine flow; non-E. coli-infection; family history of VUR.

The cumulative evidence indicates that, for detecting VUR, ceVUS may have comparable diagnostic accuracy to MCUG as per current guideline recommendation; however, with no radiation exposure. Possible limitations of ceVUS may include cost (which appears comparable to MCUG based on limited data informing the current guideline), availability, and dependency on operator expertise. Whilst the cumulative evidence shows promise for ceVUS as an alternative to MCUG for detecting VUR, it is unclear whether or how widely this technology is currently in use in the NHS; further questions remain including on practical aspects of ceVUS compared with currently recommended MCUG. Further information and comment on the potential of ceVUS is therefore being sought during stakeholder consultation; however, at this point the new and cumulative evidence is considered unlikely to impact on recommendations.

New evidence is unlikely to change guideline recommendations.

Renal bladder ultrasound (RBUS) to detect vesicoureteral reflux (VUR) and urinary tract anomalies

Previous surveillance summary

Previous surveillance reported a single study of ureteric jet Doppler Waveform (UJDW) (D'Souza et al, 2013). For detecting VUR, UJDW had sensitivity 77.3%, specificity 91.3% in children aged 2-4 years; and sensitivity 81.8%, specificity 87.1% in children ≥5 years.

2020 surveillance summary

Fourteen studies in total were identified on ultrasound for detecting urinary tract anomalies including obstruction and/or VUR, including variations of ultrasound and specific measured parameters.

Conventional renal bladder ultrasound (RBUS) to detect urinary tract anomalies including obstruction

A retrospective cohort study (Wallace et al, 2015) (n=197 infants aged <2 months, mean 33 days, with fever and culture proven UTI) assessed performance of renal ultrasound for detecting VUR and obstructive uropathies. Both ultrasound and MCUG as reference test were performed within 30 days of UTI diagnosis. Renal ultrasound results were deemed abnormal if collecting system dilation, renal size asymmetry, collecting system duplication, urothelial thickening, ureteral dilation, or bladder anomalies were present. No obstructive uropathies were diagnosed by MCUG in patients with normal renal ultrasound findings.

Conventional renal bladder ultrasound (RBUS) to detect VUR

A Cochrane review (Shaikh et al, 2016) (n=42 studies, number of children not stated) evaluated the accuracy of DMSA and RBUS in diagnosing VUR and high-grade VUR in children aged under 19 years with a culture confirmed UTI. The reference test was MCUG. Summary estimates for RBUS were: sensitivity 0.44 (95% CIs 0.34 to 0.54), and specificity 0.78 (95% CIs 0.68 to 0.86) for detecting VUR (n=20 studies); sensitivity 0.59 (95% CIs 0.45 to 0.81), and specificity 0.79 (95% CIs 0.65 to 0.87), for detecting high-grade VUR (n=11 studies).

A meta-analysis (Saltychev et al, 2016) (n=14 studies, 3,544 children, age not stated, with first UTI) assessed the accuracy of renal and bladder ultrasonography (RBUS) for predicting VUR in children with first UTI. CENTRAL, MEDLINE, Embase and Web of Science were searched, and a random effects meta-analysis conducted. Risk of bias and concern regarding applicability were considered high in 4 studies. For detecting VUR, pooled sensitivity of RBUS was 0.37 [95%CIs = 0.34 to 0.40], specificity 0.81 (95%CIs = 0.80 to 0.83), positive LR 2.0 (95%CIs = 1.61 to 2.50), negative LR 0.75 (95%CIs = 0.65 to 0.86), AUC 0.72.

A retrospective study (Wongbencharat et al, 2016) (n=387 infants aged <1 year) investigated effectiveness, including cost and benefits, of renal bladder ultrasound (RBUS) and late 6-month DMSA renal scan to detect high-grade VUR in infants aged <1 year after first febrile UTI. MCUG was the reference test. For prediction of high-grade VUR (n=8), abnormal RBUS had sensitivity 50%. The authors reported that the proportion of infants who avoided unnecessary MCUG was 75.5% for RBUS.

A prospective study (Hung et al, 2016) (n=310 children aged <=2 years hospitalised with first febrile UTI) assessed renal ultrasonography (US) for predicting VUR, and renal scarring; and, using initial US, assessed the significant urologic abnormalities impacting on management of children hospitalised with a first febrile urinary tract infection. MCUG and DMSA were the reference tests for VUR and renal scarring, respectively. For predicting Grades I to V VUR, US had sensitivity 52.3%, NPV 75.1%. For predicting Grades III to V VUR, US had sensitivity

68.4%, NPV 87.8%. Specificity, PPV and AUC were not reported. Overall, 85 children had renal scarring, including 55 with abnormal US. Accuracy of US for detecting renal scarring was not reported. Of 105 children with abnormal US, 33 needed subsequent management (surgical intervention, parental counselling, or follow up of renal function). Nephromegaly on initial US and Grades III-V VUR were risk factors of renal scarring (no data reported).

A retrospective study (Jellouli et al, 2016) (n=311 children, median age 2.5 years) assessed whether abnormalities found on renal ultrasound help indicate necessity of MCUG in children after first UTI. Overall, 44 children had VUR on MCUG (as reference test). For suggesting VUR, ultrasound had sensitivity 43%, specificity 91%, PPV 44%, NPV 91%.

A retrospective cohort study (Wallace et al, 2015) (n=197 infants aged <2 months, mean 33 days, with fever and culture proven UTI) assessed performance of renal ultrasound for detecting VUR and obstructive uropathies. Both ultrasound and MCUG as reference test were performed within 30 days of UTI diagnosis. Renal ultrasound results were deemed abnormal if collecting system dilation, renal size asymmetry, collecting system duplication, urothelial thickening, ureteral dilation, or bladder anomalies were present. Accuracy of ultrasound for detecting VUR increased with grade of VUR, for both sensitivity and specificity. Sensitivity ranged from 32.7% (95%CIs = 20.0 to 47.5%) for grades I to V VUR (n=49), up to 86.7% (95%CIs = 59.5 to 98.3%) for grades IV-V VUR (n=15). Specificity ranged from 69.6% (95%CIs = 61.5 to 76.9%) for grades I to V VUR, up to 73.6% (95%CIs = 66.6 to 79.9%) for grades IV-V VUR.

A retrospective review study (Logvinenko et al, 2015) (n=2,259 children, aged 0 to 60 months with UTI as indication for imaging, with both RBUS and MCUG performed) evaluated association of RBUS with MCUG findings, and whether models could be constructed to accurately predict patients at high risk of MCUG abnormalities, based on RBUS findings. Multivariate logistic models, and neural network machine learning algorithms, were constructed to evaluate predictive power of RBUS for MCUG abnormalities. From multivariate logistic regression, for detecting any VUR, RBUS had sensitivity 86%, specificity 25% (AUC=0.57); for detecting VUR grade>II, sensitivity 5%, specificity 99% (AUC=0.60); for detecting VUR grade>III, sensitivity 6%, specificity 99% (AUC=0.67). From neural network predictive model construction, for detecting any VUR, RBUS had sensitivity 64%, specificity 60% (AUC=0.69); for detecting VUR grade>II, sensitivity 18%, specificity 98% (AUC=0.67); for detecting VUR grade>III, sensitivity 32%, specificity 100% (AUC=0.79).

Uroepithelial thickening on ultrasound

A retrospective study (Gordon et al, 2015) (n= 226 children aged 2 to 24 months with first febrile UTI) assessed uroepithelial thickening as an indicator of high grade VUR, and whether uroepithelial thickening improves RBUS' value in diagnosing VUR prior to MCUG. Patients with uroepithelial thickening were compared to an age- and gender-matched sample without uroepithelial thickening, and factors associated with high-grade VUR identified through logistic regression. Test characteristics of RBUS to detect high-grade VUR were compared, based on different criteria for abnormal RBUS. On multivariable analysis, uroepithelial thickening was a significant independent predictor of high-grade VUR (n=37; OR 5.41;

95%CIs = 1.74 to 16.79; p=0.004). With hydronephrosis and hydroureter considered the only abnormal RBUS findings warranting MCUG, RBUS had sensitivity 84% for detecting high-grade reflux. With uroepithelial thickening also considered an abnormal finding, RBUS had sensitivity 97%. Specificity/AUC was not stated in the abstract.

Ureteral dilatation (or dilation) on ultrasound

A study (Ozen et al, 2017) (n=133 children aged 2 to 36 months, mean age 33 months, being followed up with diagnosis of recurrent UTI) aimed to determine rational usage of imaging techniques to prevent or minimise permanent renal damage in recurrent UTIs. All children underwent ultrasonography (USG) and DMSA scan; 39 had MCUG (reference test). For predicting VUR: presence of hydronephrosis in ultrasonogram had sensitivity 75.9%, specificity 73.5%; presence of ureteral dilatation in ultrasonogram had sensitivity 48.3%, specificity 89.8%.

A retrospective review study (Park et al, 2015) (n=129 infants, age not stated, with [n=68] and without [n=61] UTI) assessed ureter dilatation during ultrasonography (US) for evaluating VUR in infants. The reference test was MCUG. Abdominal US images of infants who were diagnosed with UTI or only hydronephrosis without UTI (control group) were retrospectively reviewed. Ureter dilatation had a significant relationship with VUR for the UTI group (p=0.015), including among patients with a high-grade VUR (p=0.005); but not for the control (non-UTI) group (p=0.744). The relationship between ureter dilatation and VUR was different between the two groups for both all grades (p=0.014) and high-grade (p=0.004) VUR. For detecting high-grade VUR in the UTI group, ureter dilatation during ultrasonography had sensitivity 66.7%, specificity 80.3%, accuracy 79.4%.

A prospective study (Carovac et al, 2015) (n=120 children, average age 4.3 years, range 2 months to 16 years, with history of UTI) assessed sonographically demonstrated ureteral dilatation for detecting VUR. Contrast-enhanced voiding urosonography (VUS) using SonoVue was the reference test (VUS has diagnostic accuracy very close to that of MCUG – see below). Ureteral diameter greater than 3 mm was considered pathological [i.e. cut-off value] (n=61; n=59 normal). Proven VUR (reference test not stated) was graded into one of three stages. Statistical analysis showed significant correlation between type and grade of VUR. For detecting VUR, sonographically-confirmed ureteral dilatation had sensitivity 67.2%, specificity 81.4%, PPV 78.8%, NPV 70.6%, total diagnostic accuracy 74.2%.

Ultrasound combined with other factors to detect VUR and indicate MCUG

A study (Kobayashi et al, 2019) (n=231 young children, age not stated, brought to the emergency department of the National Centre for Child Health and Development with first febrile UTI) aimed to determine the combination of clinical, laboratory and ultrasonography factors correlating with grades IV to V VUR (severe VUR) in young children with a first febrile UTI, to indicate MCUG. Clinical, laboratory and ultrasonography findings were compared between children with grades IV to V VUR (high-grade VUR: n=19) and those with no or grades I to III VUR (normal or low-grade VUR: n=212). High-grade VUR was independently associated with poor clinical appearance, presence of a uropathogen other than E.coli, positive blood culture, hydroureter, and thickened renal pelvic wall. Proportion of high-grade

VUR was 0.7% with none of these factors present; 11.3% with any one factor present; 55.6% with two factors; and 85.7% with three factors. For detecting high-grade VUR, presence of one or more of any of these factors had sensitivity 94.7%, specificity 69.4%, PPV 23.1%, NPV 99.3%, LR+ 3.1, LR- 0.1.

A retrospective review study (Kido et al, 2015) (n=200 children, age not stated, with first UTI) assessed sex, clinical variables, laboratory variables, and ultrasonography, for predicting VUR during first UTI episode in paediatric patients; also aiming to define criteria to indicate MCUG (reference test). There was significant difference between patients with and without VUR for: sex (p=0.001), peak blood C-reactive protein levels (p<0.001), duration of fever after antibiotic administration (p=0.007), ultrasonography findings grade (p< 0.001). For predicting VUR, Grade IV to V ultrasonography findings with C-reactive protein levels of >=80 mg/L had sensitivity 47.8%, specificity 87.8%, odds ratio 6.59 (95%CIs = 3.26 to 13.33) (p<0.001).

Colour Doppler ultrasound

A retrospective study (Asanuma et al, 2016) (n=125 children, age not stated [80 with VUR], 250 renal units presenting with UTI or hydronephrosis [117 with VUR]) evaluated colour Doppler ultrasound measurement of ureteral jet angle as a non-invasive tool for detecting VUR prior to MCUG; with MCUG as reference test. Ureteral jet angle was measured as angle between the direction of the ureteral jet and interureteral ridge. Mean ureteral jet angle was significantly greater in refluxing units than in non-refluxing units, and angle value in each reflux grade became significantly greater according to grade. For detecting grade III to V VUR, AUC for ureteral jet angle was 0.81; this increased to 0.88 for detecting grade IV/V reflux. At cut-off angle >=55°, ultrasound detected grade III to V reflux with sensitivity 85.5%, and grade IV/V reflux with sensitivity 94.7% (specificity and AUC not stated). At cut-off angle >=70o, ultrasound diagnosed grade IV/V reflux with sensitivity 81.6%, specificity 82.7% (AUC not stated).

Intelligence gathering

Topic experts noted a recent Cochrane review in this area (Shaikh et al, 2016), on DMSA and RBUS for detecting VUR which has been included in this surveillance review.

Impact statement

Conventional renal bladder ultrasound (RBUS) to detect urinary tract anomalies including obstruction

Results from a single study indicated that ultrasound may be a sensitive test for detecting urethral obstruction; however, the evidence was inconclusive since there was no clear gold standard reference comparator.

Based on expert opinion from the committee, the current guideline recommends conventional renal bladder ultrasound (RBUS) to identify structural abnormalities of the urinary tract such as obstruction. Whilst not making a specific research recommendation, the current guideline had reported an evidence gap for diagnostic value and clinical effectiveness of ultrasound for detecting structural abnormalities of the urinary tract.

New evidence identified through surveillance supports the use of ultrasound, as currently recommended, for detecting structural abnormalities of the urinary tract.

New evidence is unlikely to change guideline recommendations.

Conventional renal bladder ultrasound (RBUS) to detect VUR

Current surveillance evidence, from a Cochrane review, a meta-analysis and 6 primary and modelling studies found that, for detecting VUR, ultrasound tends to have moderate specificity but low sensitivity. Sensitivity increases with severity of VUR grade and may reach moderate sensitivity to detect the most severe grades of VUR (grade 4 to 5). One study, using modelling techniques to augment ultrasound results, obtained very high sensitivity to detect higher grade VUR (grade 3+), counterbalanced by very low specificity.

Based on evidence and expert opinion from the committee, the current guideline recommends conventional RBUS to indicate MCUG - both for young infants aged <6 months who respond well to treatment (based on 'abnormal ultrasound'); and for infants and children aged >6 months and <3 years with atypical or recurrent UTI (based on 'dilatation on ultrasound'). Implicitly the use of ultrasound may include identifying VUR, as well as obstruction and other urinary tract anomalies. MCUG is used to confirm VUR in these targeted subgroups of children.

New evidence from the current surveillance is consistent with evidence used to inform the current guideline, on RBUS's modest capability to detect VUR, with higher specificity than sensitivity; therefore, no impact is anticipated on recommendations.

New evidence is unlikely to change guideline recommendations.

Uroepithelial thickening on ultrasound

A single retrospective study reported that, whilst RBUS had only moderate sensitivity for detecting high-grade VUR considering hydronephrosis and hydroureter as the only abnormal RBUS findings, sensitivity was high when uroepithelial thickening was also considered (specificity/AUC not stated).

The current guideline recommends RBUS to indicate MCUG for targeted subgroups of children based on age and UTI presentation/course. However, uroepithelial thickening is not currently included as a recommended ultrasound parameter.

The single study finding of high sensitivity of uroepithelial thickening on ultrasound for detecting VUR would need further confirmatory research, and no impact is anticipated on recommendations currently.

New evidence is unlikely to change guideline recommendations.

Ureteral dilatation on ultrasound

Three studies found ureteral dilatation on ultrasound to have moderate specificity with low sensitivity to detect VUR in infants or young children. The current guideline noted evidence from a Health Technology Assessment showing slightly improved diagnostic accuracy when using ureteral dilatation as a parameter to detect VUR on ultrasound. Ureteral dilatation on ultrasound may also indicate urethral obstruction.

The current guideline recommends RBUS to indicate MCUG based on 'dilatation on ultrasound' for infants and children aged >6 months and <3 years with atypical or recurrent UTI. New evidence is consistent with the current guideline recommendation to use ureteral dilatation to indicate MCUG.

New evidence is unlikely to change guideline recommendations.

Ultrasound combined with other factors to detect VUR and indicate MCUG

Two studies combined ultrasound with other factors, including patient, clinical and laboratory variables, aiming to improve diagnostic accuracy to predict VUR over ultrasound alone. One of these studies reported improved diagnostic accuracy compared with conventional RBUS to detect high grade (4 or 5) VUR, including high sensitivity. The second study reported slightly improved specificity, with sensitivity remaining low.

Whilst recommending RBUS to indicate MCUG for targeted subgroups of children based on age and UTI presentation/course, the current guideline does not mention combining ultrasound with other factors in connection with detecting VUR.

A single study suggests that using a model combining RBUS with other parameters to detect VUR may be better for detecting VUR than using RBUS alone. Further confirmatory evidence is required, including applicability of the model in an NHS setting; therefore, no impact is currently anticipated on recommendations.

New evidence is unlikely to change guideline recommendations.

Colour Doppler ultrasound measurement of ureteral jet angle

A single study found that colour Doppler ultrasound measurement of ureteral jet angle appeared to increase sensitivity to detect VUR compared with conventional ultrasound, without reducing specificity. The children's ages were not specified.

Previous surveillance identified a single study on ureteric jet Doppler Waveform, for which colour Doppler ultrasound appears to be typically used. It found the test had moderately useful diagnostic accuracy to detect VUR in children aged >2 years, which was higher than conventional ultrasound.

The current guideline does not mention use of colour Doppler ultrasound for detecting VUR. Cumulative evidence from current and previous surveillance suggests that colour Doppler ultrasound may be a suitable alternative or adjunct to conventional ultrasound to indicate

MCUG. Further confirmatory studies are required, which should include infants aged under 2 years, and no impact is expected currently on recommendations.

New evidence is unlikely to change guideline recommendations.

Magnetic resonance imaging (MRI) for detecting vesicoureteral reflux (VUR)

Previous surveillance summary

No relevant evidence was identified.

2020 surveillance summary

A single prospective study (Murakami et al, 2018) (n=108 children, age not stated) evaluated magnetic resonance imaging (MRI) to identify VUR in children with UTI. UTI was diagnosed based on DW-MRI and urine culture. Ureteral dilatation was measured using MRI in 96 patients with UTI. The relationship between ureteral dilatation in MRI and VUR was assessed in 46 patients who underwent MCUG. Ureteral dilatation findings on MRI had sensitivity 65.2%, specificity 73.9% to detect VUR.

Intelligence gathering

No topic expert feedback was relevant to this section.

Impact statement

A single study found that ureteral dilatation findings on MRI had low diagnostic accuracy for detecting VUR, similar to that of conventional ultrasound. No evidence on MRI for detecting VUR was identified either in the current guideline or from previous surveillance.

The current guideline recommends, for a limited range of presentations, initial ultrasound for detecting obstruction and also VUR in some circumstances, and MCUG for diagnosing VUR. As the new evidence did not find any improvement of MRI over conventional ultrasound, it is not expected to impact on recommendations.

New evidence is unlikely to change guideline recommendations.

DMSA renal scintigraphy for detecting vesicoureteral reflux (VUR)

Previous surveillance summary

No relevant evidence was identified.

2020 surveillance summary

A Cochrane review (Shaikh et al, 2016) (n=42 studies, number of children not stated) evaluated the accuracy of DMSA and RBUS in diagnosing VUR and high-grade VUR in children under 19 with a culture confirmed UTI. The reference test was MCUG.

Summary estimates for DMSA were: sensitivity 0.75 (95% CIs 0.67 to 0.81), and specificity 0.48 (95% CIs 0.38 to 0.57) for detecting VUR (n=19 studies); sensitivity 0.93 (95% CIs 0.77 to 0.98), and specificity 0.44 (95% CIs 0.33 to 0.56), for detecting high-grade VUR (n=10 studies).

The full paper clarifies that studies were included only where DMSA occurred within one month of the acute infection.

A retrospective study (Balestracci et al, 2019) (n=122 children aged 3 to 18 years, median 5.4 years, with febrile UTI [fUTI] history, evaluated at a hospital nephrology unit in Argentina) assessed late (6-months) DMSA renal scan for identifying high-grade (III-V) VUR in children aged over 3 years who had a history of fUTI which had not been investigated in a timely way. The reference test was MCUG, and renal and bladder ultrasound (RBUS) was also performed. For detecting all grades of VUR (n=58), late DMSA scan (i.e. after acute phase of illness has passed) had sensitivity 93.1%, specificity 75%, NPV 92.3%, PPV 77.1%. For high-grade VUR, sensitivity and NPV reached 100%.

A retrospective study (Wongbencharat et al, 2016) (n=387 infants aged <1 year) investigated effectiveness, including cost and benefits, of renal bladder ultrasound (RBUS) and late 6-month DMSA renal scan to detect high-grade VUR in infants aged <1 year after first febrile UTI. MCUG was the reference test. For prediction of high-grade VUR (n=8), late (6-month) DMSA scan had sensitivity 87.5%. DMSA scan also identified abnormal renal parenchyma (n=22).

Intelligence gathering

Topic experts noted a recent Cochrane review in this area (Shaikh et al, 2016), on DMSA and RBUS for detecting VUR which has been included in this surveillance review.

Impact statement

Three studies were included in the current surveillance, including one Cochrane review which evaluated DMSA for detecting VUR.

Summary estimates from the Cochrane review indicated DMSA had sensitivity ranging from low to moderate, with low specificity, for detecting VUR of any grade. For detecting high-grade VUR, high sensitivity was obtained, though with low specificity. However, studies were only included for which DMSA scan was carried out within 1 month of the acute infection. This criterion may have been used since some countries routinely use DMSA for detecting APN during the acute phase of UTI, as well as renal scarring at late phase. In these countries DMSA might be considered for detecting VUR at the same time as APN, and this was likely the main concern of the Cochrane review.

The 2 individual (non-review) studies both focused on late-phase (rather than acute or near-acute phase) DMSA scan for detecting VUR. One study reported relatively high diagnostic test accuracy in children aged 3 to 18. The second study found late DMSA scan to have moderate sensitivity for predicting high-grade VUR, though did not report specificity.

Compared with ultrasound, overall, DMSA has reasonable sensitivity but lower specificity for detecting VUR. Compared with MCUG, DMSA has lower sensitivity and specificity.

No evidence on DMSA for detecting VUR was identified either in the current guideline or from previous surveillance. Topic experts noted the recent relevant Cochrane review, included in this surveillance review.

The current guideline recommends, for a limited range of presentations, initial ultrasound for detecting obstruction and also VUR in some circumstances, and MCUG for diagnosing VUR in infants aged <6 months with recurrent UTI. It recommends DMSA in specific circumstances for detecting renal parenchymal defects 4 to 6 months after acute infection (late-phase DMSA); however, not for detecting VUR.

Unlike in some other countries which routinely use DMSA to detect APN, the current guideline recommends highly targeted late-phase DMSA to detect renal scarring. Evidence from the current surveillance indicates that DMSA scan has relatively low specificity for detecting VUR compared with ultrasound, and lower diagnostic accuracy than MCUG; therefore, the new evidence is not expected to impact on recommendations.

New evidence is unlikely to change guideline recommendations.

Identifying renal damage (including renal parenchymal defects)

Magnetic resonance imaging (MRI) for detecting renal damage

Previous surveillance summary

No relevant evidence was identified.

2020 surveillance summary

A single prospective study (Bosakova et al, 2018) (n=31 children [30 girls] aged 3 to 18 years with first episode of febrile UTI, with no previously-detected congenital malformation of the urinary tract) assessed whether diffusion-weighted magnetic resonance imaging (DW-MRI) was comparable with DMSA (reference test) to demonstrate acute renal parenchymal lesions in children with febrile UTI. DMSA and DW-MRI were both performed first within 5 days of UTI diagnosis, then at 6 months to detect late lesions. DW-MRI confirmed acute inflammatory changes of the renal parenchyma (mostly unilateral) in all 31 patients (100%), while DMSA detected inflammatory lesions in 22 children (71%; p = 0.002). Lesions were multiple in 26/31 children (84%) on DW-MRI, and in 9/22 (40%) on DMSA. At the 6-month control examination, scarring of the renal parenchyma was found equally by DW-MRI and

DMSA-SRS in five patients (16%), three of whom were the same patients. Overall concordance of positive and negative late findings occurred in 87% of patients, and there was correspondence in anatomical location of acute and late lesions.

Intelligence gathering

No topic expert feedback was relevant to this section.

Impact statement

A single study evaluated diffusion-weighted MRI (DW-MRI) for detecting renal scarring, as an alternative to DMSA scan. Of 31 patients aged >3 years enrolled with febrile UTI; DW-MRI identified late-phase renal parenchymal scarring in 5 patients. Whilst DMSA scan also identified 5 patients with late-phase renal scarring, only 3 of these were the same patients as for DW-MRI.

No studies on MRI for detecting renal scarring were reported from previous surveillance. Evidence informing the current guideline on MRI for detecting renal scarring includes 3 studies, reporting diagnostic test accuracy ranging from low to high, for both sensitivity and specificity. The committee commented on the promise of MRI for detecting renal scarring. Unlike DMSA, MRI does not involve a radiation burden to the child, does not require invasive catheterisation, and may possibly be used without sedation, particularly with older children. The committee noted that experience and evidence with this method are limited, and made a research recommendation for further evaluation, including cost-effectiveness.

The current guideline recommends DMSA scan at 4 to 6 months for detecting renal scarring after the acute stage, for select groups depending on age and UTI presentation/course.

The current surveillance found very limited evidence suggesting that DW-MRI has very useful diagnostic accuracy for detecting renal scarring; and may therefore have potential as an alternative to DMSA. The limited evidence found may suggest that, whilst both DW-MRI and DMSA are highly sensitive methods to detect renal scarring, they may both also miss renal scarring. No evidence was identified on cost-effectiveness. Results would need to be confirmed through further research, and no impact is currently expected on recommendations.

New evidence is unlikely to change guideline recommendations.

Ultrasound for detecting renal damage

Previous surveillance summary

Previous surveillance in 2011 found a single study (Montini et al, 2009) evaluating diagnostic accuracy of ultrasound and MCUG for predicting long-term parenchymal renal damage after

a first UTI episode. Montini et al found that these tests were poor predictors of long-term renal damage, recommending DMSA scan at 6 months.

2020 surveillance summary

Three studies were identified on ultrasound for detecting renal damage:

A retrospective study (Sahin and Tasbent, 2018) (n=364 children with UTI, age not stated, 630 kidneys) assessed renal ultrasonography (USG) for detecting renal scars in children with UTIs, compared with DMSA scan as reference test. For detecting renal scarring, as part of evaluating development of progressive renal damage, USG had sensitivity 57.1%, specificity 89.6%, PPV 40.8%, NPV 94.4%.

A retrospective review study (Marceau-Grimard et al, 2017) (n=160 children) in a paediatric tertiary centre, age not stated) evaluated whether renal ultrasound (US) is equivalent or sufficient to assess renal anomalies, compared with DMSA as the reference standard. US had sensitivity 36% and specificity 96% to detect renal parenchymal defects. Results were no different comparing newer or older US machines.

A study (Bush et al, 2015) (n=618 children, median age 3.4 years) assessed test characteristics for renal-bladder ultrasound (RBUS) to identify renal damage following febrile UTI (fUTI), for infants aged 2 to 24 months (as per American Academy of Pediatrics [AAP] guideline recommendations) and for older children. The reference test was DMSA, >=3 months after fUTI. Timing of RBUS was not stated; however, the AAP guidelines recommend RBUS within 2 days, and/or later (exact time not specified) for children showing significant clinical improvement. For detecting renal damage, RBUS had sensitivity 34%, PPV 47%. Data was not presented for specificity/AUC.

Intelligence gathering

No topic expert feedback was relevant to this section.

Impact statement

Three studies investigated use of ultrasound for detecting renal damage. Two of these studies found ultrasound to have moderate to high specificity with low sensitivity; the third study found low sensitivity and did not report specificity. No difference was found in diagnostic accuracy between newer or older ultrasound machines.

The current guideline included evidence from 6 studies, including 4 within a Health Technology Assessment. For 3 of these studies specifying detection of late-phase renal scarring, sensitivity for ultrasound compared with late-phase DMSA scan ranged from very low to moderate, with specificity reported to be high in all 3 studies.

Previous surveillance identified a single study evaluating diagnostic accuracy of ultrasound and MCUG for predicting long-term parenchymal renal damage after a first UTI episode. The study concluded that these tests were poor predictors of long-term renal damage, recommending DMSA scan at 6 months.

Ultrasound is already currently recommended within NICE guideline CG54 for particular high-risk groups; however, this is aimed mainly at identifying obstruction and also potentially VUR prior to MCUG testing. Given sufficient diagnostic accuracy, ultrasound might potentially also be used to indicate subsequent DMSA scan.

Overall, evidence from cumulative surveillance suggests low to moderate diagnostic test performance of ultrasound for detecting renal damage. Results from evidence informing the current guideline were highly heterogeneous, and generally (with a single exception) showed very low sensitivity and high specificity. The surveillance evidence suggests that ultrasound is diagnostically inferior to currently recommended DMSA and, if used to indicate subsequent DMSA scan, would potentially miss more than half of children with renal scarring due to its low sensitivity.

Using renal ultrasound to indicate DMSA scan, for the subgroups of children who receive ultrasound according to current guideline recommendations, is thus highly unlikely to improve on the current guideline approach; therefore, no impact of the new surveillance evidence is anticipated on recommendations.

New evidence is unlikely to change guideline recommendations.

Overall imaging schedule including targeting

Previous surveillance summary

Previous surveillance, including an evidence update, identified studies focusing on tests to identify structural and functional abnormalities of the urinary tract, including vesicoureteral reflux (VUR); as well as tests to detect renal damage.

Previous surveillance reviews concluded from these studies that more aggressive imaging strategies, such as DMSA for all patients, may have higher sensitivity for detecting VUR and renal scarring. However, they also appear to have lower specificity and are associated with higher costs and radiation exposure. The imaging protocol recommended by the NICE guideline appears to have a high specificity but low sensitivity for detecting VUR and scarring. Although relatively low cost, the NICE protocol may be associated with more radiation exposure than other guidelines (Routh et al, 2012; La Scola et al, 2013).

The evidence from previous surveillance was considered to have no impact on current recommendations.

2020 surveillance summary

Two studies provided evidence to inform potential targeting of imaging, including by age, going beyond diagnostic test accuracy to focus on clinical characteristics, outcomes and value.

A prospective study (Hsu et al, 2016) (n=388 children <=24 months hospitalised with first diagnosed febrile UTI, of which 61 <=2 months) examined whether clinical characteristics,

antimicrobial resistance, imaging findings and clinical outcomes differ with age group, comparing infants <= 2 months with children 2 to 24 months. Renal ultrasonography showed abnormal findings (type not stated) in 130 patients, with no difference in rate between the age groups. VUR was present in 130 children, including 93 with high-grade (III-V) VUR. VUR was more prevalent in infants <=2 months of age (P = 0.007), with no difference in prevalence of high-grade (III-V) VUR between the age groups. Incidence of renal scarring did not differ between the age groups.

A retrospective study (Harper et al, 2016) (n=318 children aged 2 to 24 months, mean age 6.9 months, with first UTI episode) aimed, using decision curve analysis (DCA), to assess post-UTI sonography, with and without biological markers of inflammation, to predict recurrent UTI in children aged 2 to 24 months without known uropathy. 210 children presented with significant inflammation. During 30-month follow-up, significantly more children with abnormal post-UTI sonographic findings (n=30 total) experienced UTI recurrence (n=18 total), compared with children with normal sonography (relative risk of UTI recurrence 7.68; 95%CIs = 3.03 to 19.46). The authors reported that, taking into account the effect of false-positives and false negatives, DCA revealed that for threshold probabilities of >30 %, at which patients/doctors are concerned about unnecessary interventions, neither post-UTI sonography or post-UTI sonography plus biological markers of inflammation have sufficient value to improve care (no further data presented).

Intelligence gathering

A topic expert referred to Okarska-Napierala (2017) which compared various national and international paediatric UTI guidelines.

An enquiry was received from a Trust in the North East of England, where regional guidelines are preferred over the current NICE guideline. The Trust had audited their practice locally and expressed concern that the current guideline may miss too many potentially serious issues relating with UTI, even if costing less in terms of imaging required. Real-world data from the audit was presented as supporting evidence.

Impact statement

Evidence to inform potential targeting of imaging by age

A study considered differences in clinical characteristics, antimicrobial resistance, imaging findings and clinical outcomes for young infants aged <2 months hospitalised with first UTI, compared with infants and children aged between 2 months and 2 years. The only factor found to be different was higher VUR prevalence in the younger infants, though there was no difference in prevalence of high-grade VUR between the two groups.

A second study used decision curve analysis to assess whether post-UTI RBUS, potentially together with biomarkers of inflammation, has value to improve care for young children aged 2 to 24 months with first UTI episode, especially to predict recurrent UTI. Whilst ultrasound helped to predict recurrent UTI, the authors considered that overall, with or without

biomarkers, ultrasound provided insufficient added value due to its lack of diagnostic accuracy leading to potential unnecessary interventions.

The study populations in the 2 studies identified in current surveillance directly relate to the American Academy of Pediatrics (AAP) UTI guideline, which recommends ultrasound after first UTI for all children aged 2 to 24 months after first febrile UTI.

The current guideline recommends ultrasound for all children aged <6 months following first UTI, and by exception for older infants and children, e.g. for recurrent UTI. Thus, the new surveillance evidence directly relates to a slightly different, though overlapping, population compared with the current guideline recommendations.

Although the age groups do not match precisely, the new surveillance evidence appears to broadly support current guideline recommendations which minimise imaging through targeting higher-risk subgroups; including focusing RBUS more toward infants aged <6 months; therefore, no impact is anticipated on recommendations.

New evidence is unlikely to change guideline recommendations.

1.4 Surgical intervention

Surveillance proposal

This section of the guideline should not be updated.

Previous surveillance summary

Previous surveillance identified 12 studies focusing on surgical intervention for VUR. These included a Cochrane review (Nagler et al, 2011) which evaluated several treatments for VUR including surgical management – an update is included in this current 2019 surveillance review (Williams et al, 2019). Other studies (Ismaili et al, 2006; Brandstrom et al, 2010; Holmdahl et al, 2010; Jodal et al, 2006; Elder et al, 2006, 2007; Hodson et al, 2007; Venhola et al, 2007; Benoit et al, 2006; Oberson et al, 2007; Tanriverdi et al, 2009) investigated various aspects of surgical management and comparison or combination with other interventions, including: surgical correction of VUR (with or without antibiotics); endoscopic treatment; antibiotic treatment/prophylaxis and surveillance only.

Overall, the previous surveillance provided some evidence of benefit for endoscopic injection treatment: it may decrease the rate of recurrent UTI when used with antibiotic prophylaxis compared with antibiotics alone (Elder et al, 2007; Brandstrom et al, 2010), although a related publication from the same Swedish RCT also found that recurrent dilating VUR was observed in some patients after 2 years (Holmdahl et al, 2010). Elder et al, (2006) found that endoscopic treatment provides a high rate of successful VUR correction, although this may decrease with increasing VUR grade, with further treatments sometimes necessary.

Hodson et al (2007) found that surgery, including endoscopic treatment, has little if any benefit over antibiotics alone. Benoit et al (2006) considered that endoscopic treatment may

be more cost-effective than ureteral reimplantation for children who meet the standard criteria for surgery.

Overall, there was little evidence of significant clinical benefit for surgery compared with antibiotic prophylaxis, for preventing either recurrent UTI or renal damage. Previous surveillance reviews concluded that no sufficiently conclusive new evidence had been identified to impact on current recommendations.

2020 surveillance summary

An updated Cochrane review (Williams et al, 2019) (34 RCTs, 4,001 children) examined benefits and harms of management interventions specifically for children with VUR, including surgical reimplantation of ureters (7 studies), and (less-intrusive) treatment by endoscopic injection under the ureters (4 RCTs, 425 children). Both treatments are aimed at resolving VUR, to help prevent UTI recurrence and/or renal scarring. Outcomes assessed included recurrent UTI, renal scarring, and resolution of VUR.

Surgical reimplantation of ureters plus antibiotics was compared with long-term antibiotic prophylaxis alone (7 studies), though only 2 studies (429 children) reported the outcome febrile UTI. A significantly reduced risk of repeat febrile UTI was found for surgery compared with antibiotic prophylaxis alone. No significant difference was found between surgery and antibiotic prophylaxis alone for new renal parenchymal defects at 4 to 5 years, detected by intravenous pyelogram (4 studies, 572 children).

Endoscopic treatment with or without antibiotic was compared with antibiotic prophylaxis (3 RCTs, 254 children), and with a 'no treatment' arm for one of the RCTs (1 RCT, 134 children). Endoscopic treatment significantly improved both full resolution of VUR and improvement in VUR grade after 1 to 2 years. Compared with antibiotic prophylaxis, endoscopic treatment slightly reduced the risk of recurrent febrile UTI after 1 to 2 years, though this did not reach statistical significance. Compared with no treatment, endoscopic treatment marginally statistically significantly reduced the risk of recurrent febrile UTI after 1 to 2 years. No significant increase in new and progressive renal parenchymal abnormalities was found for endoscopic treatment, compared with both antibiotic prophylaxis and no treatment.

Whilst individual RCTs were also identified which addressed this question, these were included in the Cochrane review (Williams et al, 2019); hence they are not summarised here separately, to avoid 'double-counting' the evidence.

Intelligence gathering

No topic expert feedback was relevant to this section.

Impact statement

Surgical reimplantation of ureters

Results from a Cochrane review indicated that surgical reimplantation of ureters plus antibiotic prophylaxis significantly reduced risk of repeat febrile UTI compared with antibiotics alone; but had no impact on other outcomes.

The previous surveillance evidence found little evidence of significant clinical benefit for surgery (including surgical reimplantation of ureters) compared with antibiotic prophylaxis, for preventing either recurrent UTI or renal damage.

The current guideline includes 7 trials comparing surgical ureteric reimplantation with antibiotic prophylaxis, concluding that, when compared with prophylaxis, primary surgical management of VUR offers no added benefit in prevention of recurrent infections or preventing development of new renal parenchymal defects.

Endoscopic injection

Results from the same Cochrane review indicated that endoscopic injection with or without antibiotics significantly improved VUR resolution and/or grade after 1 to 2 years, slightly reduced recurrent febrile UTI after 1 to 2 years compared with no treatment - though not compared with antibiotic prophylaxis; and had no impact on renal scarring.

Trials were ongoing for endoscopic injection when the current guideline was produced. Previous surveillance evidence indicated some possible evidence of benefit for endoscopic injection in decreasing the rate of recurrent UTI; however, this was insufficient to impact on the guideline recommendations.

The current guideline states that surgical management of VUR is not routinely recommended. The cumulative surveillance evidence indicates a potential benefit of surgical reimplantation in reducing risk of repeat febrile UTI compared with antibiotic prophylaxis alone. Endoscopic injection treatment may slightly reduce recurrent febrile UTI after 1 to 2 years compared with no treatment - though not compared with antibiotic prophylaxis. Neither of these surgical interventions for VUR appears to reduce renal scarring, which is the main concern for longer-term health sequelae including hypertension and CKD.

The new and cumulative surveillance evidence appears consistent with the current guideline recommendations in that, whilst maintaining some flexibility to respond to individual clinical circumstances, the current guideline does not recommend routine surgical intervention for children with VUR.

Further research demonstrating evidence of benefit from surgery on broader outcomes including renal scarring would be required before considering this as an area for update. Therefore, no impact is currently anticipated on recommendations.

New evidence is unlikely to change guideline recommendations.

1.5 Follow-up

Surveillance proposal

This section of the guideline should not be updated.

Previous surveillance summary

Four studies were identified from previous surveillance relating with risk factors and outcomes which might indicate need for long-term follow-up following UTI.

Two studies examined particular risk factors and associations (Geback et al, 2014, Geback et al, 2015). One study, of women with childhood UTI-related renal damage, identified a link between renal damage and hypertension lasting throughout adulthood. The second study, of women who had experienced childhood UTI, found that women with bilateral or severe individual kidney damage had significantly reduced estimated glomerular filtration rate (eGFR), indicating that these women may need to be considered for regular monitoring of eGFR and blood pressure.

Two studies, including a systematic review, examined long-term outcomes of childhood UTIs, in the context of follow-up (Hannula et al, 2011, Toffolo et al, 2012). The evidence suggested that the risk of long-term complications after UTI in childhood appear to be low, which was consistent with the guideline.

The conclusion from previous surveillance reviews was that the evidence would not impact current recommendations.

2020 surveillance summary

Four studies were identified on follow-up for children who have experienced UTI. Two of these studies were on follow-up for renal parenchymal defect, relating to hypertension and chronic kidney disease (CKD) as outcomes. Two studies were found relating to obesity for children with VUR.

Follow-up for renal parenchymal defects

A retrospective review study (Bundovska-Kocev et al, 2019) (n=101 children aged 1 to 12 years, median age 5.2, years, suffering from UTI and VUR) aimed to identify risk factors predictive for renal dysfunction after long-term follow-up, in adults with VUR who had experienced childhood UTI. Outcomes examined included unilateral and bilateral renal scarring, and presence of proteinuria. Renal function was determined from eGFR. Follow-up time was between 8 and 32 years (mean 21 years). Renal scarring was found to be a significant risk factor for CKD development in patients with childhood VUR. Bilateral renal scarring was an independent predictor of greater risk for CKD development. Proteinuria was also a significant independent predictor of reduced renal function.

A prospective prevalence study (Hooman et al, 2017) (n=60 children aged 5 to 15 years with previous history of febrile UTI and various degrees of renal scars) assessed early blood

pressure abnormalities in children with a history of UTI with various degrees of renal scars. It found that abnormal blood pressure significantly correlated with severity of renal parenchymal scar, as well as with presence of VUR, microalbuminuria, and carotid intima media thickness.

Healthy weight/obesity and link with vesicoureteral reflux (VUR)

A secondary analysis of two longitudinal studies (1 RCT and 1 observational study) (Gaither et al, 2019) (n=446 children, 51% aged <1 year at study entry), examined risk factors for overweight/obesity in children at risk for recurrent UTI. It identified significant risk factors for becoming overweight as: persistent VUR; younger age; Hispanic/Latin ethnicity. It identified having bladder/bowel dysfunction (BBD), and having antibiotic prophylaxis, as insignificant risk factors for becoming overweight.

A retrospective review of medical records (Byun et al, 2017) (n=186 children) examined obesity as a risk factor for febrile UTI and renal scar formation, in children with primary VUR who had recurrent febrile UTI (more than twice). It found that obesity in patients with VUR is significantly associated with risk of both renal scar formation, and febrile UTI (based on presence of inflammatory markers).

Intelligence gathering

A topic expert highlighted mixed views among the paediatric nephrology community about recommendation 1.5.1.6: “Infants and children with a minor, unilateral renal parenchymal defect do not need long-term follow-up unless they have recurrent UTI or family history or lifestyle risk factors for hypertension.” The topic expert indicated that clinicians in practice would usually recommend follow-up for possible hypertension for all children with a renal parenchymal defect, including (by implication) children with minor unilateral defects.

Impact statement

Follow-up for renal parenchymal defects

An observational study identified through current surveillance indicated renal scarring, particularly if bilateral, as a significant risk factor for CKD development, and proteinuria as a risk factor for reduced renal function in patients with childhood VUR. Abnormal blood pressure, in children with a previous history of febrile UTI and various degrees of renal scars, significantly correlated with severity of renal parenchymal scar in a second observational study, and with presence of VUR, microalbuminuria, and carotid intima media thickness.

The current guideline noted there was no direct evidence to address any follow-up strategies for children who have had UTI, and this situation has not changed. Previous surveillance identified links between renal damage and hypertension lasting throughout adulthood. Women who had experienced childhood UTI with bilateral or severe individual kidney damage, had significantly reduced eGFR, with the study concluding these women should be considered for regular monitoring of eGFR and blood pressure.

A topic expert suggested the current recommendation to not routinely follow-up infants and children with a minor, unilateral renal parenchymal defect might be too exclusive.

Healthy weight/obesity link with VUR

New evidence from 2 studies indicated that children with VUR who are also obese are at greater risk of both renal scar formation and febrile UTI, and that persistent VUR is itself a risk factor for obesity.

The current guideline noted there was no direct evidence to address any follow-up strategies for children who have had UTI, and this situation has not changed. No evidence on children with obesity and VUR being at risk of renal scarring was identified in previous surveillance.

The current guideline recommends follow-up by a paediatric specialist for children with recurrent UTI or abnormal imaging, including monitoring and management to slow CKD progression, for children with bilateral renal abnormalities, impaired kidney function, raised blood pressure or proteinuria. Assessment for children with renal parenchymal defects should include height, weight, blood pressure and routine testing for proteinuria. Children with a minor, unilateral renal parenchymal defect are recommended to receive long-term follow-up only if they have recurrent UTI, family history or lifestyle risk factors for hypertension.

Cumulative evidence on the links between renal parenchymal defects (including from renal scarring), hypertension and clinical sequelae such as CKD broadly supports the recommendations to offer follow-up with a specialist. A topic expert suggested that all children with a renal parenchymal abnormality, including minor and unilateral, may need long-term follow-up. New surveillance evidence, whilst not directly refuting this view, suggested that having bilateral and/or severe renal defects significantly increases the risk of subsequent CKD. Previous surveillance also found that women who had experienced childhood UTI with bilateral or severe individual kidney damage had significantly reduced eGFR. Whilst noting the limited nature of the evidence on follow-up, the current guideline recommendations appear consistent with the cumulative evidence base. Further evidence would be required to recommend long-term follow-up for all children with any renal parenchymal defect following UTI, and no impact of the new evidence and information is currently anticipated on recommendations.

Evidence from the current surveillance may suggest that clinicians potentially consider links between obesity/BMI and VUR in follow-up for children who have had a UTI, though there may be limitations with the studies including their generalisability. It is unclear whether VUR on its own increases the risk of renal scarring, and whether obesity then provides an added risk over and above any risk from VUR. Further confirmatory research would be required for any change to be made to the current guideline, and no impact of the new evidence is currently anticipated on recommendations.

New evidence is unlikely to change guideline recommendations.

1.6 Information and advice for children, young people and parents or carers

Surveillance proposal

This section of the guideline should not be updated.

Previous surveillance summary

No new evidence or intelligence was found in previous surveillance on information and advice to children, young people and parents/carers.

2020 surveillance summary

A systematic review (Gates et al, 2018) (4 studies, sample size 20 to 2,726 parents, of children aged <1 to 12 years experiencing 1 to >10 UTIs) examined parents' experiences and information needs. Parents were not always aware of UTI symptoms, and generally received little information, often seeking it online though they desired it by other means. Some parents were not confident in their HCP's knowledge of UTIs. Inadequate information about diagnostic tests sometimes resulted in fear and non-compliance. No quantitative data was provided.

Intelligence gathering

No specific input was received on this area from topic experts during this surveillance. Some feedback was received from parents of children with UTI that their children had experienced missed diagnoses; and were now suffering with recurrent UTI. This was framed such that the parents were concerned about the diagnosis and treatment which their children were receiving; however, this may also raise questions around communication and information provided by health care professionals.

Impact statement

A systematic review found that parents were not always aware of UTI symptoms, and generally received little information from healthcare professionals, often seeking it online. Some parents were not confident in their health care provider's knowledge of UTIs, and inadequate information about diagnostic tests sometimes resulted in fear and non-compliance.

The current guideline noted benefits of advising parents/carers on UTI when their child is still very young and in contact with health professionals. Current recommendations are for health care professionals to ensure they provide information on aspects relating with prompt symptom recognition, diagnosis, treatment, prevention and possible recurrence, prognosis, and nature and reasons for any investigations and longer-term management.

New evidence identified in the surveillance review appears supportive of current guideline recommendations since the study notes that parents need information about UTI symptoms,

and the current guideline encourages HCPs to provide information to parents. No impact on recommendations is expected.

New evidence is unlikely to change guideline recommendations.

Areas not currently covered by the guideline

In surveillance, evidence was identified for areas not covered by the guideline. This new evidence has been considered for possible addition as a new section of the guideline.

Biomarker tests as alternative to imaging to detect VUR

Surveillance proposal

This new section should not be added.

Previous surveillance summary

No relevant evidence was identified.

2020 surveillance summary

3 studies were found relating to biomarkers for detecting VUR, including in combination with other factors, covering 4 different biomarkers in total.

Blood neutrophil percentage (BNP)

A retrospective cohort study (Bahat et al, 2019) (n=195 infants aged <=2 months with first UTI admitted to a paediatric ward) assessed predictors for grade 3 to 5 VUR in infants <=2 months of age admitted for first UTI. Reference test for VUR was MCUG, and for UTI, urine culture.

Infants with grade 3 to 5 VUR (n=20) had higher blood neutrophil percentage (BNP) (65% vs. 46%, P<0.001). With cut-off level >53%, BNP had sensitivity 100%, specificity 60%, AUC 0.82 (95%CIs = 0.75 to 0.89) for detecting grade 3 to 5 VUR; the authors reported this was the best single marker. In a multivariate model, BNP and hydronephrosis combined had AUC 0.86 (95%CIs = 0.79 to 0.93, P=0.007).

Neutrophil-to-lymphocyte ratio (NLR)

A retrospective cohort study (Bahat et al, 2019) (n=195 infants aged <=2 months with first UTI admitted to a paediatric ward) assessed predictors for grade 3 to 5 VUR in infants <=2 months of age admitted for first UTI. Reference test for VUR was MCUG, and for UTI, urine culture.

Infants with grade 3 to 5 VUR also had higher neutrophil-to-lymphocyte ratio (NLR) (2.6 vs. 1.3, P<0.001), With cut-off level >1.65, NLR had sensitivity 100%, specificity 61% for detecting grade 3 to 5 VUR.

Delta neutrophil index (DNI)

A study (Kim et al, 2017) (n=288 young infants, age not stated) evaluated delta neutrophil index (DNI) for predicting VUR, as well as acute pyelonephritis (APN) (see section 1.1.9 above). DNI was measured, together with conventional inflammatory markers: white blood cell (WBC) count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP). For VUR diagnosis, DNI demonstrated the highest AUC: 0.62 (95%CIs = 0.542 to 0.698; P<0.01; data not provided for other tests).

Intelligence gathering

No topic expert feedback was relevant to this section.

Impact statement

Two studies assessed a total of 3 specific biomarkers to indicate use of MCUG. One of these studies found promising results with very high sensitivity for both blood neutrophil percentage (BNP) and neutrophil-to-lymphocyte ratio (NLR), for detecting VUR grade 3 to 5 in young infants aged <=2 months. Delta neutrophil index (DNI) was found to be insufficiently accurate in a second study.

No other evidence is available from the current guideline or previous surveillance.

The guideline currently recommends ultrasound both in young infants aged <6 months who respond well to treatment, and for infants and children aged >6 months and <3 years with atypical or recurrent UTI.

Whilst preliminary results for the 2 biomarkers BNP and NLR appear promising, further research confirming diagnostic accuracy of these biomarkers to indicate MCUG, and their applicability in an NHS setting, is needed before considering this as an area for inclusion in the guideline.

New evidence is unlikely to impact on the guideline.

Biomarker tests as alternative to imaging to detect renal damage

Surveillance proposal

This new section should not be added.

Previous surveillance summary

No relevant evidence was identified.

2020 surveillance summary

Soluble ST2 levels

(Study also investigated: serum interferon-gamma, IL-6, IL-10, soluble tumour necrosis factor receptor 1, and TGF-beta)

A retrospective study (Ohta et al, 2019) (n=28 children, age not stated, with upper UTI, at a tertiary centre) evaluated whether soluble ST2 levels can be biomarkers of subsequent renal scarring in patients with upper urinary tract infection. DMSA was the reference test. Clinical data and serum cytokine levels, including soluble ST2 levels, were compared between children with and without renal scars. For differentiating between scar and non-scar groups, serum soluble ST2 had sensitivity 92.9%, specificity 64.3%, AUC 0.79. Only soluble ST2 showed useful diagnostic accuracy and was fully reported on.

C-megalin

A study (Yamanouchi et al, 2018) (n=37 children, median age 1.36 years, range 0.52 to 12.17 years, with history of febrile UTI who had DMSA scan 4 months or more after previous fUTI episode) assessed urinary biomarkers for diagnosing renal scarring after fUTI. A spot urine sample on the same day as DMSA scan (reference test) measured levels of: total protein, N-acetyl-beta-D-glucosaminidase (NAG), beta2-microglobulin (BMG), urine neutrophil gelatinase-associated lipocalin (uNGAL), liver-type fatty acid binding protein (L-FABP), and C-megalin (full-length megalin). Results were corrected for urinary creatinine (Cr) and compared between the groups with (n=23) and without (n=14) renal scarring. Urinary levels of C-megalin were also measured in healthy control subjects. No significant differences were found between the groups for: total protein, NGAL, L-FABP, NAG, and BMG levels. C-megalin levels were significantly higher in the renal scarring group than in both the non-renal scarring group and healthy controls ($P<0.001$). With cut-off value 6.5pmol/nmol, for detecting renal scarring, urinary C-megalin/Cr had sensitivity 92.9%, specificity 73.9%, AUC 0.85.

Plasma neutrophil gelatinase-associated lipocalin (pNGAL)

A study (Yun et al, 2018) (n=64 infants hospitalised for febrile UTI) assessed neutrophil gelatinase-associated lipocalin (NGAL) as a marker for detecting cortical defects (CD), and the appropriate diagnostic cut-off value of NGAL in infants with febrile UTI. Infants were divided into groups with (n=43) and without (n=21) CD, based on DMSA scan (reference test). White blood cell count, C-reactive protein, and plasma NGAL (pNGAL) levels were determined before antibiotic therapy and compared between the two groups. pNGAL level was significantly higher in the CD group than in the non-CD group (340 mug/L vs 214 mug/L, P=0.002), and was the only independent predictor of CD (odds ratio 2.759, P=0.039). pNGAL had the highest AUC: 0.745 (95%CIs = 0.561 to 0.821; P=0.014). At cut-off value 267 mug/L, pNGAL had sensitivity 72.1%; specificity 71.4%.

Matrix metalloproteinase 9 (MMP9) and tissue inhibitor of metalloproteinase 1 (TIMP1)

A study (Abedi et al, 2017) (n=61 children, age not stated, who had experienced an APN episode) assessed urinary concentrations of matrix metalloproteinase 9 (MMP9) and tissue inhibitor of metalloproteinase 1 (TIMP1) in children with acute pyelonephritis (APN), and the potential to develop renal scarring. Children who had experienced an APN episode were divided into those with scarring (group 1: n=16), and those (group 2: n=38) with normal DMSA scan (reference test). Urinary levels of MMP9 and TIMP1 were measured during acute phase of infection. Urinary levels were significantly higher in group 1 than in group 2 for both MMP9 (p=0.037) and TIMP1 (p=0.022).

With cut-off value 75.5 ng/mL, MMP9 had sensitivity 62.5%, specificity 71.1%, PPV 48%, NPV 82%). With cut-off value 16.1 ng/mL, TIMP1 had sensitivity 75%, specificity 55.3%, PPV 41%, NPV 84%. With cut-off value 1310.7 ng/mL, the combination of MMP9 and TIMP1 together had sensitivity 75%, specificity 60.5%, PPV 44%, NPV 85%.

Intelligence gathering

No topic expert feedback was relevant to this section.

Impact statement

Single small studies found that, for detecting renal scarring:

- Serum soluble ST2 had high sensitivity with low specificity.
- Urinary C-megalin/Cr (i.e. corrected for creatinine) had high sensitivity with lower specificity.
- pNGAL had low diagnostic accuracy for detecting renal scarring, with balanced sensitivity and specificity.
- MMP9 and TIMP1 had low diagnostic accuracy for detecting renal scarring, both singly and in combination.

No evidence was identified from previous surveillance or the current guideline, neither was any relevant information received from topic experts.

The current guideline recommends using DMSA scan to detect (late-phase) renal scarring for indicated higher risk subgroups by age and UTI presentation/course, as per the imaging schedule (1.3). DMSA results inform subsequent treatment and longer-term follow-up for these children.

Soluble ST2 may have moderate diagnostic accuracy to detect renal scarring, with high sensitivity suggesting potential to indicate subsequent (late-phase) DMSA scan. Test sensitivity appears similar to C-megalin, though specificity is not as high. C-megalin may have moderate diagnostic accuracy to detect renal scarring, with high sensitivity suggesting potential to indicate subsequent (late-phase) DMSA scan. Whilst promising, evidence from the current surveillance for both soluble ST2 and C-megalin would require further confirmatory research.

Reported diagnostic accuracy for pNGAL would mean it is not useful as a test for detecting renal scarring, particularly due to its low sensitivity. Reported diagnostic accuracy for MMP9 and TIMP 1 (singly or in combination) would mean these are also not useful as tests for detecting renal scarring. Based on this evidence, neither pNGAL or MMP9 and TIMP 1 could be recommended to indicate DMSA scan.

For the reasons outlined above, no impact of the new evidence is expected on recommendations.

New evidence is unlikely to impact on the guideline.

Research recommendations

Long-term risk

A well-designed cohort study investigating long-term outcomes including renal scarring and renal function of infants and children who have had UTI should be conducted in the UK.

Summary of findings

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Prevention

More studies with adequate sample sizes are needed to evaluate the effectiveness of breastfeeding, nappies and hygiene in preventing childhood UTI.

Summary of findings

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Diagnosis

A research recommendation from the old guideline, for research to investigate nitrite or LE dipstick testing and stratify this by age in under 3 years, was deleted as new studies have been published addressing this question which were included in the 2017 partial guideline update (addendum).

1. Combined population-based studies in primary and secondary care, with larger sample sizes are needed to evaluate the association between symptoms and signs and UTI.

Summary of findings

New evidence was identified in the current surveillance for the primary care setting from the DUTY study (Hay et al, 2016a; b; Hollingworth et al, 2017) – see section on Symptoms and signs. The new evidence may impact on recommendations.

2. Further research is needed to evaluate the effectiveness of biochemical tests for low urinary glucose for diagnosing UTI in infants and children.

Summary of findings

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

3. Further research is needed to evaluate the effectiveness of procalcitonin and other inflammatory markers in localising UTI.

Summary of findings

New evidence was found in the current surveillance on the diagnostic accuracy of biomarkers for localising UTI. Further confirmatory research would be required, and the new evidence is not expected to impact on recommendations.

Imaging tests

1. Further research on MRI for localising UTI could be considered.

Summary of findings

Limited new evidence was found in the current surveillance on MRI for localising UTI. Further confirmatory research would be required, and no impact of the new evidence is expected on recommendations.

2. MRI appears to be a promising method of detecting renal parenchymal defects although experience and evidence is limited. Further studies investigating its diagnostic accuracy and cost-effectiveness are required.

Summary of findings

Limited new evidence was found in the current surveillance on MRI for detecting renal parenchymal defects. Further confirmatory research would be required, and no impact of the new evidence is expected on recommendations.

Antibiotic prophylaxis

Well-designed randomised, double-blinded, placebo-controlled trials are required to determine the effectiveness of prophylactic antibiotics for preventing subsequent symptomatic UTIs and renal parenchymal defects in infants and children.

Summary of findings

Note that this research recommendation is now mainly relevant for the antimicrobial prescribing guidelines for UTI, specifically on prevention and management of recurrent UTI. Limited new evidence was found on the effectiveness of probiotics for prevention of recurrence after first UTI. Further confirmatory research would be required, and the new evidence is not expected to impact on recommendations.

Surgical intervention for VUR

Well-designed randomised placebo-controlled trials are required to determine the effectiveness of prophylaxis or various surgical procedures for the management of VUR in preventing recurrent UTI or renal parenchymal defects.

Summary of findings

New evidence was found on surgical intervention for VUR, through an updated Cochrane review (Williams et al, 2019). No impact of the new evidence is expected on recommendations.

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