National Collaborating Centre for Women's and Children's Health

Urinary tract infection in children

diagnosis, treatment and long-term management

Clinical Guideline

August 2007

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diagnosis, treatment and long-term management

National Collaborating Centre for Women's and Children's Health

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Stakeholder organisations

Action for Sick Children
Acute Care Collaborating Centre
Addenbrooke's NHS Trust
Airedale General Hospital – Acute Trust
Anglesey Local Health Board
Association for Continence Advice
Association for Spina Bifida & Hydrocephalus (ASBAH)
Association of Breastfeeding Mothers
Association of Medical Microbiologists

Association of Paediatric Emergency Medicine
Association of the British Pharmaceuticals Industry (ABPI)
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NHS Direct
NHS Pathways
NHS Quality Improvement Scotland
NICE – Guidelines HE for info
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Royal Liverpool Children's Hospital
Royal Society of Medicine
Royal United Hospital Bath NHS Trust
Royal West Sussex Trust
Sandwell & West Birmingham NHS Trust
Scottish Intercollegiate Guidelines Network (SIGN)
Scottish Paediatric Renal Urology Network
Sheffield Children's Hospital Trust
Sheffield PCT
Society and College of Radiographers

South & Central Huddersfield PCTs
South Birmingham PCT
South Warwickshire General Hospitals NHS Trust
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Specialist Advisory Committee on Antimicrobial Resistance (SACAR)
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Staffordshire Ambulance HQ
Staffordshire Moorlands PCT
Steering Group on Healthcare Associated Infection
Stockport PCT
Survivors Trust
Tameside and Glossop Acute Trust
UK Clinical Pharmacy Association
UK Specialised Services Public Health Network
University College London Hospitals (UCLH) Acute Trust
University Hospital Birmingham NHS Trust
Welsh Assembly Government
Welsh Scientific Advisory Committee (WSAC)
Whipps Cross University Hospital NHS Trust
Wyre Forest PCT
York NHS Trust

Abbreviations

APN	acute pyelonephritis
ARR	absolute risk reduction
ASB	asymptomatic bacteriuria
CAT	computed axial tomography
CCT	controlled clinical trial
CER	control event rate
cfu	colony-forming unit
CI	confidence interval
CKD	chronic kidney disease
CRF	chronic renal failure
CRP	C-reactive protein
CT	computed tomography
CUS	cystourethrosonography
CVU	clean voided urine
DES	dysfunctional elimination syndrome
df	degrees of freedom
DMSA	dimercaptosuccinic acid
DOR	diagnostic odds ratio
DRC	direct radionuclide cystography
EDTA	European Dialysis and Transplant Association
eGFR	estimated glomerular filtration rate
EL	evidence level
EQA	external quality assurance
ERF	established renal failure
ESR	erythrocyte sedimentation rate
ESRD	end-stage renal disease
GDG	Guideline Development Group
GFR	glomerular filtration rate
GP	general practitioner
GPP	good practice point
hpf	high power field
HTA	Health Technology Appraisal
ICD	international classification of diseases
IL-1ß	interleukin 1 beta
IL-6	interleukin 6
IM	intramuscular
IQA	internal quality assurance
IQR	interquartile range
IRC	indirect radionuclide cystogram
IV	intravenous
IVP	intravenous pyelogram
IVU	intravenous urogram
LE	leucocyte esterase
LR+	positive likelihood ratio
LR–	negative likelihood ratio
MAG3	mercaptoacetyltriglycine
MCUG	micturating cystourethrogram
MRI	magnetic resonance imaging
NAG	N-acetyl-beta-glucosaminidase
NCC-WCH	National Collaborating Centre for Women's and Children's Health
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence

NMB	net monetary benefit
NNH	number needed to harm
NNT	number needed to treat
NPV	negative predictive value
NSF	National Service Framework
OR	odds ratio
PCT	primary care trust
PDU	power Doppler ultrasonography/ultrasound
PHLS	Public Health Laboratory Service
pmp	per million population
PPIP	Patient and Public Involvement Programme
PPV	positive predictive value
QALY	quality-adjusted life year
QOF	Quality and Outcomes Framework
RCGP	Royal College of General Practitioners
RCP	Royal College of Physicians
RCPCH	Royal College of Paediatrics and Child Health
RCT	randomised controlled trial
RN	reflux nephropathy
ROC	receiver operating characteristic
RR	relative risk (or risk ratio)
RRT	renal replacement therapy
SD	standard deviation
SIGN	Scottish Intercollegiate Guidelines Network
SPA	suprapubic aspiration
SROC	summary receiver operating characteristic
STING	submucosal Teflon injection
TNF-α	tumour necrosis factor alpha
UK	United Kingdom of Great Britain and Northern Ireland
US	ultrasound
USA	United States of America
UTI	urinary tract infection
VCUG	voiding cystourethrogram
VUR	vesicoureteric reflux
VUS	voiding urosonography
WBC	white blood cell
WHO	World Health Organization
WMD	weighted mean difference
WTP	willingness to pay

Glossary of terms

Absolute risk — Measures the probability of an event or outcome occurring (e.g. an adverse reaction to the drug being tested) in a group of people or a population under study. Studies that compare two or more groups of patients may report results in terms of the **absolute risk reduction (ARR)**. 1/ARR is a calculation that gives us numbers needed to treat (see later). Absolute risk reductions are similar to relative risk reductions for common events but differ for rare events. For example, if a group of children has a risk of recurrent UTI of 15% when untreated, but this reduces to 10% as a result of intervention, then the ARR is 5% (15–10%) but the relative risk reduction (RRR) is 33% (5/15 × 100%). If, however, the reduction is from 100% to 95 % both the ARR and the RRR are 5%. In both cases the NNT is unchanged at 20 (1/5%).

Absolute risk reduction (ARR) — The ARR is the difference in the risk of an event occurring between two groups of patients in a study – for example, if 6% of patients die after receiving a new experimental drug and 10% of patients die after having the old drug treatment then the ARR is 10% – 6% = 4%. Thus by using the new drug instead of the old drug 4% of patients can be prevented from dying. Here the ARR measures the risk reduction associated with a new treatment. See also **absolute risk**.

Acute pyelonephritis — A bacterial infection of the upper urinary tract causing inflammation of the kidney(s).

Acute sector — Hospital-based health services which are provided on an inpatient, day case or outpatient basis.

Acute trust — A trust is an NHS organisation responsible for providing a group of healthcare services. An acute trust provides hospital services (but not mental health hospital services, which are provided by a **mental health trust**).

Allied health professionals — Healthcare professionals, other than doctors and nurses, directly involved in the provision of healthcare. Includes several groups such as physiotherapists, occupational therapists, dieticians, etc. (Formerly known as professions allied to medicine or PAMs.)

Antibiotic prophylaxis — See **prophylactic antibiotic**.

Applicability — The extent to which the results of a study or review can be applied to the target population for a clinical guideline.

Appraisal of evidence — Formal assessment of the quality of research evidence and its relevance to the clinical question or guideline under consideration, according to predetermined criteria.

Asymptomatic bacteriuria — The presence of bacteria in the urine without the presentation of symptoms specific to the disease.

Bacteriuria — The presence of bacteria in the urine with or without consequent urinary tract infection.

Best available evidence — The strongest research evidence available to support a particular guideline recommendation.

Bias — Influences on a study that can lead to invalid conclusions about a treatment or intervention. Bias in research can make a treatment look better or worse than it really is. Bias can even make it look as if the treatment works when it actually does not. Bias can occur by chance or as a result of **systematic** influences caused by the design and/or execution of a study. Bias can occur at various stages in the research process, e.g. in the collection, analysis, interpretation, publication or review of research data. For examples see **selection bias**, **performance bias**, **information bias**, and **publication bias**.

Bladder instability — Inappropriate bladder contractions, resulting in an involuntary loss of urine.

Blinding or masking — The practice of keeping the investigators or subjects of a study ignorant of the group to which a subject has been assigned. For example, a clinical trial in which the participating patients or their doctors are unaware of whether they (the patients) are taking the experimental drug or a placebo (dummy treatment). The purpose of 'blinding' or 'masking' is to protect against **bias**. See also **double-blind study**, **single-blind study**, **triple-blind study**.

C-reactive protein (CRP) — A protein produced by the liver that is normally present in trace amounts in the blood but is elevated during episodes of infection, inflammation and after tissue damage.

Case–control study — A study that starts with the identification of a group of individuals sharing the same characteristics (e.g. people with a particular disease) and a suitable comparison (control) group (e.g. people without the disease). All subjects are then assessed with respect to things that happened to them in the past, e.g. things that might be related to getting the disease under investigation. Such studies are also called **retrospective** as they look back in time from the outcome to the possible causes.

Case report (or case study) — Detailed report on one patient (or case), usually covering the course of that person's disease and their response to treatment.

Case series — Description of several cases of a given disease, usually covering the course of the disease and the response to treatment. There is no comparison (**control**) group of patients.

Catheter — A tubular medical device for insertion into a duct, blood vessel, hollow organ or body cavity for injecting or withdrawing fluids for diagnostic or therapeutic purposes.

Causal relationship — Describes the relationship between two **variables** whenever it can be established that one causes the other. For example, there is a causal relationship between a treatment and a disease if it can be shown that the treatment changes the course or outcome of the disease. Usually **randomised controlled trials** are needed to ascertain causality. Proving cause and effect is much more difficult than just showing an association between two variables. For example, if it happened that everyone who had eaten a particular food became sick, and everyone who avoided that food remained well, then the food would clearly be associated with the sickness. However, even if leftovers were found to be contaminated, it could not be proved that the food caused the sickness – unless all other possible causes (e.g. environmental factors) had been ruled out.

Checklist — See **study checklist**.

Chronic kidney disease (CKD) — Previously known as chronic renal failure (CRF), or chronic renal insufficiency. The stages of chronic kidney disease are as follows:

Stage 1: kidney damage but normal kidney function (GFR > 90 ml/min/m^2)

Stage 2: mild decrease of GFR (60–89 ml/min/m^2)

Stage 3: moderate decrease of GFR (30–59 ml/min/m^2)

Stage 4: severe decrease in GFR (15–29 ml/min/m^2)

Stage 5: kidney failure (GFR < 15 ml/min/m^2 or dialysis)[1]

Clean catch urine — A clean catch urine is a urine caught cleanly during voiding.

Clinical audit — A **systematic** process for setting and monitoring standards of clinical care. Whereas 'guidelines' define what the best clinical practice should be, 'audit' investigates whether best practice is being carried out. Clinical audit can be described as a cycle or a spiral. Within a cycle there are stages that follow a systematic process of establishing best practice, measuring care against specific criteria, taking action to improve care, and monitoring to sustain improvement. The spiral suggests that as the process continues, each cycle aspires to a higher level of quality.

Clinical effectiveness — The extent to which a specific treatment or intervention, when used under *usual or everyday conditions*, has a beneficial effect on the course or outcome of disease compared with no treatment or other routine care. (Clinical trials that assess effectiveness are sometimes called management trials.) Clinical 'effectiveness' is not the same as **efficacy**.

Clinical governance — A framework through which NHS organisations are accountable for both continuously improving the quality of their services and safeguarding high standards of care by creating an environment in which excellence in clinical care will flourish.

Clinical impact — The effect that a guideline recommendation is likely to have on the treatment, or treatment outcomes, of the **target population**.

Clinical importance — The importance of a particular guideline recommendation to the clinical management of the **target population**.

Clinical question — This term is sometimes used in guideline development work to refer to the questions about treatment and care that are formulated in order to guide the search for research evidence. When a clinical question is formulated in a precise way, it is called a **focused question**.

Clinical trial — A research study conducted with patients which tests out a drug or other intervention to assess its effectiveness and safety. Each trial is designed to answer scientific questions and to find better ways to treat individuals with a specific disease. This general term encompasses **controlled clinical trials** and **randomised controlled trials**.

Clinician A healthcare professional providing patient care, e.g. doctor, nurse, physiotherapist.

Cluster A group of patients, rather than an individual, used as the basic unit for investigation. See also **cluster design**, **cluster randomisation**.

Cluster design Cluster designs are those where research subjects are not sampled or selected independently, but in a group. For example, a clinical trial where patients in a general practice are allocated to the same intervention; the general practice forming a cluster. See also **cluster**, **cluster randomisation**.

Cluster randomisation A study in which groups of individuals (e.g. patients in a GP surgery or on a hospital ward) are randomly allocated to treatment groups. Take, for example, a smoking cessation study of two different interventions – leaflets and teaching sessions. Each GP surgery within the study would be randomly allocated to administer one of the two interventions. See also **cluster**, **cluster design**.

Cochrane Collaboration An international organisation in which people find, appraise and review specific types of studies called **randomised controlled trials**. The Cochrane Database of Systematic Reviews contains regularly updated reviews on a variety of health issues and is available electronically as part of the **Cochrane Library**.

Cochrane Library The Cochrane Library consists of a regularly updated collection of evidence-based medicine databases including the Cochrane Database of Systematic Reviews (reviews of **randomised controlled trials** prepared by the **Cochrane Collaboration**). The Cochrane Library is available on CD-ROM and the internet.

Cohort A group of people sharing some common characteristic (e.g. patients with the same disease), followed up in a research study for a specified period of time.

Cohort study An **observational study** that takes a group (cohort) of patients and follows their progress over time in order to measure outcomes such as disease or mortality rates and make comparisons according to the treatments or interventions that patients received. Thus, within the study group, subgroups of patients are identified (from information collected about patients) and these groups are compared with respect to outcome, e.g. comparing mortality between one group that received a specific treatment and one group which did not (or between two groups that received different levels of treatment). Cohorts can be assembled in the present and followed into the future (a 'concurrent' or '**prospective**' cohort study) or identified from past records and followed forward from that time up to the present (a 'historical' or '**retrospective**' cohort study). Because patients are not randomly allocated to subgroups, these subgroups may be quite different in their characteristics and some adjustment must be made when analysing the results to ensure that the comparison between groups is as fair as possible.

Colony-forming unit (cfu) Colony-forming unit (cfu) is a measure of the number of viable bacteria present in a sample. A sample is spread or poured onto the surface of an agar plate, incubated overnight and the number of colonies formed is counted. Each colony equates with a single bacterium present in the original sample.

Combined modality Use of different treatments in combination (e.g. surgery, chemotherapy and radiotherapy used together for cancer patients).

Commercial 'in confidence' material Information (e.g. the findings of a research project) defined as 'confidential' as its public disclosure could have an impact on the commercial interests of a particular company. (Academic 'in confidence' material is information (usually work produced by a research or professional organisation) that is pending publication.)

Co-morbidity Co-existence of a disease or diseases in the people being studied in addition to the health problem that is the subject of the study.

Computed tomography (CT) A method of body imaging using X-rays and computer algorithms to generate cross-sectional and three-dimensional models of organs. Also known as **CT scan**.

Concomitant Occurring during the same time period, usually referring to secondary symptoms that occur with a main symptom.

Confidence interval (CI) A way of expressing certainty about the findings from a study or group of studies, using statistical techniques. A confidence interval describes a range of possible effects (of a treatment or intervention) that are consistent with the results of a study or group of studies. A wide confidence interval indicates a lack of certainty or precision about the true size of the clinical effect and is seen in studies with too few patients. Where confidence intervals are narrow they indicate more precise estimates of effects and a larger sample of patients studied. It is usual to interpret a '95%' confidence interval as the range of effects within which we are 95% confident that the true effect lies.

Confounder or confounding factor

Confounders are variables that are both associated with the condition being studied and have an independent effect on its outcomes. It can contribute to misleading findings if it is not understood or appropriately dealt with. For example, if a group of people exercising regularly and a group of people who do not exercise have an important age difference then any difference found in outcomes about heart disease could well be due to one group being older than the other rather than due to the exercising. Age is the confounding factor here and the effect of exercising on heart disease cannot be assessed without adjusting for age differences in some way.

Consensus development conference

A technique used for the purpose of reaching an agreement on a particular issue. It involves bringing together a group of about ten people who are presented with evidence by various interest groups or experts who are not part of the decision-making group. The group then retires to consider the questions in the light of the evidence presented and attempts to reach a consensus. See also **consensus methods**.

Consensus methods

A variety of techniques that aim to reach an agreement on a particular issue. Formal consensus methods include **Delphi** and **nominal group techniques**, and **consensus development conferences**. In the development of clinical guidelines, consensus methods may be used where there is a lack of strong research evidence on a particular topic.

Consensus statement

A statement of the advised course of action in relation to a particular clinical topic, based on the collective views of a body of experts.

Considered judgement

The application of the collective knowledge of a guideline development group to a body of evidence, to assess its applicability to the **target population** and the strength of any recommendation that it would support.

Consistency

The extent to which the conclusions of a collection of studies used to support a guideline recommendation are in agreement with each other. See also **homogeneity**.

Control event rate

See **event rate**.

Control group

A group of patients recruited into a study that receives no treatment, a treatment of known effect, or a placebo (dummy treatment), in order to provide a comparison for a group receiving an experimental treatment, such as a new drug.

Controlled clinical trial (CCT)

A study testing a specific drug or other treatment involving two (or more) groups of patients with the same disease. One (the experimental group) receives the treatment that is being tested, and the other (the comparison or **control group**) receives an alternative treatment, a **placebo** (dummy treatment) or no treatment. The two groups are followed up to compare differences in outcomes to see how effective the experimental treatment was. A CCT where patients are randomly allocated to treatment and comparison groups is called a **randomised controlled trial**.

Cost–benefit analysis

A type of **economic evaluation** where both costs and benefits of healthcare treatment are measured in the same monetary units. If benefits exceed costs, the evaluation would recommend providing the treatment.

Cost-effectiveness

Value for money. A specific healthcare treatment is said to be 'cost-effective' if it gives a greater health gain than could be achieved by using the resources in other ways.

Cost-effectiveness analysis

A type of **economic evaluation** comparing the costs and the effects on health of different treatments. Health effects are measured in 'health-related units', for example, the cost of preventing one additional heart attack.

Cost–utility analysis

A special form of **cost-effectiveness analysis** where health effects are measured in **quality-adjusted life years**. A treatment is assessed in terms of its ability to both extend life and to improve the quality of life.

Crossover study design

A study comparing two or more interventions in which the participants, upon completion of the course of one treatment, are switched to another. For example, for a comparison of treatments A and B, half the participants are randomly allocated to receive them in the order A, B and half to receive them in the order B, A. A problem with this study design is that the effects of the first treatment may carry over into the period when the second is given. Therefore a crossover study should include an adequate 'wash-out' period, which means allowing sufficient time between stopping one treatment and starting another so that the first treatment has time to wash out of the patient's system.

Cross-sectional study

The observation of a defined set of people at a single point in time or time period – a snapshot. (This type of study contrasts with a **longitudinal study**, which follows a set of people over a period of time.)

CT scan	A method of body imaging using X-rays and computer algorithms to generate cross-sectional and three-dimensional models of organs. Also known as **computerised tomography**.
Culture	A technique for growing and maintaining bacteria under controlled laboratory conditions.
Cystitis	Inflammation of the bladder.
Cystography	See **micturating cystourethrogram (MCUG)**.
Cystourethrogram	See **micturating cystourethrogram (MCUG)**.
Cystosonography/ cystourethrosonography	Method of looking for **vesicoureteric reflux (VUR)** using **ultrasound** and sonographic contrast medium instilled into the bladder. The urinary bladder is catheterised and a mixture of water and sonographic contrast medium (microparticles in suspension) are instilled. The renal tract is scanned as the fluid is instilled and VUR is identified by seeing echoes from these particles in the ureters and renal collecting systems. It has the advantage that no ionising radiation is used and that the anatomy of the renal tract can be assessed at the same time.
Data set	A list of required information relating to a specific disease.
Decision analysis	Decision analysis is the study of how people make decisions or how they *should* make decisions. There are several methods that decision analysts use to help people to make better decisions, including **decision trees**.
Decision tree	A decision tree is a method for helping people to make better decisions in situations of uncertainty. It illustrates the decision as a succession of possible actions and outcomes. It consists of the probabilities, costs and health consequences associated with each option. The overall effectiveness or overall cost-effectiveness of various actions can then be compared.
Declaration of interest	A process by which members of a working group or committee 'declare' any personal or professional involvement with a company (or related to a technology) that might affect their objectivity, e.g. if their position or department is funded by a pharmaceutical company.
Delphi method	A technique used for the purpose of reaching an agreement on a particular issue, without the participants meeting or interacting directly. It involves sending participants a series of postal questionnaires asking them to record their views. After the first questionnaire, participants are asked to give further views in the light of the group feedback. The judgements of the participants are aggregated, sometimes after weighting for expertise. See also **consensus methods**.
Diagnostic odds ratio (DOR)	Expresses the odds of positive test results in patients with disease compared with patients without the disease. The diagnostic odds ratio is defined as the **positive likelihood ratio** divided by the **negative likelihood ratio**.
Diagnostic study	A study to assess the effectiveness of a test or measurement in terms of its ability to accurately detect or exclude a specific disease.
Dipstick	A diagnostic test consisting of a chemically sensitive strip which when dipped into a sample can be used to detect the presence of leucocyte esterase, nitrites, glucose or protein.
Direct radionuclide cystogram (DRC)	In a direct radionuclide cystogram (DRC), a small dose of a radionuclide (pertechnetate – Tc-99m) diluted in water is instilled into the urinary bladder through a catheter placed for this purpose. Images of the bladder and kidneys are taken as the bladder is filled and during voiding. This test is sensitive for small degrees of **vesicoureteric reflux (VUR)** but lacks the anatomic detail of a **micturating cystourethrogram (MCUG)**. The radiation dose is small (0.05 mSv) – approximately 2–3 days' worth of exposure to natural background radiation.
Dimercaptosuccinic acid (DMSA) scintigraphy	DMSA scintigraphy is a radionuclide scan of the kidneys utilising dimercaptosuccinic acid. It is used to identify renal parenchymal defects, some of which are due to chronic pyelonephritic scarring. Intravenously injected Tc-99m-labelled DMSA binds to the kidneys and emits gamma rays which are detected by a camera. The outline and distribution of renal tissue on these images can be seen. Uptake of DMSA by each kidney can be compared to give an estimate of the relative function of right and left kidneys. The radiation dose incurred is approximately 1 mSv, equivalent to 4 months of natural background radiation (about 40–50 chest radiographs).
Dominance	A term used in **health economics** describing when an option for treatment is both less clinically effective and more costly than an alternative option. The less effective and more costly option is said to be 'dominated'.

Doppler ultrasound	See **ultrasound**.
Double-blind study	A study in which neither the subject (patient) nor the observer (investigator/clinician) is aware of which treatment or intervention the subject is receiving. The purpose of blinding is to protect against bias.
Dysuria	The difficult or painful discharge of urine.
Dysfunctional elimination syndrome (DES)	Dysfunctional elimination syndrome refers to an abnormal pattern of elimination of unknown aetiology characterised by faecal and urinary incontinence and withholding.
Economic evaluation	A comparison of alternative courses of action in terms of both their costs and consequences. In **health economic** evaluations the consequences should include health outcomes.
Effectiveness	See **clinical effectiveness**.
Efficacy	The extent to which a specific treatment or intervention, under *ideally controlled conditions* (e.g. in a laboratory), has a beneficial effect on the course or outcome of disease compared with no treatment or other routine care.
Elective	A term for clinical procedures that are regarded as advantageous to the patient but not urgent.
Empirical	Based directly on experience (observation or experiment) rather than on reasoning alone.
Encopresis	Repeated soiling in children 4 years or older, most often involuntarily but occasionally intentionally.
End-stage kidney disease	See **established renal failure**.
End-stage renal disease (ESRD)	See **established renal failure.**
End-stage renal failure	See **established renal failure**.
Epidemiology	The study of diseases within a population, covering the causes and means of prevention.
Erythrocyte sedimentation rate (ESR)	A non-specific screening test for various diseases that measures the distance (in millimetres) that red blood cells settle in unclotted blood toward the bottom of a specially marked test tube.
Established renal failure (ERF)	The final stage of kidney failure that is marked by the complete, or nearly complete, irreversible loss of kidney function.
Event rate	The proportion of patients in a group for whom a specified health event or outcome is observed. Thus, if out of 100 patients, the event is observed in 27, the event rate is 0.27 or 27%. Control event rate (CER) and experimental event rate (EER) are the terms used in **control** and experimental groups of patients, respectively.
Evidence based	The process of systematically finding, appraising and using research findings as the basis for clinical decisions.
Evidence-based clinical practice	Evidence-based clinical practice involves making decisions about the care of individual patients based on the best research evidence available rather than basing decisions on personal opinions or common practice (which may not always be evidence based). Evidence-based clinical practice therefore involves integrating individual clinical expertise and patient preferences with the best available evidence from research.
Evidence level (EL)	A code (e.g. 1++, 1+) linked to an individual study, indicating where it fits into the **hierarchy of evidence** and how well it has adhered to recognised research principles.
Evidence table	A table summarising the results of a collection of studies which, taken together, represent the evidence supporting a particular recommendation or series of recommendations in a guideline.
Exclusion criteria	See **selection criteria**.
Experimental event rate (EER)	See **event rate**.
Experimental study	A research study designed to test whether a treatment or intervention has an effect on the course or outcome of a condition or disease – where the conditions of testing are to some extent under the control of the investigator. **Controlled clinical trial** and **randomised controlled trial** are examples of experimental studies.
Experimental treatment	A treatment or intervention (e.g. a new drug) being studied to see whether it has an effect on the course or outcome of a condition or disease.

External quality assurance (EQA)	The managed process whereby the comparison of care against predetermined standards is guaranteed to lead to action to implement changes, and ensuring that these have produced the desired improvement. (From: Donabedian A. *The Definition of Quality and Approaches to its Assessment. Explorations in Quality Assessment and Monitoring*. Volume I. Ann Arbor/Michigan: Health Administration Press; 1980.)
External validity	The degree to which the results of a study hold true in non-study situations, e.g. in routine clinical practice. May also be referred to as the **generalisability** of study results to non-study patients or populations.
Extrapolation	The application of research evidence based on studies of a specific population to another population with similar characteristics.
Febrile	See **fever**.
Fever	The elevation of body temperature above normal daily variation. (See NICE Clinical Guideline 'Feverish illness in children' for details.)
Focus group	A **qualitative research** technique (originally a market research technique). It is a method of group interview or discussion, commonly involving 6–12 people, focused around a particular issue or topic. The method explicitly includes and uses the group interaction to generate data.
Focused question	A study question that clearly identifies all aspects of the topic that are to be considered while seeking an answer. Questions are normally expected to identify the patients or population involved, the treatment or intervention to be investigated, what outcomes are to be considered, and any comparisons that are to be made. For example, do antibiotics (intervention) eliminate bacteriuria (outcome) in children with UTI (population) compared with alternative therapies (comparison)? See also **clinical question**.
Forest plot	A graphical display of results from individual studies on a common scale, allowing visual comparison of results and examination of the degree of **heterogeneity** between studies.
Funnel plot	Funnel plots are simple scatter plots on a graph. They show the treatment effects estimated from separate studies on the horizontal axis against a measure of sample size on the vertical axis. **Publication bias** may lead to asymmetry in funnel plots.
Generalisability	The extent to which the results of a study hold true for a population of patients beyond those who participated in the research. See also **external validity**.
Glomerular filtration rate (GFR)	Measure of the kidneys' ability to filter and remove waste products.
Gold standard	A method, procedure or measurement that is widely accepted as being the best available.
Good practice point (GPP)	Recommended good practice based on the expert experience of the guideline development group (and possibly incorporating the expertise of a wider reference group). A guideline development group may produce a 'good practice point' (rather than an evidence-based recommendation) on an important topic when there is a lack of research evidence.
Grade of recommendation	A code (e.g. A, B, C) linked to a guideline recommendation, indicating the strength of the evidence supporting that recommendation.
Grey literature	Reports that are unpublished or have limited distribution, and are not included in bibliographic retrieval systems.
Guideline	A systematically developed tool which describes aspects of a patient's condition and the care to be given. A good guideline makes recommendations about treatment and care, based on the best research available, rather than opinion. It is used to assist clinician and patient decision making about appropriate health care for specific clinical conditions.
Guideline recommendation	Course of action advised by the guideline development group on the basis of their assessment of the supporting evidence.
Haematuria	The presence of blood in the urine.
Haemocytometer	A ruled microscope slide used to count red and white blood cells in body fluids.
Health economics	A branch of economics which studies decisions about the use and distribution of healthcare resources.
Health technology	Health technologies include medicines, medical devices such as artificial hip joints, diagnostic techniques, surgical procedures, health promotion activities (e.g. the role of diet versus medicines in disease management) and other therapeutic interventions.

Health technology appraisal (HTA) A health technology appraisal, as undertaken by NICE, is the process of determining the clinical and cost-effectiveness of a **health technology**. NICE health technology appraisals are designed to provide patients, health professionals and managers with an authoritative source of advice on new and existing health technologies.

Heterogeneity Or lack of **homogeneity**. The term is used in **meta-analyses** and **systematic reviews** when the results or estimates of effects of treatment from separate studies seem to be very different – in terms of the size of treatment effects or even to the extent that some indicate beneficial and others suggest adverse treatment effects. Such results may occur as a result of differences between studies in terms of the patient populations, outcome measures, definition of **variables**, or duration of follow-up.

HG tube Commercially available urine collection tube.

Hierarchy of evidence An established hierarchy of study types, based on the degree of certainty that can be attributed to the conclusions that can be drawn from a well-conducted study. Well-conducted **randomised controlled trials** (RCTs) are at the top of this hierarchy. (Several large statistically significant RCTs which are in agreement represent stronger evidence than say one small RCT.) Well-conducted studies of patients' views and experiences would appear at a lower level in the hierarchy of evidence.

Homogeneity This means that the results of studies included in a **systematic review** or **meta-analysis** are similar and there is no evidence of **heterogeneity**. Results are usually regarded as homogeneous when differences between studies could reasonably be expected to occur by chance. See also **consistency**.

Hydronephrosis Distension or dilation of the pelvis and calyces of the kidney.

Hypertension, renal See **renal hypertension**.

Iatrogenic Any adverse condition in a patient occurring as the result of treatment by a health professional.

Incidence The number of new cases of a given disease during a given period in a specified population. It also is used for the rate at which new events occur in a defined population.

Inclusion criteria See **selection criteria**.

In-depth interview A **qualitative research** technique. It is a face-to-face conversation between a researcher and a respondent with the purpose of exploring issues or topics in detail. It does not use pre-set questions, but is shaped by a defined set of topics or issues.

Indirect radionuclide cystogram (IRC) Indirect radionuclide cystogram (IRC) can be performed as a supplement to a standard MAG3 scan in toilet-trained children. At the end of the MAG3 scan the bladder contains the secreted radionuclide mixed with urine. Images are obtained as the child voids, and an objective assessment of bladder emptying can be made. Any **vesicoureteric reflux (VUR)** of MAG3 from the bladder to the kidneys can also be identified. Although not as sensitive for the detection of VUR as direct forms of cystography (DRC, MCUG, cystosonography), the need for bladder catheterisation is avoided.

Infant A child that is under the age of 12 months.

Information bias Pertinent to all types of study and can be caused by inadequate questionnaires (e.g. difficult or biased questions), observer or interviewer errors (e.g. lack of **blinding**), response errors (e.g. lack of **blinding** if patients are aware of the treatment they receive) and measurement error (e.g. a faulty machine).

Intention-to-treat analysis An analysis of a clinical trial where patients are analysed according to the group to which they were initially randomly allocated, regardless of whether or not they had dropped out, fully complied with the treatment, or crossed over and received the alternative treatment. Intention-to-treat analyses are favoured in assessments of **clinical effectiveness** as they mirror the non-compliance and treatment changes that are likely to occur when the treatment is used in practice.

Interleukin 1 beta (IL-1β) A soluble factor produced by monocytes, macrophages and other cells which activates T-lymphocytes and potentiates their response to mitogens or antigens. IL-1 consists of two distinct forms, IL-1α and IL-1β, which perform the same functions but are distinct proteins. The biological effects of IL-1 include the ability to replace macrophage requirements for T-cell activation.

Interleukin 6 (IL-6)	A cytokine that stimulates the growth and differentiation of human B-cells and is also a growth factor for hybridomas and plasmacytomas. It is produced by many different cells including T-cells, monocytes and fibroblasts. It is a single-chain 25 kDa cytokine originally described as a pre B-cell growth factor, now known to have effects on a number of other cells including T-cells which are also stimulated to proliferate.
Internal quality assurance (IQA)	The managed process within the organisation whereby the comparison of care against predetermined standards is guaranteed to lead to action to implement changes, and ensuring that these have produced the desired improvement. (From: Donabedian A. *The Definition of Quality and Approaches to its Assessment. Explorations in Quality Assessment and Monitoring*. Volume I. Ann Arbor/Michigan: Health Administration Press; 1980.)
Internal validity	Refers to the integrity of the study design.
International classification of disease (ICD)	A classification of diseases developed by the World Health Organization (WHO).
Interquartile range (IQR)	In descriptive statistics, the interquartile range (IQR) is the difference between the third and first quartiles and is a measure of statistical dispersion. The interquartile range is a more stable statistic than the range, and is often preferred to that statistic. Since 25% of the data are less than or equal to the first quartile and 25% are greater than or equal to the third quartile, the difference is the length of an interval that includes about half of the data. This difference should be measured in the same units as the data.
Intervention	Healthcare action intended to benefit the patient, e.g. drug treatment, surgical procedure, psychological therapy, etc.
Interventional procedure	A procedure used for diagnosis or treatment that involves making a cut or hole in the patient's body, entry into a body cavity or using electromagnetic radiation (including X-rays or lasers). The National Institute for Health and Clinical Excellence (NICE) has the task of producing guidance about whether specific interventional procedures are safe enough and work well enough for routine use.
Intramuscular (IM)	Administration into a muscle.
Intravenous (IV)	Administration into a vein.
Intravenous pyelogram (IVP)	See **intravenous urogram (IVU)**.
Intravenous urogram (IVU)	Intravenous urography involves the intravenous injection of a radiographic contrast medium (iodine based) that is taken up and excreted by the kidneys. X-ray images of the abdomen are then taken showing detailed anatomy of the urinary tract. The dose of radiation is moderately high and there is a small but real risk of an allergic reaction to the contrast medium. It is no longer used for the routine evaluation of children who have had UTI.
Leucocyte esterase (LE)	An enzyme present in white blood cells which can be detected in the urine during infection.
Level of evidence	See **evidence level**.
Likelihood ratio	See **positive likelihood ratio** and **negative likelihood ratio**.
Literature review	A process of collecting, reading and assessing the quality of published (and unpublished) articles on a given topic.
Longitudinal study	A study of the same group of people at more than one point in time. (This type of study contrasts with a **cross-sectional study** which observes a defined set of people at a single point in time.)
MAG3 scan	See **mercaptoacetyltriglycine (MAG3) scan**.
Magnetic resonance imaging (MRI)	Magnetic resonance imaging uses a combination of radiowaves and strong magnetic fields to generate detailed images of the body. In many ways it is an ideal technique for children as it does not utilise ionising radiation (X- and gamma rays). It has potential to define clearly the anatomy of the kidneys, ureters and bladder, and can provide some functional information. Its role in the management of urinary tract infection in children is yet to be established.
Masking	See **blinding**.
Mental health trust	A trust is an NHS organisation responsible for providing a group of healthcare services. A mental health trust provides both hospital- and community-based mental health services.

Mercaptoacetyltriglycine (MAG3) scan Also known as dynamic renography, MAG3 is a radionuclide scan of the kidneys utilising mercaptoacetyltriglycine. It is used to evaluate drainage of urine from the kidneys into the bladder. Intravenously injected Tc-99m-labelled MAG3 is taken up by the kidneys, is secreted into the renal collecting system and drains into the bladder. The radiation dose incurred is approximately equivalent to 2 months of natural background radiation (about 20–25 chest radiographs). The MAG3 scan can be extended by imaging while the child voids urine – an indirect radionuclide cystogram.

Meta-analysis Results from a collection of independent studies (investigating the same treatment) are pooled, using statistical techniques to synthesise their findings into a single estimate of a treatment effect. Where studies are not compatible, e.g. because of differences in the study populations or in the outcomes measured, it may be inappropriate or even misleading to statistically pool results in this way. See also **systematic review** and **heterogeneity**.

Methodology The overall approach of a research project, e.g. the study will be a **randomised controlled trial**, of 200 people, over 1 year.

Methodological quality The extent to which a study has conformed to recognised good practice in the design and execution of its research methods.

Microscopy The use of a microscope for visualising material that cannot be seen by the unaided eye.

Micturating cystourethrogram (MCUG) The micturating cystourethrogram is the most common test used in the UK for the detection **of vesicoureteric reflux (VUR)** in children. It also provides good anatomic detail of the bladder and urethra. Radiographic contrast medium is instilled into the bladder through a urethral catheter and X-ray images are taken showing the bladder, urethra and any VUR present. The radiation dose from MCUG is greater than for **direct radionuclide cystogram (DRC)** but the introduction of dose reduction techniques can minimise this. Even so, the estimated dose for a 1-year-old infant is 1 mSv, equivalent to about 4 months of natural background radiation.

Morbidity A diseased state or symptom.

Multicentre study A study where subjects were selected from different locations or populations, e.g. a cooperative study between different hospitals or an international collaboration involving patients from more than one country.

Multivariable analysis Multivariable analysis is a tool for determining the relative contributions of different causes to a single event.

N-acetyl-beta-glucosaminidase (NAG) An enzyme marker of renal tubular damage.

Negative likelihood ratio (LR–) The negative likelihood ratio describes the probability of having a negative test result in the diseased population compared with that of a non-diseased population and corresponds to the ratio of the false negative rate divided by the true negative rate (1 – sensitivity/specificity).

Negative predictive value (NPV) The negative predictive value expresses the probability that a patient with a negative test result does not have the target condition.

Neonate A newly born child aged up to and including 28 days.

Newborn See **neonate**.

Nitrite Nitrite is a chemical compound produced by bacterial metabolism. Its presence in urine is used as a marker of the presence of bacteria. Not all bacteria are able to produce nitrite.

Nominal group technique A technique used for the purpose of reaching an agreement on a particular issue. It uses a variety of postal and direct contact techniques, with individual judgements being aggregated statistically to derive the group judgement. See also **consensus methods**.

Non-experimental study A study based on subjects selected on the basis of their availability, with no attempt having been made to avoid problems of bias.

Non-systematic review See **review**.

Nosocomial infection Hospital-acquired infection.

Number needed to harm (NNH) See **number needed to treat**.

Number needed to treat (NNT) This measures the impact of a treatment or intervention. It states how many patients need to be treated with the treatment in question in order to prevent an event which would otherwise occur. for example, if the NNT = 4, then four patients would have to be treated to prevent a particular outcome. The closer the NNT is to 1, the better the treatment is. Analogous to the NNT is the **number needed to harm (NNH)**, which is the number of patients that would need to receive a treatment to cause one additional adverse event. For example, if the NNH = 4, then four patients would have to be treated for one adverse event to occur.

Objective measure A measurement that follows a standardised procedure which is less open to subjective interpretation by potentially biased observers and study participants.

Observation Observation is a research technique used to help understand complex situations. It involves watching, listening to and recording behaviours, actions, activities and interactions. The settings are usually natural, but they can be laboratory settings, as in psychological research.

Observational study In research about diseases or treatments, this refers to a study in which nature is allowed to take its course. Changes or differences in one characteristic (e.g. whether or not people received a specific treatment or intervention) are studied in relation to changes or differences in other(s) (e.g. whether or not they died), without the intervention of the investigator. There is a greater risk of **selection bias** than in **experimental studies**. As per the comments on non-experimental studies, this is often true but is a function of selection criteria, rather than the type of study.

Odds ratio (OR) Odds are a way of representing probability, especially familiar for betting. In recent years odds ratios have become widely used in reports of clinical studies that use indirect calculations, e.g. case–control studies, or in regression techniques. They provide an estimate (usually with a **confidence interval**) for the effect of a treatment. Odds are used to convey the idea of 'risk' and an odds ratio of 1 between two treatment groups would imply that the risks of an adverse outcome were the same in each group. For rare events the odds ratio and the **relative risk** (which uses actual risks and not odds) will be very similar. See also **relative risk** and **risk ratio**.

Off-label prescribing When a drug or device is prescribed outside its **specific indication**, to treat a condition or disease for which it is not specifically licensed.

Outcome The end result of care and treatment and/or rehabilitation. In other words, the change in health, functional ability, symptoms or situation of a person, which can be used to measure the effectiveness of care/treatment/rehabilitation. Researchers should decide what outcomes to measure before a study begins; outcomes are then assessed at the end of the study.

Peer review Review of a study, service or recommendations by those with similar interests and expertise to the people who produced the study findings or recommendations. Peer reviewers can include professional and/or patient/carer representatives.

Performance bias Systematic differences in care provided apart from the intervention being evaluated. For example, if study participants know they are in the **control group** they may be more likely to use other forms of care; people who know they are in the experimental group may experience **placebo effects**, and care providers may treat patients differently according to what group they are in. Masking (**blinding**) of both the recipients and providers of care is used to protect against performance bias.

Pilot study A small-scale 'test' of the research instrument. For example, testing out (piloting) a new questionnaire with people who are similar to the population of the study, in order to highlight any problems or areas of concern, which can then be addressed before the full-scale study begins.

Placebo Placebos are fake or inactive treatments received by participants allocated to the **control group** in a clinical trial which are indistinguishable from the active treatments being given in the experimental group. They are used so that participants are ignorant of their treatment allocation in order to be able to quantify the effect of the experimental treatment over and above any **placebo effect** due to receiving care or attention.

Placebo effect A beneficial (or adverse) effect produced by a placebo and not due to any property of the **placebo** itself.

Point estimate A best single estimate (taken from research data) for the true value of a treatment effect or other measurement. For example, researchers in one clinical trial take their results as their best estimate of the real treatment effect – this is their estimate at their point in time. The precision or accuracy of the estimate is measured by a **confidence interval**. Another clinical trial of the same treatment will produce a different point estimate of treatment effect.

Positive likelihood ratio (LR+) The positive likelihood ratio describes the probability of having a positive test result in the diseased population compared with that of a non-diseased population and corresponds to the ratio of the true positive rate divided by the false positive rate (sensitivity/(1–specificity)).

Positive predictive value (PPV) The positive predictive value expresses the probability that a patient with a positive test result does have the condition.

Power See **statistical power**.

Power Doppler ultrasound (PDU) See **ultrasound**.

Prevalence The total number of cases of a given disease in a specified population at a designated time.

Primary care Health care delivered to patients outside hospitals. Primary care covers a range of services provided by GPs, nurses and other healthcare professionals, dentists, pharmacists and opticians. See comments for **secondary care**.

Primary care trust (PCT) A primary care trust is an NHS organisation responsible for improving the health of local people, developing services provided by local GPs and their teams (called **primary care**) and making sure that other appropriate health services are in place to meet local people's needs.

Probability How likely an event is to occur, e.g. how likely a treatment or intervention will alleviate a symptom.

Procalcitonin Procalcitonin is a precursor of the hormone calcitonin, which is involved with calcium homeostasis, and is produced by the C-cells of the thyroid gland. It is there that procalcitonin is cleaved into calcitonin, katacalcin and a protein residue. It is not released into the bloodstream of healthy individuals, therefore measurement of procalcitonin can be used as a marker of severe sepsis and generally grades well with the degree of sepsis.

Prognostic factor Patient or disease characteristics, e.g. age or **co-morbidity**, which influence the course of the disease under study. In a randomised trial to compare two treatments, chance imbalances in **variables** (prognostic factors) that influence patient outcome are possible, especially if the size of the study is fairly small. In terms of analysis these prognostic factors become **confounding factors**. See also **prognostic marker**.

Prognostic marker A **prognostic factor** used to assign patients to categories for a specified purpose – for example for treatment, or as part of a clinical trial – according to the likely progression of the disease. For example, the purpose of randomisation in a clinical trial is to produce similar treatment groups with respect to important **prognostic factors**. This can often be achieved more efficiently if randomisation takes place within subgroups defined by the most important prognostic factors. Thus if age was very much related to patient outcome then separate randomisation schemes would be used for different age groups. This process is known as stratified random allocation.

Prophylactic antibiotic For the purpose of this guideline, prophylactic antibiotic indicates long-term treatment with antibiotics aiming to prevent recurrent episodes of UTI and renal scarring.

Prophylaxis See **prophylactic antibiotic**.

Prospective study A study in which people are entered into the research and then followed up over a period of time with future events recorded as they happen. This contrasts with studies that are retrospective.

Proteinuria The presence of proteins in the urine. A protein to creatinine ratio over 20 mg/mmol in early morning urine in a child is abnormal.

Protocol A plan or set of steps which defines appropriate action. A research protocol sets out, in advance of carrying out the study, what question is to be answered and how information will be collected and analysed. Guideline implementation protocols set out how guideline recommendations will be used in practice by the NHS, both at national and local levels.

Publication bias

Studies with statistically significant results are more likely to get published than those with non-significant results. **Meta-analyses** that are exclusively based on published literature may therefore produce biased results. This type of bias can be assessed by a **funnel plot**.

***P* value**

If a study is done to compare two treatments then the *P* value is the probability of obtaining the results of that study, or something more extreme, if there really was no difference between treatments. (The assumption that there really is no difference between treatments is called the 'null hypothesis'.) Suppose the *P* value was $P = 0.03$. What this means is that if there really was no difference between treatments then there would only be a 3% chance of getting the kind of results obtained. Since this chance seems quite low we should question the validity of the assumption that there really is no difference between treatments. We would conclude that there probably is a difference between treatments. By convention, where the value of *P* is below 0.05 (i.e. less than 5%) the result is seen as statistically significant. Where the value of *P* is 0.001 or less, the result is seen as highly significant. *P* values just tell us whether an effect can be regarded as statistically significant or not. In no way do they relate to how big the effect might be, for which we need the **confidence interval**.

Pyelonephritic scarring

Fibrotic defected area of renal parenchyma due to previous acute pyelonephritis. Also referred to as reflux nephropathy as **vesicoureteric reflux (VUR)** is a contributing factor in the majority of cases. Also referred to as chronic pyelonephritis.

Pyelonephritis

See **acute pyelonephritis** and **pyelonephritic scarring**.

Pyuria

The production of urine which contains white blood cells.

Qualitative research

Qualitative research is used to explore and understand people's beliefs, experiences, attitudes, behaviour and interactions. It generates non-numerical data, e.g. a patient's description of their pain rather than a measure of pain. Analysis of qualitative data can and should be done using explicit, systematic and reproducible methods. Qualitative research techniques such as **focus groups** and **in-depth interviews** have been used in one-off projects commissioned by guideline development groups to find out more about the views and experiences of patients and carers.

Quality-adjusted life years (QALYs)

A measure of health outcome which looks at both length of life and quality of life. QALYs are calculated by estimating the years of life remaining for a patient following a particular care pathway and weighting each year with a quality of life score (on a zero to one scale). One QALY is equal to 1 year of life in perfect health, or 2 years at 50% health, and so on.

Quantitative research

Research that generates numerical data or data that can be converted into numbers, for example clinical trials or the national census which counts people and households.

Quasi-experimental study

A study designed to test whether a treatment or intervention has an effect on the course or outcome of disease. It differs from a **controlled clinical trial** and a **randomised controlled trial** in that:

- the assignment of patients to treatment and comparison groups is not done randomly, or patients are not given equal probabilities of selection, or
- the investigator does not have full control over the allocation and/or timing of the intervention, but nonetheless conducts the study as if it were an experiment, allocating subjects to treatment and comparison groups.

Random allocation or randomisation

A method that uses the play of chance to assign participants to comparison groups in a research study, for example by using a random numbers table or a computer-generated random sequence. Random allocation implies that each individual (or each unit in the case of **cluster randomisation**) being entered into a study has the same chance of receiving each of the possible interventions.

Randomised controlled trial (RCT)

A study to test a specific drug or other treatment in which people are randomly assigned to two (or more) groups: one (the experimental group) receiving the treatment that is being tested, and the other (the comparison or **control group**) receiving an alternative treatment, a placebo (dummy treatment) or no treatment. The two groups are followed up to compare differences in outcomes to see how effective the experimental treatment was. (Through randomisation, the groups should be similar in all aspects apart from the treatment they receive during the study.)

Receiver operating characteristic (ROC) curve

ROC curves are used to show the pattern of sensitivities and specificities observed when the performance of a test is evaluated at several different diagnostic thresholds. An ROC curve is a plot of sensitivity (i.e. the true positive rate) versus 1–specificity (i.e. the false positive rate). The overall diagnostic performance of a test can be judged by measuring the area under the ROC curve.

Reflux	See **vesicoureteric reflux (VUR)**.
Reflux nephropathy	A condition in which one or both kidneys are damaged in association with **vesicoureteric reflux (VUR)** (backward flow of urine into the kidney). This can be either congenital, i.e. part of the same malformation as the VUR, or acquired from an episode of acute pyelonephritis. In the latter case it is synonymous with **pyelonephritic scarring**.
Relative risk (RR)	A summary measure which represents the ratio of the risk of a given event or outcome (e.g. an adverse reaction to the drug being tested) in one group of subjects compared with another group. When the 'risk' of the event is the same in the two groups the relative risk is 1. In a study comparing two treatments, a relative risk of 2 would indicate that patients receiving one of the treatments had twice the risk of an undesirable outcome than those receiving the other treatment. Relative risk is sometimes used as a synonym for **risk ratio**.
Reliability	Reliability refers to a method of measurement that consistently gives the same results. For example, someone who has a high score on one occasion tends to have a high score if measured on another occasion very soon afterwards. With physical assessments it is possible for different clinicians to make independent assessments in quick succession – and if their assessments tend to agree then the method of assessment is said to be reliable.
Renal hypertension	High blood pressure due to kidney disease.
Renal National Service Framework (NSF)	Department of Health policy on the management of chronic kidney disease and established renal failure.[2]
Retrospective study	A retrospective study deals with the past and does not involve studying future events. This contrasts with studies that are **prospective**.
Review	Summary of the main points and trends in the research literature on a specified topic. A review is considered non-systematic unless an extensive literature search has been carried out to ensure that all aspects of the topic are covered and an objective appraisal made of the quality of the studies.
Risk ratio	Ratio of the risk of an undesirable event or outcome occurring in a group of patients receiving experimental treatment compared with a comparison (**control**) group. The term **relative risk** is sometimes used as a synonym for risk ratio.
Royal Colleges	In the UK medical/nursing world the term Royal Colleges, as for example in 'The Royal College of …', refers to organisations which usually combine an educational standards and examination role with the promotion of professional standards.
Sample	A part of the study's **target population** from which the subjects of the study will be recruited. If subjects are drawn in an unbiased way from a particular population, the results can be generalised from the sample to the population as a whole.
Sampling	Refers to the way participants are selected for inclusion in a study.
Sampling frame	A list or register of names which is used to recruit participants to a study.
Scottish Intercollegiate Guidelines Network (SIGN)	SIGN was established in 1993 to sponsor and support the development of evidence-based clinical guidelines for the NHS in Scotland.
Secondary care	Care provided by hospital-based professionals (e.g. hospital care, community paediatrics/outreach services).
Selection bias	Selection bias occurs when the method of selecting a population for a study alters the outcomes. Clues that selection bias has occurred are: • the characteristics of the **sample** differ from those of the wider population from which the sample has been drawn, or • there are systematic differences between comparison groups of patients in a study in terms of prognosis or disease progression unrelated to the treatment.
Selection criteria	Explicit standards used by guideline development groups to decide which studies should be included and excluded from consideration as potential sources of evidence.
Semi-structured interview	Both structured and semi-structured interviews involve asking people pre-set questions. Unlike a **structured interview**, a semi-structured interview allows the interviewer and the respondent flexibility to change the questions and the direction of the interview. The interviewer asks a number of open-ended questions, following up areas of interest in response to the information given by the respondent.

Sensitivity — In diagnostic testing, sensitivity refers to the chance of having a positive test result given that you have the disease. 100% sensitivity means that all those with the disease will test positive, but this is not the same the other way around. A patient could have a positive test result but not have the disease – this is called a 'false positive'. The sensitivity of a test is also related to its **negative predictive value** (true negatives) – a test with a sensitivity of 100% means that all those (or almost all those in very large studies) who get a negative test result do not have the disease. To fully judge the accuracy of a test, its **specificity** must also be considered.

Single-blind study — A study in which either the subject (patient/participant) or the observer (clinician/investigator) is not aware of which treatment or intervention the subject is receiving.

Specific indication — When a drug or a device has a specific remit to treat a specific condition and is not licensed for use in treating other conditions or diseases.

Specificity — In diagnostic testing, specificity refers to the chance of having a negative test result given that you do not have the disease. 100% specificity means that all those without the disease will test negative, but this is not the same the other way around. A patient could have a negative test result yet still have the disease – this is called a 'false negative'. The specificity of a test is also related to its **positive predictive value** (true positives) – a test with a specificity of 100% means that all those (or almost all those in very large studies) who get a positive test result definitely have the disease. To fully judge the accuracy of a test, its **sensitivity** must also be considered.

Standard deviation (SD) — A measure of the spread, scatter or variability of a set of measurements. Usually used with the mean (average) to describe numerical data. 95% of a population will lie within three standard deviations either side of the mean.

Statistical power — The ability of a study to demonstrate an association or causal relationship between two **variables**, given that an association exists. For example, 80% power in a clinical trial means that the study has an 80% chance of ending up with a *P* value of less than 5% in a statistical test (i.e. a statistically significant treatment effect) if there really was an important difference (e.g. 10% versus 5% mortality) between treatments. If the statistical power of a study is low, the study results will be questionable (the study might have been too small to detect any differences). By convention, 80% is an acceptable level of power. See also ***P* value**.

Structured interview — A research technique where the interviewer controls the interview by adhering strictly to a questionnaire or interview schedule with pre-set questions.

Study checklist — A list of questions addressing the key aspects of the research methodology that must be in place if a study is to be accepted as valid. A different checklist is required for each study type. These checklists are used to ensure a degree of consistency in the way that studies are evaluated.

Study population — People who have been identified as the subjects of a study.

Study quality — See **methodological quality**.

Study type — The kind of design used for a study. **Randomised controlled trials**, **case–control studies**, and **cohort studies** are all examples of study types.

Subject — A person who takes part in an experiment or research study.

Summary receiver operating characteristic (SROC) curve — A summary receiver operating characteristic curve is generated by using weighted linear regression as a way to avoid the underestimation of test performance that results when the correlation between sensitivity and specificity is ignored.

Suprapubic aspiration (SPA) — The collection of a urine sample by inserting a needle directly into the bladder through the anterior abdominal wall above the pubic bone.

Survey — A study in which information is systematically collected from people (usually from a sample within a defined population).

Systematic — Methodical, according to plan; not random.

Systematic error — Errors may be systematic or random. Errors that are systematic are inherent in studies. Examples of errors are incorrect data measurements/collection/analyses caused by humans, machines, acts of God, or inappropriate acts of interpretation – e.g. over-diagnosis of UTI due to reliance on the leucocyte test alone would be an error (but not a bias).

Systematic review — A review in which evidence from scientific studies has been identified, appraised and synthesised in a methodical way according to predetermined criteria. May or may not include a **meta-analysis**.

Systemic	Involving the whole body.
Target population	The people to whom guideline recommendations are intended to apply. Recommendations may be less valid if applied to a population with different characteristics from the participants in the research study, for example in terms of age, disease state or social background.
Tertiary centre	A major medical centre providing complex treatments which receives referrals from both primary and secondary care. Sometimes called a tertiary referral centre. See also **primary care** and **secondary care**.
Triangulation	Use of more than one research method in combination; principally used as a check of validity. The more the different methods produce similar results, the more valid the findings.
Triple-blind study	A study in which the statistical analysis is carried out without knowing which treatment patients received, in addition to the patients and investigators/clinicians being unaware which treatment patients were getting.
Trust	A trust is an NHS organisation responsible for providing a group of healthcare services. An **acute trust** provides hospital services. A **mental health trust** provides most mental health services. A **primary care trust** buys hospital care on behalf of the local population, as well as being responsible for the provision of community health services.
Tumour necrosis factor alpha	Serum glycoprotein produced by activated macrophages and other mammalian mononuclear leucocytes. It has necrotising activity against tumour cell lines and increases the ability to reject tumour transplants. Also known as TNF-α, it is only 30% homologous to TNF-β (lymphotoxin), but they share TNF receptors.
Ultrasound	High-frequency sound waves reflected off internal structures are reconstructed into images providing excellent anatomic information without the use of ionising radiation. There are no known hazards associated with ultrasound, making it an ideal first-line investigation of the renal tract in children. The use of **Doppler ultrasound** permits some functional information about the blood flow and perfusion of the kidneys. **Power Doppler** is a refinement of conventional Doppler ultrasound, and is very sensitive for assessing blood flow.
Urgency (urinary)	A strong, sudden need to urinate immediately.
Urinalysis	Examination of urine by chemical, physical, or microscopic means. Routine urinalysis usually includes performing chemical screening tests, performing microscopy to determine the presence of white blood cells and bacteria and performing quantitative culture.
Urine culture	See **culture**.
Validity	Assessment of how well a tool or instrument measures what it is intended to measure. See also **external validity** and **internal validity**.
Variable	A measurement that can vary within a study, for example the age of participants. Variability is present when differences can be seen between different people or within the same person over time, with respect to any characteristic or feature which can be assessed or measured.
Vesicoureteric reflux (VUR)	The passage of urine from the bladder back into a ureter and, in higher grades of VUR, to the kidneys. Grade I: ureter only Grade II: ureter, pelvis and calyces; no dilatation, normal calyceal fornices Grade III: mild or moderate dilatation and/or tortuosity of the ureter and mild or moderate dilatation of the renal pelvis; no or slight blunting of the fornices Grade IV: moderate dilatation and/or tortuosity of the ureter and moderate dilatation of the renal pelvis and calyces; complete obliteration of the sharp angle of the fornices but maintenance of the papillary impressions in the majority of calyces Grade V: gross dilatation and tortuosity of the ureter; gross dilatation of the renal pelvis and calyces; the papillary impressions are no longer visible in the majority of calyces.[3]
Voiding cystourethrogram (VCUG)	See **micturating cystourethrogram (MCUG)**.
Voiding urosonography (VUS)	See **cystosonography**.
Weighted mean difference	A summary effect size measure for continuous data where studies that have measured the outcome on the same scale have been pooled.

1 Scope and methodology

1.1 Urinary tract infection

In the past 30–50 years, the natural history of urinary tract infection (UTI) in children has changed as a result of the introduction of antibiotics and improvements in health care. This change has contributed to uncertainty about the most appropriate and effective way to diagnose and treat UTI in children and whether or not investigations and follow-up are justified.

UTI is a common bacterial infection causing illness in children. It may be difficult to recognise UTI in children because the presenting symptoms and/or signs are non-specific, particularly in younger children. Urine collection and interpretation of urine tests in children are not easy and therefore it may not always be possible to unequivocally confirm the diagnosis.

Current management involving imaging, prophylaxis and prolonged follow-up has placed a heavy burden on NHS primary and secondary care resources. It is unpleasant for children and families, costly and based on limited evidence. The aim of this guideline is to lead to more consistent clinical practice by considering the importance of accurate diagnosis and the effectiveness of subsequent investigations and treatment (including surgical intervention) and follow-up in altering the outcome.

1.2 Guideline objectives

Clinical guidelines have been defined as 'systematically developed statements which assist clinicians and patients in making decisions about appropriate treatment for specific conditions'.[4] The guideline has been developed with the aim of providing guidance on the following:

a) when to consider the diagnosis of UTI in sick and/or symptomatic children who were previously healthy
b) when and how to collect urine for the diagnosis of UTI in children
c) which tests establish or exclude UTI as the cause of illness in children
d) how to treat sick and/or symptomatic children, including:
   - when to admit to hospital
   - when to start treatment
   - which antibiotics to use
   - what route of administration to use
   - how long to treat
e) how and when to treat symptomatic re-infection
f) when to use prophylactic antibiotics, which antibiotics to use and when to stop them
g) when to use investigations to assess the structure and function of the urinary tract
h) when to refer to secondary and tertiary care
i) when to offer surgical intervention
j) when to do long-term follow-up
k) what advice to give carers and parents, including what to do if another UTI occurs.

1.3 Areas outside of the remit of the guideline

a) children with urinary catheters *in situ*
b) children with neurogenic bladders
c) children already known to have significant pre-existing uropathies
d) children with underlying renal disease (for example, nephrotic syndrome)
e) immunosuppressed children
f) infants and children in intensive care units
g) preventative measures or long-term management of sexually active girls with recurrent UTI.

1.4 For whom is the guideline intended?

This guideline is relevant to those who work in or use the National Health Service (NHS) in England and Wales, in particular:

a) all healthcare professionals involved in providing care for children who have a UTI (including GPs, nurses, paediatricians, nephrologists and urologists)
b) those responsible for commissioning and planning healthcare services, including primary care trust commissioners, Health Commission Wales commissioners, and public health and trust managers
c) children who have UTI and their families.

A version of this guideline for children, young people, parents, carers and the public is available, entitled *Understanding NICE Guidance*. It can be downloaded from the National Institute for Health and Clinical Excellence (NICE) website (www.nice.org.uk/CG054) or ordered via the NHS Response Line (0870 1555 455) quoting reference number N1305.

1.5 Who has developed the guideline?

The guideline was developed by a multi-professional and lay working group (the Guideline Development Group or GDG) convened by the National Collaborating Centre for Women's and Children's Health (NCC-WCH). The membership is listed on page v.

Staff from the NCC-WCH provided methodological support for the guideline development process, undertook systematic searches, retrieval and appraisal of the evidence, health economics modelling and wrote successive drafts of the guideline as described below (Section 1.7).

All GDG members' interests were recorded on declaration forms provided by NICE. The form covered consultancies, fee-paid work, shareholdings, fellowships, and support from the healthcare industry.

1.6 Other relevant documents

This guideline is intended to complement other existing and proposed works of relevance, including:

- Health Technology Appraisal: *Clinical and cost-effectiveness of tests for the diagnosis and evaluation of urinary tract infection (UTI) in children: a systematic review and economic model* (Vol.10: No.36, 2006)
- NICE Clinical Guideline: *Feverish Illness in Children* (published June 2007).

1.7 Guideline development methodology

This guideline was commissioned by NICE and developed in accordance with the guideline development process outlined in the NICE *Guidelines Manual*.[5]

Literature search strategy

Initial scoping searches were executed to identify relevant guidelines (local, national and international) produced by other development groups. The reference lists in these guidelines were checked against subsequent searches to identify missing evidence.

Relevant published evidence to inform the guideline development process and answer the clinical questions was identified by systematic search strategies. Additionally, stakeholder organisations were invited to submit evidence for consideration by the GDG provided it was relevant to the clinical questions and of equivalent or better quality than evidence identified by the search strategies.

Systematic searches to answer the clinical questions formulated and agreed by the GDG were executed using the following core databases via the OVID platform: MEDLINE (1966 onwards), Cochrane Central Register of Controlled Trials (2nd quarter 2006), Cochrane Database of

Systematic Reviews (2nd quarter 2006), Database of Abstracts of Reviews of Effects (2nd quarter 2006), Embase (1980 onwards) and Cumulative Index to Nursing and Allied Health Literature (1982 onwards). Other databases, also via the OVID platform, utilised for specific questions were PsycINFO (1967 onwards) and Allied and Complementary Medicine Database (Datastar, 1985 onwards).

Search strategies combined relevant controlled vocabulary and natural language in an effort to balance sensitivity and specificity. Unless advised by the GDG, searches were not date specific (e.g. the search for antibiotic treatment for symptomatic UTI was restricted to studies published since 1986). Both generic and specially developed methodological search filters were used appropriately.

Searches were not restricted by language but non-English papers were only translated where they were identified as highly significant to the clinical question or a paucity of equivalent quality English language research meant the clinical question could not be addressed any other way.

Searches to identify economic studies were undertaken using the above databases and the NHS Economic Evaluations Database (NHS EED) produced by the Centre for Reviews and Dissemination at the University of York.

There was no systematic attempt to search grey literature (conferences, letters, abstracts, theses and unpublished trials). Hand searching of journals not indexed on the databases was not undertaken.

At the end of the guideline development process searches were updated and re-executed, thereby including evidence published and included in the databases up to 1 June 2006. The searches for effectiveness of imaging tests were conducted on 10 January 2007. Any evidence published after this date was not included. These dates should be considered the starting point for searching for new evidence for future updates to this guideline.

Further details of the search strategies, including the methodological filters employed, are provided on the accompanying CD-ROM.

Synthesis of clinical effectiveness evidence

Evidence relating to clinical effectiveness was reviewed using established guides[5–12] and classified using the established hierarchical system shown in Table 1.1.[12] This system reflects the susceptibility to bias that is inherent in particular study designs.

The type of clinical question dictates the highest level of evidence that may be sought. In assessing the quality of the evidence, each study receives a quality rating coded as '++', '+' or '–'. For issues of therapy or treatment, the highest possible evidence level (EL) is a well-conducted systematic review or meta-analysis of randomised controlled trials (RCTs) (EL = 1++) or an individual

Table 1.1 Levels of evidence for intervention studies[9]

Level	Source of evidence
1++	High-quality meta-analyses, systematic reviews of randomised controlled trials (RCTs) or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of RCTs or RCTs with a low risk of bias
1–	Meta-analyses, systematic reviews of RCTs or RCTs with a high risk of bias
2++	High-quality systematic reviews of case–control or cohort studies; high-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2–	Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal
3	Non-analytical studies (for example case reports, case series)
4	Expert opinion, formal consensus

RCT (EL = 1+). Studies of poor quality are rated as '–'. Usually, studies rated as '–' should not be used as a basis for making a recommendation, but they can be used to inform recommendations. For issues of prognosis, the highest possible level of evidence is a cohort study (EL = 2–).

For each clinical question, the highest available level of evidence was selected. Where appropriate, for example, if a systematic review, meta-analysis or RCT existed in relation to a question, studies of a weaker design were not included. Where systematic reviews, meta-analyses and RCTs did not exist, other appropriate experimental or observational studies were sought. For diagnostic tests, test evaluation studies examining the performance of the test were used if the efficacy of the test was required, but where an evaluation of the effectiveness of the test in the clinical management of patients and the outcome of disease was required, evidence from RCTs or cohort studies was used.

The system described above covers studies of treatment effectiveness. However, it is less appropriate for studies reporting diagnostic tests of accuracy. In the absence of a validated ranking system for this type of test, NICE has developed a hierarchy for evidence of accuracy of diagnostic tests that takes into account the various factors likely to affect the validity of these studies (Table 1.2).[5]

Staff from the NCC-WCH provided methodological support for the guideline development process, undertook systematic searches, retrieved and appraised literature and wrote systematic reviews. The GDG appraised and edited the systematic reviews and generated evidence statements and recommendations based on their content.

For economic evaluations, no standard system of grading the quality of evidence exists. Economic evaluations that are included in the review have been assessed using a quality assessment checklist based on good practice in decision-analytic modelling.[13]

Evidence was synthesised qualitatively by summarising the content of identified papers in evidence tables and agreeing brief statements that accurately reflected the evidence. Quantitative synthesis (meta-analysis) was performed where appropriate.

Summary results and data are presented in the guideline text. More detailed results and data are presented in the evidence tables on the accompanying CD-ROM. Where possible, dichotomous outcomes are presented as relative risks (RRs) with 95% confidence intervals (CIs), and continuous outcomes are presented as mean differences with 95% CIs or standard deviations (SDs). Meta-analyses based on dichotomous outcomes are presented as pooled odds ratios (ORs) with 95% CIs, and meta-analyses based on continuous outcomes are presented as weighted mean differences (WMDs) with 95% CIs.

Table 1.2 Levels of evidence for studies of the accuracy of diagnostics tests[5]

Level	Type of evidence
Ia	Systematic reviews (with homogeneity)[a] of level-1 studies[b]
Ib	Level-1 studies[b]
II	Level-2 studies[c]; systematic reviews of level-2 studies
III	Level-3 studies[d]; systematic reviews of level-3 studies
IV	Consensus, expert committee reports or opinions and/or clinical experience without explicit critical appraisal; or based on physiology, bench research or 'first principles'

[a] Homogeneity means there are no or minor variations in the directions and degrees of results between individual studies that are included in the systematic review.

[b] Level-1 studies are studies that use a blind comparison of the test with a validated reference standard (gold standard) in a sample of patients that reflects the population to whom the test would apply.

[c] Level-2 studies are studies that have only one of the following:
- narrow population (the sample does not reflect the population to whom the test would apply)
- use a poor reference standard (defined as that where the 'test' is included in the 'reference', or where the 'testing' affects the 'reference')
- the comparison between the test and reference standard is not blind
- case–control studies.

[d] Level-3 studies are studies that have at least two or three of the features listed above.

Health economics

The aim of the economic input into the guideline was to inform the GDG of potential economic issues relating to UTI in children.

The health economist helped the GDG by identifying topics within the guideline that might benefit from economic analysis, reviewing the available economic evidence and, where necessary, conducting (or commissioning) economic analysis. Reviews of published health economic evidence are presented alongside the reviews of clinical evidence where appropriate. Where no published economic evidence was available to inform the GDG in their decision making, the health economist advised the GDG on the potential impact on resource use resulting from the recommendations made in the guideline.

Forming and grading recommendations

For each clinical question, recommendations were derived using, and explicitly linked to, the highest available evidence that supported them. In the first instance, informal consensus methods were used by the GDG to agree evidence statements and recommendations. Shortly before the consultation period, formal consensus methods were used to agree guideline recommendations (modified Delphi technique) and to select 5–10 key priorities for implementation (nominal group technique).

External review

This guideline has been developed in accordance with the NICE guideline development process. This has included giving registered stakeholder organisations the opportunity to comment on the scope of the guideline at the initial stage of development and on the evidence and recommendations at the concluding stage. The developers have carefully considered all of the comments during the consultation period by registered stakeholders and validation by NICE. After the consultation period, changes were made to the final document.

Outcome measures used in the guideline

- diagnosis of UTI
- response to antibiotics
- recurrence of UTI
- renal scarring
- long-term complications
- adverse outcomes of treatment or investigation
- health economics
- The GDG considered other outcomes as they were relevant to specific questions.

1.8 Schedule for updating the guideline

Clinical guidelines commissioned by NICE are published with a review date 4 years from date of publication. Reviewing may begin earlier than 4 years if significant evidence that affects guideline recommendations is identified sooner. The updated guideline will be available within 2 years of the start of the review process.

2 Summary of recommendations, patient flow pathway and algorithm

2.1 Key priorities for implementation (key recommendations)

Diagnosis (Chapter 4)

Symptoms and signs

Infants and children presenting with unexplained fever of 38 °C or higher should have a urine sample tested after 24 hours at the latest.

Infants and children with symptoms and signs suggestive of urinary tract infection (UTI) should have a urine sample tested for infection. Table 4.15 is a guide to the symptoms and signs that infants and children present with.

Urine collection

A clean catch urine sample is the recommended method for urine collection. If a clean catch urine sample is unobtainable:

- Other non-invasive methods such as urine collection pads should be used. It is important to follow the manufacturer's instructions when using urine collection pads. Cotton wool balls, gauze and sanitary towels should not be used to collect urine in infants and children.
- When it is not possible or practical to collect urine by non invasive methods, catheter samples or suprapubic aspiration (SPA) should be used.
- Before SPA is attempted, ultrasound guidance should be used to demonstrate the presence of urine in the bladder.

Urine testing

The urine-testing strategies shown in Tables 4.16–4.19 are recommended.*

History and examination on confirmed UTI

The following risk factors for UTI and serious underlying pathology should be recorded:

- poor urine flow
- history suggesting previous UTI or confirmed previous UTI
- recurrent fever of uncertain origin
- antenatally diagnosed renal abnormality
- family history of vesicoureteric reflux (VUR) or renal disease
- constipation
- dysfunctional voiding
- enlarged bladder
- abdominal mass
- evidence of spinal lesion
- poor growth
- high blood pressure.

* Assess the risk of serious illness in line with 'Feverish illness in children' (NICE clinical guideline 47) to ensure appropriate urine tests and interpretation, both of which depend on the child's age and risk of serious illness.

Acute management (Chapter 5)

Antibiotic treatment

Infants younger than 3 months with a possible UTI should be referred immediately to the care of a paediatric specialist. Treatment should be with intravenous (IV) antibiotics in line with 'Feverish illness in children' (NICE clinical guideline 47).

For infants and children 3 months or older with acute pyelonephritis/upper urinary tract infection:

- Consider referral to secondary care.
- Treat with oral antibiotics for 7–10 days. The use of an oral antibiotic with low resistance patterns is recommended, for example, cephalosporin or co-amoxiclav.
- If oral antibiotics cannot be used, treat with an IV antibiotic agent such as cefotaxime or ceftriaxone for 2–4 days followed by oral antibiotics for a total duration of 10 days.

For infants and children 3 months or older with cystitis/lower urinary tract infection:

- Treat with oral antibiotics for 3 days. The choice of antibiotics should be directed by locally developed multidisciplinary guidance. Trimethoprim, nitrofurantoin, cephalosporin or amoxicillin may be suitable.
- The parents or carers should be advised to bring the infant or child for reassessment if the infant or child is still unwell after 24–48 hours. If an alternative diagnosis is not made, a urine sample should be sent for culture to identify the presence of bacteria and determine antibiotic sensitivity if urine culture has not already been carried out.

Long-term management (Chapter 6)

Antibiotic prophylaxis

Antibiotic prophylaxis should not be routinely recommended in infants and children following first-time UTI.

Imaging tests

Infants and children who have had a UTI should be imaged as outlined in Tables 6.13, 6.14 and 6.15.

2.2 Summary of recommendations

Diagnosis (Chapter 4)

Symptoms and signs

Infants and children presenting with unexplained fever of 38 °C or higher should have a urine sample tested after 24 hours at the latest.

Infants and children with an alternative site of infection should not have a urine sample tested. When infants and children with an alternative site of infection remain unwell, urine testing should be considered after 24 hours at the latest.

Infants and children with symptoms and signs suggestive of urinary tract infection (UTI) should have a urine sample tested for infection. Table 4.15 is a guide to the symptoms and signs that infants and children present with.

Assessment of risk of serious illness

The illness level in infants and children should be assessed in accordance with recommendations in 'Feverish illness in children' (NICE clinical guideline 47).

Table 4.15 Presenting symptoms and signs in infants and children with UTI

Age group		**Symptoms and signs** Most common ⟷ Least common		
Infants younger than 3 months		Fever Vomiting Lethargy Irritability	Poor feeding Failure to thrive	Abdominal pain Jaundice Haematuria Offensive urine
Infants and children, 3 months or older	Preverbal	Fever	Abdominal pain Loin tenderness Vomiting Poor feeding	Lethargy Irritability Haematuria Offensive urine Failure to thrive
	Verbal	Frequency Dysuria	Dysfunctional voiding Changes to continence Abdominal pain Loin tenderness	Fever Malaise Vomiting Haematuria Offensive urine Cloudy urine

Urine collection

A clean catch urine sample is the recommended method for urine collection. If a clean catch urine sample is unobtainable:

- Other non-invasive methods such as urine collection pads should be used. It is important to follow the manufacturer's instructions when using urine collection pads. Cotton wool balls, gauze and sanitary towels should not be used to collect urine in infants and children.
- When it is not possible or practical to collect urine by non invasive methods, catheter samples or suprapubic aspiration (SPA) should be used.
- Before SPA is attempted, ultrasound guidance should be used to demonstrate the presence of urine in the bladder.

In an infant or child with a high risk of serious illness it is highly preferable that a urine sample is obtained; however, treatment should not be delayed if a urine sample is unobtainable.

Urine preservation

If urine is to be cultured but cannot be cultured within 4 hours of collection, the sample should be refrigerated or preserved with boric acid immediately.

The manufacturer's instructions should be followed when boric acid is used to ensure the correct specimen volume to avoid potential toxicity against bacteria in the specimen.

Urine testing

The urine-testing strategies shown in Tables 4.16–4.19 are recommended.*

As with all diagnostic tests there will be a small number of false negative results; therefore clinicians should use clinical criteria for their decisions in cases where urine testing does not support the findings.

Indication for culture

Urine samples should be sent for culture:

- in infants and children who have a diagnosis of acute pyelonephritis/upper urinary tract infection
- in infants and children with a high to intermediate risk of serious illness
- in infants and children younger than 3 years

* Assess the risk of serious illness in line with 'Feverish illness in children' (NICE clinical guideline 47) to ensure appropriate urine tests and interpretation, both of which depend on the child's age and risk of serious illness.

Table 4.16 Urine-testing strategy for infants younger than 3 months

All infants younger than 3 months with suspected UTI (see Table 4.15) should be referred to paediatric specialist care and a urine sample should be sent for urgent microscopy and culture. These infants should be managed in accordance with the recommendations for this age group in 'Feverish illness in children' (NICE clinical guideline 47).

Table 4.17 Urine-testing strategies for infants and children 3 months or older but younger than 3 years

Urgent microscopy and culture is the preferred method for diagnosing UTI in this age group; this should be used where possible.	
If the infant or child has specific urinary symptoms	Urgent microscopy and culture should be arranged and antibiotic treatment should be started. When urgent microscopy is not available, a urine sample should be sent for microscopy and culture, and antibiotic treatment should be started.
If the symptoms are non-specific to UTI	• For an infant or child with a high risk of serious illness: the infant or child should be urgently referred to a paediatric specialist where a urine sample should be sent for urgent microscopy and culture. Such infants and children should be managed in line with 'Feverish illness in children' (NICE clinical guideline 47). • For an infant or child with an intermediate risk of serious illness: if the situation demands, the infant or child may be referred urgently to a paediatric specialist. For infants and children who do not require paediatric specialist referral, urgent microscopy and culture should be arranged. Antibiotic treatment should be started if microscopy is positive (see Table 4.19). When urgent microscopy is not available, dipstick testing may act as a substitute. The presence of nitrites suggests the possibility of infection and antibiotic treatment should be started (see Table 4.18). In all cases, a urine sample should be sent for microscopy and culture. • For an infant or child with a low risk of serious illness: microscopy and culture should be arranged. Antibiotic treatment should only be started if microscopy or culture is positive.

Table 4.18 Urine-testing strategies for children 3 years or older

Dipstick testing for leucocyte esterase and nitrite is diagnostically as useful as microscopy and culture, and can safely be used.	
If both leucocyte esterase and nitrite are positive	The child should be regarded as having UTI and antibiotic treatment should be started. If a child has a high or intermediate risk of serious illness and/or a history of previous UTI, a urine sample should be sent for culture.
If leucocyte esterase is negative and nitrite is positive	Antibiotic treatment should be started if the urine test was carried out on a fresh sample of urine. A urine sample should be sent for culture. Subsequent management will depend upon the result of urine culture.
If leucocyte esterase is positive and nitrite is negative	A urine sample should be sent for microscopy and culture. Antibiotic treatment for UTI should not be started unless there is good clinical evidence of UTI (for example, obvious urinary symptoms). Leucocyte esterase may be indicative of an infection outside the urinary tract which may need to be managed differently.
If both leucocyte esterase and nitrite are negative	The child should not be regarded as having UTI. Antibiotic treatment for UTI should not be started, and a urine sample should not be sent for culture. Other causes of illness should be explored.

Table 4.19 Guidance on the interpretation of microscopy results

Microscopy results	Pyuria positive	Pyuria negative
Bacteriuria positive	The infant or child should be regarded as having UTI	The infant or child should be regarded as having UTI
Bacteriuria negative	Antibiotic treatment should be started if clinically UTI	The infant or child should be regarded as not having UTI

- in infants and children with a single positive result for leucocyte esterase or nitrite
- in infants and children with recurrent UTI
- in infants and children with an infection that does not respond to treatment within 24–48 hours, if no sample has already been sent
- when clinical symptoms and dipstick tests do not correlate.

History and examination on confirmed UTI

The following risk factors for UTI and serious underlying pathology should be recorded:

- poor urine flow
- history suggesting previous UTI or confirmed previous UTI
- recurrent fever of uncertain origin
- antenatally diagnosed renal abnormality
- family history of vesicoureteric reflux (VUR) or renal disease
- constipation
- dysfunctional voiding
- enlarged bladder
- abdominal mass
- evidence of spinal lesion
- poor growth
- high blood pressure.

Clinical differentiation between acute pyelonephritis/upper urinary tract infection and cystitis/lower urinary tract infection

Infants and children who have bacteriuria and fever of 38 °C or higher should be considered to have acute pyelonephritis/upper urinary tract infection. Infants and children presenting with fever lower than 38 °C with loin pain/tenderness and bacteriuria should be considered to have acute pyelonephritis/upper urinary tract infection. All other infants and children who have bacteriuria but no systemic symptoms or signs should be considered to have cystitis/lower urinary tract infection.

Laboratory tests for localising UTI

C-reactive protein alone should not be used to differentiate acute pyelonephritis/upper urinary tract infection from cystitis/lower urinary tract infection in infants and children.

Imaging tests for localising UTI

The routine use of imaging in the localisation of a UTI is not recommended.

In the rare instances when it is clinically important to confirm or exclude acute pyelonephritis/upper urinary tract infection, power Doppler ultrasound is recommended. When this is not available or the diagnosis still cannot be confirmed, a dimercaptosuccinic acid (DMSA) scintigraphy scan is recommended.

Acute management (Chapter 5)

Note that the antibiotic requirements for infants and children with conditions that are outside the scope of this guideline (for example, children already known to have significant pre-existing uropathies) have not been addressed and may be different from those given here.

Infants and children with a high risk of serious illness should be referred urgently to the care of a paediatric specialist.

Infants younger than 3 months with a possible UTI should be referred immediately to the care of a paediatric specialist. Treatment should be with parenteral antibiotics in line with 'Feverish illness in children' (NICE clinical guideline 47).

For infants and children 3 months or older with acute pyelonephritis/upper urinary tract infection:

- Consider referral to secondary care.
- Treat with oral antibiotics for 7–10 days. The use of an oral antibiotic with low resistance patterns is recommended, for example cephalosporin or co-amoxiclav.
- If oral antibiotics cannot be used, treat with an intravenous (IV) antibiotic agent such as cefotaxime or ceftriaxone for 2–4 days followed by oral antibiotics for a total duration of 10 days.

For infants and children 3 months or older with cystitis/lower urinary tract infection:

- Treat with oral antibiotics for 3 days. The choice of antibiotics should be directed by locally developed multidisciplinary guidance. Trimethoprim, nitrofurantoin, cephalosporin or amoxicillin may be suitable.
- The parents or carers should be advised to bring the infant or child for reassessment if the infant or child is still unwell after 24–48 hours. If an alternative diagnosis is not made, a urine sample should be sent for culture to identify the presence of bacteria and determine antibiotic sensitivity if urine culture has not already been carried out.

For infants and children who receive aminoglycosides (gentamicin or amikacin), once-daily dosing is recommended.

If parenteral treatment is required and IV treatment is not possible, intramuscular treatment should be considered.

If an infant or child is receiving prophylactic medication and develops an infection, treatment should be with a different antibiotic, not a higher dose of the same antibiotic.

Asymptomatic bacteriuria in infants and children should not be treated with antibiotics.

Laboratories should monitor resistance patterns of urinary pathogens and make this information routinely available to prescribers.

Long-term management (Chapter 6)

Prevention of recurrence

Dysfunctional elimination syndromes and constipation should be addressed in infants and children who have had a UTI.

Children who have had a UTI should be encouraged to drink an adequate amount.

Children who have had a UTI should have ready access to clean toilets when required and should not be expected to delay voiding.

Antibiotic prophylaxis

Antibiotic prophylaxis should not be routinely recommended in infants and children following first-time UTI.

Antibiotic prophylaxis may be considered in infants and children with recurrent UTI.

Asymptomatic bacteriuria in infants and children should not be treated with prophylactic antibiotics.

Imaging tests

Infants and children with atypical UTI (see Table 6.12) should have ultrasound of the urinary tract during the acute infection to identify structural abnormalities of the urinary tract such as obstruction as outlined in Tables 6.13, 6.14 and 6.15. This is to ensure prompt management.

For infants younger than 6 months with first-time UTI that responds to treatment, ultrasound should be carried out within 6 weeks of the UTI, as outlined in Table 6.13.

For infants and children 6 months or older with first-time UTI that responds to treatment, routine ultrasound is not recommended unless the infant or child has atypical UTI, as outlined in Tables 6.14 and 6.15.

Infants and children who have had a lower urinary tract infection should undergo ultrasound (within 6 weeks) only if they are younger than 6 months or have had recurrent infections.

A DMSA scan 4–6 months following the acute infection should be used to detect renal parenchymal defects as outlined in Tables 6.13, 6.14 and 6.15.

If the infant or child has a subsequent UTI while awaiting DMSA, the timing of the DMSA should be reviewed and consideration given to doing it sooner.

Table 6.12 Definitions of atypical and recurrent UTI

Atypical UTI includes:
- seriously ill (for more information refer to 'Feverish illness in children' (NICE clinical guideline 47)
- poor urine flow
- abdominal or bladder mass
- raised creatinine
- septicaemia
- failure to respond to treatment with suitable antibiotics within 48 hours
- infection with non-*E. coli* organisms.

Recurrent UTI:
- two or more episodes of UTI with acute pyelonephritis/upper urinary tract infection, or
- one episode of UTI with acute pyelonephritis/upper urinary tract infection plus one or more episode of UTI with cystitis/lower urinary tract infection, or
- three or more episodes of UTI with cystitis/lower urinary tract infection.

Table 6.13 Recommended imaging schedule for infants younger than 6 months

Test	Responds well to treatment within 48 hours	Atypical UTI[a]	Recurrent UTI[a]
Ultrasound during the acute infection	No	Yes[c]	Yes
Ultrasound within 6 weeks	Yes[b]	No	No
DMSA 4–6 months following the acute infection	No	Yes	Yes
MCUG	No	Yes	Yes

[a] See Table 6.12 for definition.
[b] If abnormal consider MCUG.
[c] In an infant or child with a non-*E. coli* UTI, responding well to antibiotics and with no other features of atypical infection, the ultrasound can be requested on a non-urgent basis to take place within 6 weeks.

Table 6.14 Recommended imaging schedule for infants and children 6 months or older but younger than 3 years

Test	Responds well to treatment within 48 hours	Atypical UTI[a]	Recurrent UTI[a]
Ultrasound during the acute infection	No	Yes[c]	No
Ultrasound within 6 weeks	No	No	Yes
DMSA 4–6 months following the acute infection	No	Yes	Yes
MCUG	No	No[b]	No[b]

[a] See Table 6.12 for definition.
[b] While MCUG should not be performed routinely it should be considered if the following features are present:
- dilatation on ultrasound
- poor urine flow
- non-*E. coli* infection
- family history of VUR.

[c] In an infant or child with a non-*E. coli* UTI, responding well to antibiotics and with no other features of atypical infection, the ultrasound can be requested on a non-urgent basis to take place within 6 weeks.

Table 6.15 Recommended imaging schedule for children 3 years or older

Test	Responds well to treatment within 48 hours	Atypical UTI[a]	Recurrent UTI[a]
Ultrasound during the acute infection	No	Yes[b c]	No
Ultrasound within 6 weeks	No	No	Yes[b]
DMSA 4–6 months following the acute infection	No	No	Yes
MCUG	No	No	No

[a] See Table 6.12 for definition.
[b] Ultrasound in toilet-trained children should be performed with a full bladder with an estimate of bladder volume before and after micturition.
[c] In a child with a non-*E. coli* UTI, responding well to antibiotics and with no other features of atypical infection, the ultrasound can be requested on a non-urgent basis to take place within 6 weeks.

Routine imaging to identify VUR is not recommended for infants and children who have had a UTI, except in specific circumstances as outlined in Tables 6.13, 6.14 and 6.15.

When micturating cystourethrogram (MCUG) is performed, prophylactic antibiotics should be given orally for 3 days with MCUG taking place on the second day.

Infants and children who have had a UTI should be imaged as outlined in Tables 6.13, 6.14 and 6.15.

Surgical intervention for VUR

Surgical management of VUR is not routinely recommended.

Follow-up

Infants and children who do not undergo imaging investigations should not routinely be followed up.

The way in which the results of imaging will be communicated should be agreed with the parents or carers or the young person as appropriate.

When results are normal, a follow-up outpatient appointment is not routinely required. Parents or carers should be informed of the results of all the investigations in writing.

Infants and children who have recurrent UTI or abnormal imaging results should be assessed by a paediatric specialist.

Assessment of infants and children with renal parenchymal defects should include height, weight, blood pressure and routine testing for proteinuria.

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.

Infants and children who have bilateral renal abnormalities, impaired kidney function, raised blood pressure and/or proteinuria should receive monitoring and appropriate management by a paediatric nephrologist to slow the progression of chronic kidney disease.

Infants and children who are asymptomatic following an episode of UTI should not routinely have their urine re-tested for infection.

Asymptomatic bacteriuria is not an indication for follow-up.

Information and advice to children, young people, and parents/carers (Chapter 7)

Healthcare professionals should ensure that when a child or young person has been identified as having a suspected UTI, they and their parents or carers as appropriate are given information about the need for treatment, the importance of completing any course of treatment and advice about prevention and possible long-term management.

Healthcare professionals should ensure that children and young people, and their parents or carers as appropriate, are aware of the possibility of a UTI recurring and understand the need to be vigilant and to seek prompt treatment from a healthcare professional for any suspected reinfection.

Healthcare professionals should offer children and young people and/or their parents or carers appropriate advice and information on:

- prompt recognition of symptoms
- urine collection, storage and testing
- appropriate treatment options
- prevention
- the nature of and reason for any urinary tract investigation
- prognosis
- reasons and arrangements for long-term management if required.

2.3 Research recommendations

Background (Chapter 3)

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.

Diagnosis (Chapter 4)

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

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.

Further investigation of leucocyte esterase and nitrite dipstick tests alone and in combination, stratified by age and method of urine collection, is required to determine their accuracy in diagnosing UTI.

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

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

Long-term management (Chapter 6)

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.

Imaging tests

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.

Further research on MRI for localising UTI could be considered.

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.

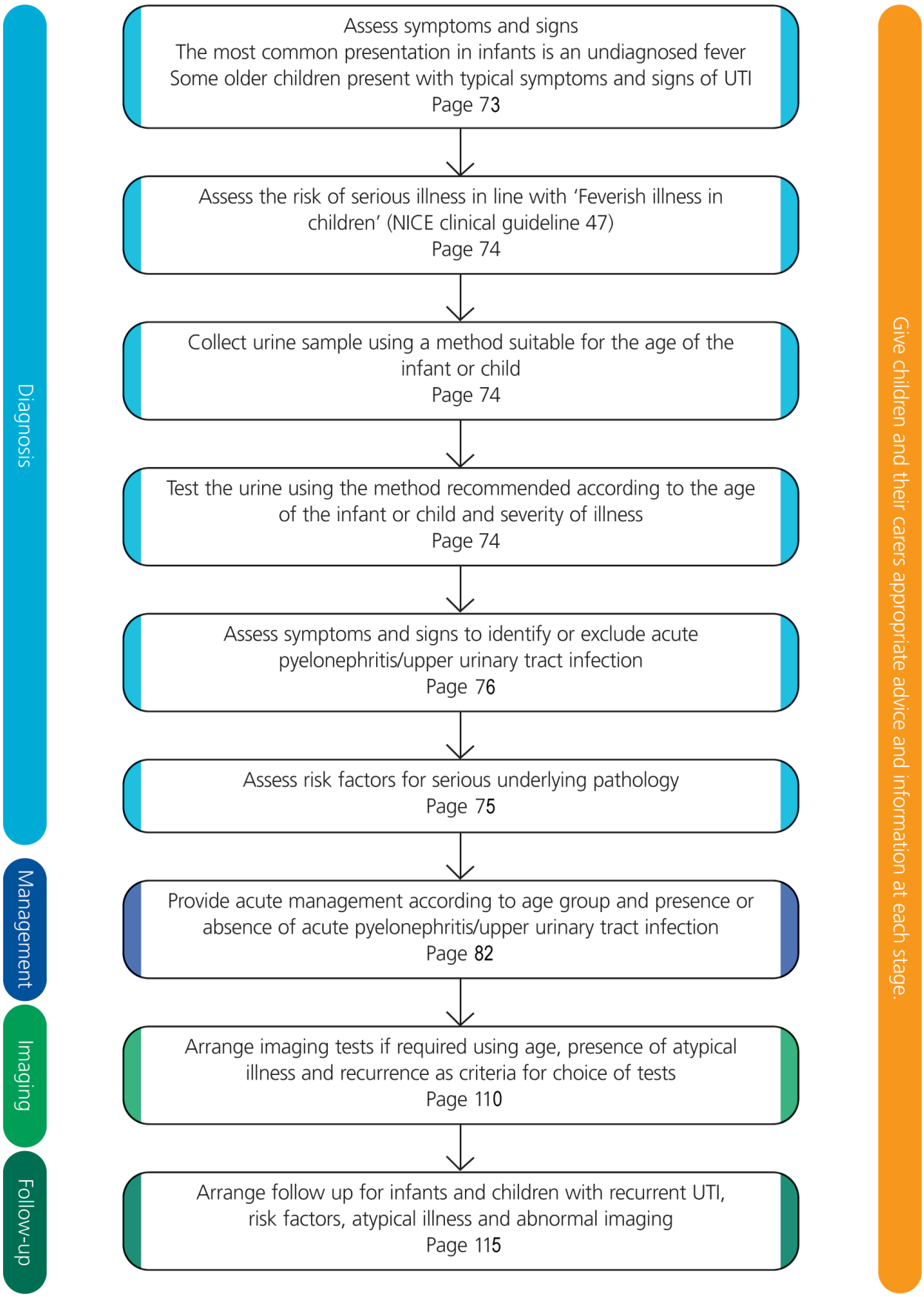
2.4 Patient flow pathway

The patient flow pathway shown opposite is taken from the NICE Quick Reference Guide version of this guideline (www.nice.org.uk/CG054). The page numbers within the pathway have been amended to refer correctly to the relevant recommendations in this full version.

2.5 Algorithm

The algorithm appears on pages 16–19.

Patient flow pathway



Diagnosis, treatment and long-term management of urinary tract infection in infants and children

Note: This algorithm should not be applied for infants or children with dilated pelvis or other urinary tract abnormalities identified from antenatal ultrasound screening or to other groups not within the scope of the guideline

Appropriate information and advice must be provided at each stage

Infants younger than 3 months	Infants and children 3 months or older but younger than 3 years	Children 3 years or older

Suspecting UTI

Symptoms and signs suggesting UTI

The presence of risk factors for UTI with serious underlying pathology should be recorded

Infants younger than 3 months

Most common ⟷ Least common		
Fever Vomiting Lethargy Irritability	Poor feeding Failure to thrive	Abdominal pain Jaundice Haematuria Offensive urine

Infants and children 3 months or older but younger than 3 years and children 3 years or older

	Most common ⟷ Least common		
Preverbal	Fever	Abdominal pain Loin tenderness Vomiting Poor feeding	Lethargy Irritability Haematuria Offensive urine Failure to thrive
Verbal	Frequency Dysuria	Dysfunctional voiding Changes to continence Abdominal pain Loin tenderness	Fever Malaise Vomiting Haematuria Offensive urine Cloudy urine

Assess the risk of serious illness using the traffic light system described in the *Feverish Illness in Children* guideline

Collecting urine

Urine should be tested in infants and children who have symptoms suggesting UTI described above. Those with unexplained fever of 38 °C or higher should have a urine sample tested after 24 hours at the latest

Collect urine using a clean catch sample

if not possible see guideline for details

Testing urine

Infants younger than 3 months

- ***Refer to paediatric specialist care***
- ***Urine sample for urgent microscopy and culture***
- ***Manage in line with 'Feverish illness in children' (NICE clinical guideline 47)***

Infants and children 3 months or older but younger than 3 years

Use urgent microscopy and culture to diagnose UTI

Specific urinary symptoms		Urine sample for urgent microscopy and culture Start antibiotic treatment If urgent microscopy is not available, send a urine sample for microscopy and culture, and start antibiotic treatment.
Non-specific urinary symptoms	**High risk of serious illness**	Urgent referral to paediatric specialist care Urine sample for urgent microscopy and culture Manage in line with 'Feverish illness in children' (NICE clinical guideline 47).
	Intermediate risk of serious illness	Consider urgent referral to a paediatric specialist as described in 'Feverish illness in children' (NICE clinical guideline 47) When specialist paediatric referral is not required: • Urgent microscopy and culture should be arranged • Antibiotic treatment should be started if microscopy is positive • When urgent microscopy is not available, dipstick testing may be used as a substitute • The presence of nitrites suggests the possibility of infection and antibiotic treatment should be started In all cases, a urine sample should be sent for microscopy and culture.
	Low risk of serious illness	Urine sample for microscopy and culture Start antibiotic treatment if microscopy or culture is positive.

Children 3 years or older

Use dipstick test to diagnose UTI

Both leucocyte esterase and nitrite positive	Start antibiotic treatment for UTI If high or intermediate risk of serious illness or past history of UTI, send urine sample for culture
Leucocyte esterase negative and nitrite positive	Start antibiotic treatment if fresh sample was tested. Send urine sample for culture
Leucocyte esterase positive and nitrite negative	Send urine sample for microscopy and culture Only start antibiotic treatment for UTI if there is good clinical evidence of UTI Result may indicate infection elsewhere Treat depending on results of culture
Both leucocyte esterase and nitrite negative	Do not start treatment for UTI Explore other causes of illness Do not send urine sample for culture unless recommended in 'Indications for sending for culture'

Guidance on microscopy results

	Pyuria positive	**Pyuria negative**
Bacteriuria positive	Having UTI	Having UTI
Bacteriuria negative	Start antibiotics if clinically UTI	Not having UTI

Indications for sending for culture

- acute pyelonephritis/upper urinary tract infection
- a high to intermediate risk of serious illness
- younger than 3 years
- a single positive result for leucocyte esterase or nitrite
- recurrent UTI
- an infection that does not respond to treatment within 24–48 hours
- when clinical symptoms and dipstick tests do not correlate.

Symptomatic infants or children with a positive urine culture should be treated.

Acute management

Treatment required

Treatment should be provided according to the risk of serious illness as shown below. When there is doubt about the level of risk of serious illness the child should be managed in accordance with the higher risk level. *Children with atypical UTI should have early imaging (see 'Imaging strategies')

High risk of serious illness and/or **Children younger than 3 months with suspicion of UTI**	Immediately refer to paediatric specialist care Microscopy and culture Treat with IV antibiotics if younger than 3 months
Acute pyelonephritis/upper urinary tract infection Children who have bacteriuria and fever 38 °C or higher Children presenting with fever lower than 38 °C with loin pain/tenderness and bacteriuria	Consider referral to paediatric specialist care Urine culture if not already done Treat with 7–10 days oral antibiotics (if oral antibiotics cannot be used, consider IV antibiotics)
Cystitis/lower urinary tract infection All other infants and children with symptoms or signs of UTI who have bacteriuria but no systemic symptoms or signs	Treat with 3 days oral antibiotics Review if still unwell after 24–48 hours

Imaging strategies

Children with cystitis/lower urinary tract infection should undergo ultrasound (within 6 weeks) only if they are younger than 6 months or have had recurrent infection. No other investigations are required for any child with cystitis/lower urinary tract infection unless they have recurrent UTI and/or abnormality on ultrasound, in which case late DMSA should be considered

Children younger than 6 months	Responds well to treatment within 48 hours without any features for atypical and/or recurrent UTI	Atypical UTI	Recurrent UTI
Ultrasound during the acute infection	No	Yes[b]	Yes
Ultrasound within 6 weeks	Yes[a]	No	No
DMSA 4–6 months following the acute infection	No	Yes	Yes
MCUG	No	Yes	Yes

[a] If abnormal consider MCUG.
[b] In a child with a non-*E. coli* UTI, responding well to antibiotics and with no other features of atypical infection, the ultrasound can be requested on a non-urgent basis to take place within 6 weeks.

Children 6 months or older but younger than 3 years	Responds well to treatment within 48 hours without any features for atypical and/or recurrent UTI	Atypical UTI	Recurrent UTI
Ultrasound during the acute infection	No	Yes[b]	No
Ultrasound within 6 weeks	No	No	Yes
DMSA 4–6 months following the acute infection	No	Yes	Yes
MCUG	No	No[a]	No[a]

[a] While MCUG should not be performed routinely it should be considered if the following features are present: dilatation on ultrasound; poor urine flow; non-*E. coli* infection; family history of VUR..
[b] In a child with a non-*E. coli* UTI, responding well to antibiotics and with no other features of atypical infection, the ultrasound can be requested on a non-urgent basis to take place within 6 weeks.

Children 3 years or older	Responds well to treatment within 48 hours without of features for atypical and/or recurrent UTI	Atypical UTI	Recurrent UTI
Ultrasound during the acute infection	No	Yes[a b]	No
Ultrasound within 6 weeks	No	No	Yes[a]
DMSA 4–6 months following the acute infection	No	No	Yes
MCUG	No	No	No

[a] Ultrasound in toilet-trained children should be performed with a full bladder with an estimate of bladder volume before and after micturition.
[b] In a child with a non-*E. coli* UTI, responding well to antibiotics and with no other features of atypical infection, the ultrasound can be requested on a non-urgent basis to take place within 6 weeks.

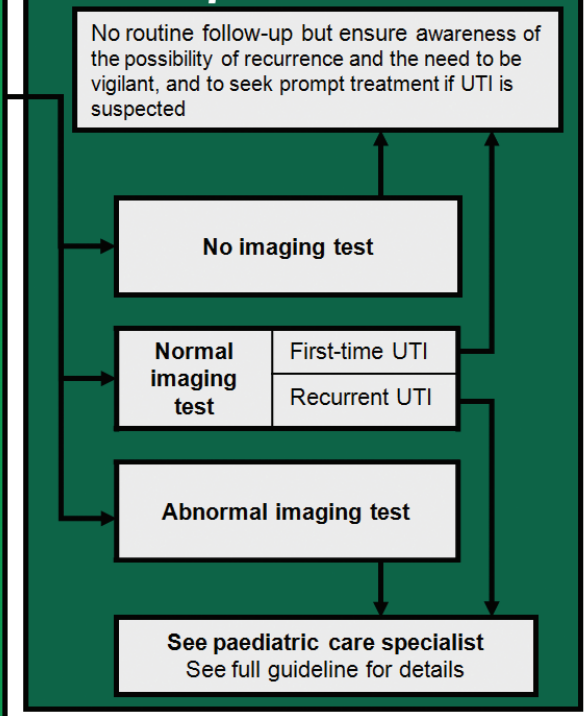
Definitions

Atypical UTI* includes:
- seriously ill
- poor urine flow
- abdominal or bladder mass
- raised creatinine
- septicaemia
- failure to respond to treatment with suitable antibiotics within 48 hours
- infection with non-*E. coli* organisms.

Recurrent UTI:
- two or more episodes of UTI with acute pyelonephritis/upper urinary tract infection, or
- one episode of UTI with acute pyelonephritis/upper urinary tract infection plus one or more episode of UTI with cystitis/lower urinary tract infection, or
- three or more episodes of UTI with cystitis/lower urinary tract infection.

***Presence of any of these features should be documented**

Follow-up



3 Background

3.1 Introduction

3.1.1 Clinical challenge

Urine infection is one of the most common bacterial infections[14] and its occurrence in childhood may carry special significance. Making the diagnosis is difficult particularly in young children and infants. This is because in this age group the clinical presentation of urine infection is often with non-specific clinical signs such as fever, irritability and vomiting that are also commonly seen in many acute self-limiting childhood viral illnesses. Seeking laboratory confirmation of the diagnosis requires the initial step of collecting an uncontaminated urine sample and this is a challenge in infants and children who are not toilet-trained. Failure to consider a diagnosis of urine infection or delaying the antibiotic treatment of a urine infection can have the effect of producing an acute clinical deterioration and in addition it may result in long-term renal damage.

Although the vast majority of children who have a urine infection recover promptly and do not have any long-term complications, there is a small subgroup at risk of significant morbidity. This group of children falls broadly into two categories. In the first category, urine infections may be the signal of a serious underlying congenital anomaly such as obstruction that, if not relieved, will lead not only to more serious illness but also to renal damage. In the other, the infections may be associated with progressive loss of kidney function either in association with renal dysplasia or with recurrent episodes of acute pyelonephritis/upper urinary tract infection.[15] It is necessary, therefore, to develop clinical pathways to identify this small but important subgroup of children from the very many children presenting with urine infections who will recover with no residual ill health.

3.1.2 Historical perspective

Examination of the early literature on this subject reveals that there has indeed been an improvement in the outlook for children who have had UTI.[16] In the past, large series of patients have been described who at post mortem were found to have chronic infection and kidneys with renal scarring due to pyelonephritic scarring. Their clinical course was one of recurrent episodes of acute pyelonephritis/upper urinary tract infection, renal failure, hypertension and proteinuria.[17,18] Approximately 50 years ago,[19] using intravenous urogram (IVU) and micturating cystourethrogram (MCUG), many studies identified the relationship between UTI and renal parenchymal defects seen on IVU and vesicoureteric reflux (VUR).

In addition to clinical observation, practice has been influenced by animal experiments, such as those by Ransley and Risdon[20] who demonstrated that, in the presence of VUR and UTI, contrast and infected urine could enter the renal parenchyma in a retrograde direction via collecting ducts opening into compound papillae and cause renal scarring in the corresponding segments of renal cortex which drain into these ducts. They demonstrated how the first infection could be devastating to the renal parenchyma of the mini-pig, and how early antibiotic treatment could prevent or attenuate the renal scarring. They also described a hypothetical process whereby progression of renal scarring might evolve following the first insult as a result of further infections. These animal studies tended to reinforce the importance of prompt diagnosis and treatment of the first infection as well as the importance of recognising and treating recurrent infection, particularly recurrent acute pyelonephritis/upper urinary tract infection.

3.1.3 Guidelines on the management of UTIs by the Royal College of Physicians in 1991

Since 1991 many paediatricians and some general practitioners have adopted the guidance of the Working Group of the Research Unit of the Royal College of Physicians (RCP) who produced

an opinion-based consensus statement on the diagnosis and management of a first UTI in childhood.[21] These guidelines advocate that UTI should be considered in every child with a fever or urinary symptoms, that the diagnosis should be confirmed by culture of a urine sample and that, following treatment of the acute illness, all infants and children younger than 7 years should have specific renal imaging and receive prophylactic antibiotics until these investigations have been completed.

The association between UTIs, VUR and renal scarring (chronic pyelonephritis or reflux nephropathy) formed the basis of the recommendations. Looking for VUR by means of an MCUG was considered in the recommendations a first-line investigation in children younger than 1 year. The imaging tests proposed were an ultrasound for all children, and a late dimercaptosuccinic acid (DMSA) scan for all infants and children younger than 7 years. The recommendations suggested that VUR should also be looked for in the older child with recurrent infections or if the ultrasound or DMSA scan was abnormal. Long-term low-dose prophylaxis was recommended for children found to have VUR. The use of prophylactic antibiotics in children with VUR was based on the belief that a small nightly dose of trimethoprim or nitrofurantoin will sterilise the residual bladder urine, preventing recurrent symptomatic infection and progression of renal scarring. The fundamental concept was that VUR plays a key role in the pathology of UTIs and renal scarring and that detection of VUR would prevent progressive renal damage. The hypothesis was that the results of imaging tests informed subsequent management and that the management strategies were effective in preventing subsequent acquired renal damage.

For paediatricians who had previously grappled with an array of management proposals, with greater or lesser numbers of imaging tests linked to surgery or prophylaxis, this authoritative document was most welcome and reasonably clear. Practice in secondary care became more consistent and paediatricians were particularly assiduous in following the guidance on imaging.[22,23]

3.1.4 Post-1991 guidelines: assessment and evolving evidence

Over time it has become clear that the vast majority of children having an ultrasound and a DMSA scan following a UTI have normal results. The yield of information on preventable long-term renal damage was relatively poor. For children 6 months or older and for children with minor symptoms or straightforward cases of acute pyelonephritis/upper urinary tract infection, the results of ultrasound are largely normal. For example, DMSA scans showed evidence of renal parenchymal defects assumed to be due to pyelonephritic scarring in 22% of children admitted to hospital but only 11% overall and 1% for children not ill enough to be admitted to hospital.[22] VUR was detected in one-third of cases, as expected from the literature.[23]

The recommendations from the Working Group of the RCP on imaging for all children younger than 7 years after a first UTI imposed a huge load on local radiology departments. In some cases, children and their families found that the burden of the imaging, particularly of the more invasive investigations, far exceeded the burden from a relatively straightforward and short illness. The psychological trauma of imaging tests, particularly those involving catheterisation, are well known.[24]

However, a small minority of children are found to have abnormal results. Although within this small group the imaging abnormalities are mostly trivial and of little clinical significance, there is undoubtedly a subgroup that has significant pathology in the form of either obstruction or severe bilateral renal damage.[22,23]

3.1.5 Further studies on the relationship between VUR, UTIs and renal damage

In the last 15 years there has been a plethora of publications exploring further the association of VUR and renal scarring as well as the role of VUR in predisposing to infections.[25–28] Although there is no doubt that in some children the combination of VUR with acute pyelonephritis/upper urinary tract infection can be dangerous for the kidney, these associations are not always that simple. For example, renal scarring can be found in the absence of VUR.[29,30] It has become clear that not all small kidneys are small as a result of acquired scarring through a UTI in the presence of VUR. Some poorly functioning kidneys, recognised following renal tract imaging after a UTI, are congenital dysplastic kidneys occurring in association with VUR.[31] These two causes of small kidneys are indistinguishable on routine imaging tests and can both be associated with VUR and UTI.

Another useful study in this context is the International Reflux Study, where children with VUR were randomly allocated to receive either prophylaxic antibiotics or have surgical reimplantation of their refluxing ureters.[32] Both groups had the same rate of UTIs on follow-up. Curing the VUR did not confer an advantage on these children in terms of the number of UTIs. Although the reimplantation group had fewer febrile UTIs, the degree of renal scarring was the same in both groups.

Some clinicians have questioned the effectiveness of long-term low-dose prophylaxis in the prevention of recurrent symptomatic UTIs or progressive renal scarring. Invasive tests such as the MCUG would be difficult to justify in the absence of an effective prevention strategy.[22–24,31]

3.1.6 Back to first steps: dealing with underdiagnosis of UTIs

Although included in the 1991 RCP guideline, relatively little emphasis has been placed on improving the diagnosis of UTI in infancy and early childhood in primary care, where most cases present and urine collection is particularly difficult. Although this was clearly stated, there was no mechanism for getting this information to GPs and there has been little evidence that the diagnosis of UTI in primary care in the UK has improved in pre-toilet-trained infants and childrens.[33–36]

Better detection rates of UTI have been thought to be associated with a significant drop in the number of patients reaching end-stage renal failure as a consequence of acquired renal scarring.[37–39] A study in the North of England showed that when a model of appropriate education is combined with prompt diagnosis and access to a nurse-led UTI service, the pick-up rate of children appropriately diagnosed with UTI was four times that of the control group.[36]

To prevent acquired renal scarring[40] it may be equally effective if not more effective to concentrate resources on the early recognition of UTI and its prompt treatment in all infants and children with symptoms rather than on imaging carried out after recovery from treatment of UTI.

3.1.7 This guideline

The research quality of studies on children who have had UTI is variable. In 2000 the NHS R&D HTA programme commissioned a review of the tests used for diagnosing and imaging UTI in childhood. This has provided a valuable source of evidence-based information for this guideline. The analysis was largely confined to an assessment of the performance of one test compared with another and there is no high-quality evidence to show whether or not any of these tests made any difference to the outcome for the patient.

The data on the epidemiology of UTI and its complications such as renal scarring and the risk of hypertension and renal failure is by no means complete. The GDG analysed the data available to ascertain the risk of renal failure after a UTI.

The recommendations in this guideline are based on the limited evidence available that has been examined against the inclusion/exclusion criteria described in the methodology section (Section 1.7). Where the area being addressed by the guideline has not been the subject of studies of sufficient research strength, the GDG has made recommendations based on clinical observation studies assessed as having the least risk of bias. The 'Translation' sections give the rationale for the final recommendations at the end of each chapter.

This guideline gives advice on the diagnosis and management of UTI in children. Children already known to have underlying renal abnormalities because of antenatal screening or known to have obstruction, hydronephrosis or neuropathic bladder are outside the remit of this guideline. It aims to provide information to enable diagnosis and treatment of UTI in infants and children of all ages and makes recommendations on the clinical indications for additional interventions such as renal imaging. It makes recommendations on what these investigations should be, based on an assessment of risk factors, such as the clinical features at the time of the acute episode of UTI. It also aims to provide sufficient advice to enable the very small number of children with progressive chronic kidney disease (CKD) to be identified and offered support in accordance with the aims of the National Service Framework (NSF) for renal services.[2]

This guideline has examined aspects of current practice against the ability to achieve these aims by considering the evidence for benefits of each intervention alongside the associated risks and disadvantages.

3.2 Defining UTI

Clinical question
What is the definition of UTI in infants and children?

Urinary tract infection
A urinary tract infection is defined in this guideline by a combination of clinical features and the presence of bacteria in the urine.

3.2.1 Severity of illness

Acute pyelonephritis/upper urinary tract infection
This is the term used to describe inflammation of the kidneys due to UTI. Macroscopically, the kidney shows segments of inflamed and swollen tissue. Histology shows infiltration by polymorphs and bacteria in the parenchyma and tubules as well as oedema and sometimes architectural disruption. Acute pyelonephritis/upper urinary tract infection is most common in infants and the principal presenting symptom is fever. Other common symptoms are irritability and vomiting. In older children, the classic symptoms of fever and loin pain may be present but non-specific illness with fever may occur in children of any age. For the purpose of this guideline, acute pyelonephritis/upper urinary tract infection has been defined as UTI with a fever of 38 °C or higher. (See Chapter 4, Diagnosis.)

Cystitis/lower urinary tract infection
This term describes a urine infection confined to the lower urinary tract giving rise to inflammation of the bladder. On microscopy the urothelial lining of the bladder wall is inflamed and shows signs of oedema, the presence of inflammatory cells and bacteria adhering to or entering cells, some of which are shed into the urine. Cystitis/lower urinary tract infection gives rise to a collection of well-recognised symptoms including dysuria, frequency, and suprapubic pain in toilet-trained children. (See Chapter 4, Diagnosis.)

3.2.2 Illness risk level

In clinical practice, assessing the level of illness is an important first step when managing a sick infant or child. Three levels of illness risk have been identified in febrile children. These are described in detail in the 'Feverish illness in children' NICE clinical guideline.

Excluding children with life-threatening conditions who require emergency transfer to hospital by phoning 999, the highest risk level represents children (red group) who require immediate transfer to hospital. If UTI is the cause of the illness then it would be acute pyelonephritis/upper urinary tract infection and possibly septicaemia.

The intermediate level of risk (amber group) represents children with some systemic features of ill health and includes children with acute pyelonephritis/upper urinary tract infection.

The lowest risk level represents children without risk of serious illness (green group) and is broadly comparable to cystitis/lower urinary tract infection. A child with this level of illness is unlikely to have acute pyelonephritis/upper urinary tract infection although there may be a small number of cases with fever greater than 38 °C who should be regarded as having acute pyelonephritis/upper urinary tract infection. (See NICE clinical guideline 'Feverish illness in children'.)

Table 3.1 indicates the relationship between the terms used in defining types of UTI and the illness severity.

Table 3.1 Level of UTI and relationship with bacterial count and pathological terms

Classification	Bladder involvement	Renal involvement	Spread to other systems
Level of UTI	Likely to be confined to the lower urinary tract	Likely to involve the kidneys	Likely to involve the kidneys and possibly spread to the blood stream
Pathological term	Bladder involvement is called cystitis/lower urinary tract infection	Kidney involvement is referred to as acute pyelonephritis/upper urinary tract infection	Septicaemia
Bacteriology	96% > 10^5 cfu/ml[a]	96% > 10^5 cfu/ml[a]	Blood culture positive

[a] These numbers are from a study conducted in a adult population with acute pyelonephritis/upper urinary tract infection and catheter samples.[41]

3.2.3 Bacterial count

For the purpose of laboratory diagnosis, microbiologists use the colony count. This represents the concentration of organisms in the urine as a measure of the likelihood that bacteria in a urine sample represent a true infection. Typically, a urine infection is caused by a single organism which is present in a high concentration, usually > 100 000 colony-forming units (cfu) per ml.[41]

When contaminating organisms have entered the sample after the urine has left the bladder, there is usually either a smaller concentration of bacteria or a mixed growth of organisms. However, it is possible to have an infection which gives rise to a lower colony count or to a mixed growth and it is possible to have contamination with a pure growth of a single organism.

Although the colony count is the best tool currently available for establishing the diagnosis, and has been regarded as the gold standard, for a number of reasons this measurement may not provide an accurate diagnosis in every case. It was not formally validated in children. Occasionally, it is necessary to repeat a sample or to treat on the basis of clinical suspicion rather than to rely solely on the laboratory tests.

The colony count has often been used to define UTI in research studies and publications. Although this has an important place in confirming the diagnosis of UTI as defined by bacteria present in the urine, it does not provide any information on severity of illness or renal involvement.

This guideline is concerned with aiding the clinical process and, although the value of the colony count is recognised, it has clinical limitations which need to be understood when considering the care of the individual. It is valuable for confirming the diagnosis in the majority of cases but cannot be considered to be the only criterion for diagnosing a UTI.

Asymptomatic bacteriuria
Asymptomatic bacteriuria (also known as occult or covert or screening bacteriuria) is defined as the presence of bacteria in the urine without symptoms.

3.3 Epidemiology

3.3.1 Introduction

This section aims to provide basic epidemiological data on incidence and prevalence of UTI and associated renal anomalies relevant to management of UTI discussed in this guideline.

Clinical question
What is the epidemiology of UTI in the UK?

3.3.2 Population statistics

Researchers have calculated rates of UTI according to annual incidence, cumulative incidence, prevalence, and incidence in cohorts or selected groups. Some authors also quote related rates, for example referral rates and diagnostic rates.

Annual incidence rates of childhood UTI can provide information on the frequency of disease, and workload.

The cumulative incidence of childhood UTI is a useful measure of risk, as clinical complications, for example renal failure, may happen many years after the initial event. These rates are usually estimates obtained by combining annual incidence rates for various age ranges of children.

Prevalence data is the measure of choice for chronic disease, but is not suitable for an acute illness such as UTI. Prevalence data reported in this section relate to the presence of asymptomatic bacteriuria or underlying abnormalities.

Incidence data is often presented for specific cohorts of children or groups of children sharing a common characteristic, for example all admissions, all febrile UTIs, or attending a clinic. Subsequent analysis can be subject to unpredictable bias.

When all children with first-time UTI are referred from primary care (as in the UK), referral rates can be used as a proxy for incidence and cumulative incidence rates, if case finding is comprehensive and reliable.

Diagnostic rates are another measure, which can approximate to incidence. They can use clinical, laboratory or near-patient testing. Some studies have used these rates to give a range of incidence.

3.3.3 Incidence

An early study in Sweden suggested that 3% of girls and 1.1% of boys had had UTIs by the age of 11 years.[42] Later studies, however, indicate that the population incidence of symptomatic UTI in developed countries is likely to be higher than previously recognised.

Figures from Sweden show that UTI occurs in a minimum of 2.1% of girls and 2.2% of boys before the age of 2 years. These figures are based on the confirmation of a UTI by a positive culture ($> 10^5$ cfu/ml) and a positive nitrite test. Up to a further 0.5% might have had a UTI; their rates of complications matched those with firmer diagnoses rather than population norms, suggesting that, generally, they had valid diagnoses. The rates of diagnosis were subject to geographical variation. The highest rates occurred in the region surrounding the major specialist centre, which suggests an influence from education and vigilance.[37]

In an area of the UK, where similar enthusiasm for diagnosis occurs, a population-based study (data collected for 4 years) suggested that 11.3% of girls and 3.6% of boys will have had a UTI by the age of 16 years. The referral rate formed the basis for these figures, although 15% had no microbiological confirmation of the diagnosis.[43]

A study conducted in Sweden reported the cumulative incidence of UTI in children up to the age of 7 years using a questionnaire about urinary symptoms at a school entrance health examination. Previous UTIs were reported in 274 children but, after checking original records UTIs were confirmed in 145/1719 (8.4%) of girls and 32/1834 (1.7%) of boys.[44]

A small study from English general practice published in 1979 (14 UTIs over 2 years in 2789 children), using strict diagnostic criteria, found the annual incidence of first-time UTI to be 0.31% for girls and 0.17% for boys. This suggests a cumulative incidence of 5% for girls and 2.7% for boys during childhood, although this small population study is unlikely to be representative. Only 9% of children whose differential diagnosis included UTI had positive samples.[45] Six of 14 children diagnosed with UTI during the study period had a history suggesting previous UTI.

A study from Sweden of children younger than 10 years reported that 59% of boys have their first UTI detected under the age of 1 year, but only 19% of girls.[47]

A study of UK and Finnish hospital discharge data reported a doubling of rates in boys and girls under and over 4 years between 1987 and 1993 in the UK. In Finland, rates in girls reduced between 1979 and 1994 but remained the same for boys. These results suggest that vigilance and medical management influence incidence rates.[48]

A study in the UK looked at the effect of a nurse-led education programme on the rate of diagnosis of childhood UTI. This showed a doubling of the rate overall, a four-fold increase in the rate of diagnosis in infants and and a six-fold increase in the diagnosis in children in whom there were no specific urinary symptoms. This indicates that current practice severely underdiagnoses childhood UTI, particularly in the youngest children.[36]

GP consultation

The Royal College of General Practitioners Birmingham Research Unit produces annual morbidity statistics. The table below is an adaptation of the 2004 data for urinary tract infection and cystitis.[46]

	Girls			Boys		
Age (years)	< 1	1–4	5–14	< 1	1–4	5–14
Incidence[a]	1104	1797	1402	616	351	172
Consultations per episode[b]	1.81	2.16	2.24	3.32	2.40	2.6

[a] Incidence: mean annual incidence (in spotter practices) of a recorded diagnosis of UTI per 100 000 children in each age band. Recorded diagnosis includes first-time and recurrent episodes of UTI; it may be definite or presumptive. It may exclude consultations prior to diagnosis in children, particularly younger children, who present with ill-defined illness, and whose initial disease coding is something other than UTI. Episodes managed entirely in secondary care may also be missed.

[b] Every time a diagnosis of UTI is made, children will have one or more consultations (e.g. initial diagnosis, follow-up).

According to these figures, In a general practice of 10 000 patients, six GPs and 100 births per year, each GP will expect to have:

- two consultations a year with a child younger than 5 years about UTI (girls : boys = 3 : 1)
- one consultation a year with a boy (aged 0–14 years) about UTI
- four consultations a year with a girl (aged 0–14 years) about UTI.

Summary and interpretation of data on incidence of UTI

Calculating a definitive accurate cumulative incidence rate for UTI during childhood is difficult. Studies use a variety of methods and cut-off points, and enthusiasm for diagnosis has a significant effect on reported rates.

We conclude, therefore, that around 1/10 girls and 1/30 boys will have had a UTI by the age of 16 years. Cumulative incidence figures are most accurate for infants: 2.1% of girls and 2.2% of boys will have had a UTI before the age of 2 years.

Boys have a greater incidence of UTI in the neonatal period and early infancy. Depending on the study viewed, girls overtake boys in the incidence of UTI at somewhere between 3 and 6 months of age. About half of boys with UTI will present for the first time before age 1 year, but four out of five girls will present at a later age.

Evidence is limited to one study, but 1/10 children with UTI-like symptoms are found to have positive cultures in primary care.

3.3.4 Incidence of acute pyelonephritis/upper urinary tract infection

Studies of acute pyelonephritis/upper urinary tract infection use various combinations of signs, symptoms and laboratory tests to establish a diagnosis.

In a study conducted in Sweden, 47/1719 (2.7%) of girls and 19/1834 (1%) of boys had an episode of acute pyelonephritis/upper urinary tract infection by the age of 7 years. As a proportion of those with a history of UTI, this equated to 47/145 (32%) of girls and 19/32 (59%) of boys.[44]

The annual incidence of acute pyelonephritis/upper urinary tract infection in a study in South Korea based on insurance claim diagnosis was 0.15% for girls and 0.07% for boys. Only 1/7 were treated in hospital.[49] In Italy a study evaluated data from a children's health referral centre in the Trieste region and found annual rates of 0.13% in girls and 0.02% in boys.[50] In the USA hospital discharge data showed rates of 0.09% in girls and 0.01% in boys.[51] Serious bacteraemic UTI is rare: 1.5/100 000 children/year in a study from Finland. Sixty-six percent of these were younger than 3 months and 88% younger than 1 year. Boys were affected almost twice as much as girls, although male predominance decreased with age.[52]

Summary and interpretation of data on incidence of acute pyelonephritis/upper urinary tract infection

In population-based studies, acute pyelonephritis/upper urinary tract infection is more common in girls.

No studies were found that report annual incidence rates for the UK. Retrospectively obtained figures for Sweden give a cumulative incidence rate of at least one episode of pyelonephritis in 2.7% of girls and 1% of boys by the age of 7 years; this is likely to be a good benchmark. Quoted annual incidence rates from data collection in three countries are of the order of ten episodes/10 000 girls per year and a range of one to seven episodes/10 000 boys per year. In the light of the Swedish figures, these may be underestimates, caused by problems in sampling.

Boys are more likely than girls to have an episode of acute pyelonephritis/upper urinary tract infection if they have a history of UTI (1/2 boys versus 1/3 girls). This is probably caused by differences between boys and girls in the age at presentation rather than as a result of any other underlying predisposition. Girls also experience more recurrences than boys and differences in annual and cumulative incidence rates often reflect recurrences rather than first-time UTIs.

Serious bacteraemic illness from UTI is quite rare. Around 9/10 children presenting in this way will be younger than 1 year, most younger than 3 months, and pyelonephritis itself is not com-

mon. Estimates suggest that approximately 1/150 episodes of acute pyelonephritis/upper urinary tract infection in girls are bacteraemic and 1/10 or possibly more episodes in boys.

3.3.5 Demographic characteristics of UTI

Two studies in children with febrile UTI investigated characteristics associated with presentation. Further details on predisposing factors can be found in Section 4.2.

In two studies from the USA, higher rates of febrile UTI were noted in girls, uncircumcised boys and those with a previous history of UTI. Lower levels were noted in children of African-American descent.[53,54]

One study noted a cyclical pattern in incidence over two consecutive years with June the most common and December the least common month for childhood UTI.[37] A study of acute pyelonephritis/upper urinary tract infection in South Korea also showed a summer peak.[49]

Summary and interpretation of data demographics of UTI
Two studies reporting on seasonal influence suggest that childhood UTI is more common in the summer. Other demographic differences are discussed in more detail in Section 4.2.

3.3.6 Prevalence

Prevalence studies have assessed the presence of bacteriuria (predominantly asymptomatic) in the population, as UTI itself is a transient and acute illness. Cohorts of children found to have asymptomatic bacteriuria (ASB) during screening will be made up of those with no discernible history of UTI, some with a previous history of UTI, and some who have had symptomatic UTIs but have not been diagnosed. Thus they constitute a heterogeneous group that will bear some of the characteristics of cohorts of children with previous infection.

The studies below were population based and had large sample sizes. Each study was unique, but where they overlapped similarities in findings were observed.

A study of schoolchildren aged 4–12 years in England and Wales found that 1.7% of girls have asymptomatic bacteriuria.[55] A further study in England of schoolchildren aged 4–18 years found the rate to be higher in ages 7–11 years than in age ranges either side. The overall prevalence was 1.9% for girls and 0.2% for boys.[56] A study in Scotland came to similar conclusions.[57]

A study in Sweden looked at asymptomatic bacteriuria in infancy. The rates for boys were highest in the first 2 months of life (1.6%), reducing to 0.2% for the cohort aged 8 to 14 months (the same rate as studies of schoolchildren). The rates in girls showed an opposite trend, rising, respectively, from 0.2% to 0.5%.[58]

Summary and interpretation of data on prevalence
Asymptomatic bacteriuria shows the same sex differences as symptomatic UTI. It is difficult to say whether the age-related patterns differ from symptomatic UTI, as no reliable data exist for overall rates of infection (first-time and recurrent).

Asymptomatic bacteriuria is most common in boys in early infancy (1.6% in boys younger than 2 months) and shows a steady drop thereafter. It affects 0.2% (1/500) of school-age boys.

Girls have lower rates than boys until sometime between age 8 and 14 months. Between 1.5% and 2% (up to 1/50) of primary school-aged girls have asymptomatic bacteriuria. The peak prevalence appears to be in the junior school years (ages 7–11 years).

The differences in peaks of prevalence rate do not mirror those for first-time UTI. However, recurrent UTI is common and much more common for girls, reducing only after primary school age (see Section 6.2) If this is taken into account, the rates of asymptomatic bacteriuria may actually be closely related to those of symptomatic UTI.

3.3.7 Rates of recurrence of UTI

Many studies identified were case series of children presenting to secondary care settings with recurrent UTI. One study was of neonates alone. Many also had short follow-up times. An

Australian study reported 46 recurrent UTIs in 34/290 children during 12 months of follow-up; 20 children had one recurrence; 14 had two or more recurrences.[72]

A study from Sweden showed that 32% of girls and 23% of boys younger than 10 years had a recurrence of UTI, although two or more recurrences were much more common in girls (8% versus 1%).[47] A small study in the USA also found that girls were more prone to multiple recurrences.[59]

An older study from Sweden reported a recurrence rate of 26% in neonates of both sexes; boys younger than 1 year had a recurrence rate of 18% and boys over 1 year had a recurrence rate of 32%. In girls older than 28 days, the recurrence rate was 40%.[42]

In one UK case series, 41% of children younger than 1 year had a history of recurrent UTI, rising to 73% aged 5 years and over. In girls, but not boys, the number presenting with recurrent UTI increased with age.[60] A previous study from the same centre suggested that children with renal parenchymal defects developed more recurrences although children with VUR had no increased risk of recurrence.[61]

In another UK study, 78% of girls and 71% of boys presenting before age 1 year had further infections, whereas 45% and 39%, respectively, had further infections if they presented after the age of 1 year.[62,63]

Risk factors for recurrence are discussed in detail in Section 6.2.2.

Summary and interpretation of data on recurrence of UTI

It is difficult to be sure about rates of recurrence in children in the UK. Girls are more prone to recurrence and those with recurrent UTI have more episodes than boys. Children who present early in life with UTI are more prone to recurrences. Three-quarters of children presenting before the age of 1 year will have a recurrence. After the age of 1 year roughly 40% of girls and 30% of boys will have a recurrence. Girls, but not boys, have increasing rates of recurrence with age. These findings appear to mirror the reported age-specific prevalence data on asymptomatic bacteriuria.

3.3.8 Vesicoureteric reflux

The reported incidence of VUR in children diagnosed with UTI ranges from 8% to 40%, although the majority of studies, including those with the largest samples, showed rates between 20% and 38%.

Where rates have been reported separately for boys and girls, they are generally very similar. VUR in girls with UTI ranges from 17% to 34% and in boys from 18% to 45%.

The prevalence of VUR in the general population was calculated around 50 years ago. The calculated population incidence of 1–3% seems reliable.[40]

A population-based study from Sweden (rate of investigation = 97%) showed that under the age of 2 years, 30% of children presenting with UTI had VUR: 36% of girls and 24% of boys. One-third of girls with VUR (13% of girls with UTI) and two-thirds of boys had dilating VUR. In this study, boys presented earlier than girls.[65]

An earlier study in Sweden reported rates of 34% in girls and 33% in boys. Eleven percent of boys and 8% of girls had dilated VUR.[47] This study also found that in girls VUR was most common between the ages of 1 and 3 years.

Unilateral and bilateral VUR

Three studies separately report the numbers of children in their studies with VUR and the numbers of kidneys affected. Thirty-one percent of children and 24% of kidneys had VUR in a study based in a surgical clinic in Scotland,[66] and 29% and 21%, respectively, in a study from Taiwan.[64] Fifty-five percent of children with VUR had bilateral VUR in the first study[66] and, in the second, 46%.[64] In a cohort of girls screened for asymptomatic bacteriuria, 28/82 (34%) had bilateral VUR.[55]

Influence on serious presentations

Higher rates of bacteraemic illnesses are found in children with more severe grades of VUR (III–V): 30% versus 16% of matched non-bacteraemic patients.[52]

Fever was a major symptom in more children with VUR.[67] Children managed surgically had less febrile UTIs than those managed medically.[68]

Spontaneous resolution

VUR appears to be worst in the youngest children and to resolve spontaneously in many, but many studies lack the detail to provide sufficiently accurate data. Children managed medically may also have had milder degrees of VUR than those managed surgically in non-randomised studies.

A large population study from Sweden reported that more severe degrees of VUR occurred in younger children.[65] An Italian study produced a similar progression.[50]

A number of studies following up children in outpatient clinics observed spontaneous resolution of VUR. In one study, 31–84% of cases of VUR resolved and in two studies improvement without full resolution was noted in a further 15–21%. Dysfunctional elimination syndrome (DES) appear to slow down the resolution of VUR.[69]

A randomised trial of surgical and medical treatment of Grade III–IV VUR found that, of those managed medically, 73% had had a reduction to Grade II or lower after 10 years. Absence of VUR was noted in 47%, and was more likely if they had Grade III VUR at study entry.[70]

In an RCT of antibiotic prophylaxis from the USA,[71] spontaneous resolution of VUR occurred in 37.5% (Grade I), 12.5% (Grade II) and 10.3% (Grade III).

Recurrent UTIs

A cohort study from Australia found that VUR was present in 14/34 (41%) with recurrent infection and 65/256 (27%) without recurrent infection. Comparison between groups showed that the presence of VUR was not associated with recurrent infection but with the grade of VUR; bilateral VUR and intrarenal VUR were significantly associated with recurrence. Higher grades of VUR (Grades III–V) were the only independent predictor of recurrence (OR 3.6; 95% CI 1.5 to 8.3; $P < 0.001$).[72]

Inheritance

The inheritance of VUR may be important in preventing UTI in high-risk neonates.

An evidence-based review reported that, from the average of 11 studies analysed, 32% of siblings of affected children also had VUR. Only 2% had VUR greater than Grade III.[73]

In an Australian study of infants of mothers with known VUR nephropathy, VUR was found in 17/40 (43%).[74] This supports the laboratory findings of geneticists who suggest a mode of inheritance of autosomal dominance with variable penetrance and expressivity. Exact chromosomal deficiencies have proved elusive.[75]

Racial differences in a study in the USA also support this concept: 10% of African-Americans investigated had VUR compared with an index rate of 31%.[76]

Summary and interpretation of data on VUR

Around one-third children diagnosed with UTI have VUR. It is bilateral in around half of cases. In comparison, the incidence in the general population is probably around 1–3%.[40]

VUR spontaneously resolves in the majority of children. The evidence on the comparative prevalence of VUR in boys and girls is contradictory: studies show that VUR is equally prevalent in girls and boys presenting with UTI, whereas a recent study of healthy neonates suggests a much higher incidence of VUR in boys. Girls present later than boys with UTI, and should by means of spontaneous resolution and reduced prevalence at birth have a much lower rate of detected VUR, but this is not observed. The reasons for this contradiction are unclear.

One study suggests that severe VUR is more common in infants with bacteraemia than those without bacteraemia. No other studies report on the differential rates of VUR in children presenting with more serious illness.

Severe VUR is likely to contribute to more severe presentations of UTI. VUR is an inherited condition, and the risk of VUR in siblings equates to that in unselected populations of children who have had UTI rather than that of the general population.

3.3.9 Structural renal tract abnormality

The most common abnormality in children who have had UTI is VUR. This is discussed in the section above. Other common abnormalities included hydronephrosis, obstruction and duplex kidneys. Two larger case series from the UK suggested duplex kidneys occur in 6–7% of children who have had UTI, and hydronephrosis in 2.5–7.5% The percentages occurring in normal or other populations of children were not stated.[66,67] In the latter study, 13% of children with no VUR had other radiological abnormalities (and a further 4% had minor urethral irregularities). A similar proportion of those with VUR had abnormalities.

A study in Sweden reported that 70% of children with obstruction of the urinary flow presented with UTI in the first 2 months of life. It is more common in boys: 10.3% versus 2.1% in girls. However, girls had more duplex systems: 12% versus 5%.[77]

Of 905 neonates in an Australian study who were investigated for possible sepsis, 64 were found to have a UTI, of whom 12 (19%) had significant non-VUR urinary tract abnormalities.[78]

In China a study using ultrasound screened 130 000 normal children aged 6 to 15 years, of whom 1/500 had hydronephrosis.[79]

Severity of presentation

Urinary tract obstruction is associated with higher rates of bacteraemic illness (9% bacteraemic versus 1% of a matched group of non-bacteraemic children).[52]

In another study, 14% of children presenting with acute pyelonephritis/upper urinary tract infection had urinary tract abnormalities compared with 3% who had lower UTI or asymptomatic bacteriuria.[80]

Summary and interpretation of data on underlying abnormalities

Excluding VUR, the most common abnormalities found are hydronephrosis, urinary obstruction and duplex kidneys. Studies vary quite substantially in their context and findings.

Children with urinary tract obstruction are more likely to present with severe illness, and most will present in early infancy.

3.3.10 Other associations

Sixty-seven percent of girls with dysfunctional elimination syndromes (DES) develop UTIs and of these 20% have VUR. Conversely, 40% of girls with UTI have DES.[81] In a study of DES and VUR, half had constipation and half had either bladder instability or infrequent voiding. A fourth cause of DES, Hinman syndrome, was excluded from the study. DES was associated with an increase in time to resolution of VUR.

Summary and interpretation of data on other associations

Dysfunctional elimination syndromes appear to be a risk factor for UTI, and may contribute to slower resolution of VUR. VUR, however, may be a less frequent finding than in other children who have had UTI. The significance of these findings has not been established. Constipation is the most common cause, but infrequent voiding (< 4 times a day) contributes most to breakthrough infections.

3.3.11 Renal scarring

Rate of renal parenchymal defects

One population-based study in the UK reported that 4.7% of girls and 4.3% of boys presenting with their first UTI had renal parenchymal defects on DMSA. Logistic regression showed no independent association of renal parenchymal defects with age or sex. The rate of renal parenchymal defects remained constant throughout the 4 years of the study, and the cumulative rate of UTI was 11.3% and 3.6%, respectively.[43] From this study 0.53% of all girls in a population will develop renal parenchymal defects, and 0.16% of boys.

A population-based study in Sweden found the annual incidence of renal parenchymal defects in girls and boys with UTI to be 9.3/100 000 with a ratio of 2:1.From this study 0.18% of girls and 0.11% boys in a population would be expected to have renal parenchymal defects.[82]

An early Swedish study suggested that 4.5% of girls and 13% of boys have renal parenchymal defects.[42] The cumulative incidences of UTI in this study were 3% and 1.1%, respectively, giving a population rate of renal parenchymal defects of 0.14% for both sexes.

A systematic review[83] drew on four prospective studies: 5–15% of children in these studies had evidence of renal parenchymal defects.

Another study, which appeared to be population based, gave rates of renal parenchymal defects of 6.4%.[84]

Two studies considered whether renal parenchymal defects pre-dated the first suspected UTI: one suggested that 32–77% pre-dated the first UTI,[80] and the other found that 86% of boys had primary (rather than acquired from UTI) renal parenchymal defects, and only 30% of girls.[85] A summary statement on four studies reported that up to 30% of children with VUR had evidence of renal damage *in utero*.[86] Fourteen percent of neonates were judged to have congenital renal dysplasia in one study.[87]

Risk factors

By inference, acute pyelonephritis/upper urinary tract infection is a cause of a renal parenchymal defect. Two studies attempted to confirm this: one found a history of acute pyelonephritis/upper urinary tract infection in all children with renal parenchymal defects,[80] another was unable to find such a history in 8.8%.[47]

In another study, between one-half and three-quarters of infants and one-third of children 4 years or older were febrile, had vomiting, anorexia, or malaise and required hospital admission. None of these indicators nor a history suggesting previous UTIs were of value for predicting renal scarring.[43]

An international study of children with febrile UTI assessed a number of possible risk factors by comparing acute and late DMSA scans.[88] They found late positive scans for renal parenchymal defects in:

- 73% of those with recurrent UTI versus 56% with first-time UTI
- 72% with VUR (61% if mild, 77% if severe) versus 52% without VUR
- 86% where the infective organism was non-*E. coli* versus 57% *E. coli*.

In the presence of VUR, renal parenchymal defects were more frequent in boys and children 1 year or older. In the absence of VUR, the only significant factor was recurrent UTI.

Recurrent UTI was a significant factor for girls but not boys.[88] However, as recurrence is rare in boys, this may have influenced the results.

A large case series in the UK reported that VUR was associated with renal parenchymal defects in only 19% of cases, unless complicated by recurrent UTI, where the rate rose to 46%.[67]

Renal scarring and VUR

A study in Scotland suggested that VUR was the single most important factor in identifying girls under 1 year of age at risk of developing progressive renal damage.[62,63]

A systematic review, however, reported that VUR was only a weak indicator (twice as likely) of the risk of renal parenchymal defects in patients admitted to hospital.[89] A further study in infants under 1 year with a lower incidence of renal parenchymal defects came to similar conclusions. It showed the presence of VUR to increase the chances of renal parenchymal defects from 4% to 16%.[90] Another study compared acute and late DMSA scans: those with severe significant renal parenchymal defects lesions on the acute scan had an 88% chance of renal parenchymal defects on a late scan. Others with less severe lesions on the acute scan still had a 14–38% chance of renal parenchymal defects on a late scan. Those with normal acute scans had a 0% chance of late renal parenchymal defects.[91]

Renal parenchymal defects and grade of VUR

Most studies indicate an association between renal parenchymal defects and grade of VUR. Most studies reporting on this used the old three-level grading: 5–29% of children with mild VUR had renal parenchymal defects; 28–50% of those with moderate VUR; and 42–100% of those with severe VUR.[47,55,92–94]

Renal scarring and other urinary tract abnormalities

Children with duplex systems account for one-third of those with renal parenchymal defects, and just under one-third of children with duplex have renal parenchymal defects.[93]

Obstructive anomalies accounted for 0–4% of renal parenchymal defects.[83]

Effect of delay in treatment on degree of renal scarring

One study using a case–control design found differences in severity of renal parenchymal defects between children with VUR and delays in treatment: OR 14.1 (95% CI 1.6 to 120.9) for any significant delay versus no significant delay and OR 2.8 (95% CI 0.8 to 9.2) for delay > 6 months versus lesser delays.

Do children without VUR get renal scars?

A case series study in Sweden (children younger than 10 years with a definite history of UTI) reported renal parenchymal defects in 5% of those without demonstrable VUR.[47,62,63]

Recurrent UTI

A cohort study from Australia found that recurrent UTI and recurrent febrile UTI were significantly associated with DMSA abnormalities at 1 year follow-up.[72]

In one case series, 55% of children 5 years or older with a history of recurrent UTI had abnormal scans compared with 15% without such a history.[60] A further case series found that of children who had experienced one episode of acute pyelonephritis/upper urinary tract infection, 9% had renal parenchymal defects. In children with a history of more than four episodes, 58% had renal parenchymal defects.[47]

Renal scarring and inheritance

Siblings of children with VUR have higher rates of VUR, and more so if they are twins. VUR is present in one-third of siblings, and one in ten of those have accompanying renal parenchymal defects. Only half have a known history of UTI.[73]

Progressive renal scarring

One study in the UK followed up a group of children diagnosed when aged 3 and 4 years for 2–11 years. Of the children aged 3 years at presentation, 1.4% had formed new renal parenchymal defects. No children aged 4 years developed new renal parenchymal defects.[95]

A randomised trial of medical or surgical management followed up children with Grades III or IV VUR for 10 years. Fourteen percent of children developed new renal parenchymal defects in the first 5 years, but only 1% in years 5–10. Progressive renal parenchymal defects occurred mostly in children younger than 5 years and in those with Grade IV VUR.[96]

A study from Sweden reported that 36% of children being followed up intensively had renal parenchymal defects at initial urography. At the final urography after puberty or later, 48% had renal parenchymal defects. The median age of detection was 9.9 years. Over half of those with renal parenchymal defects at final urography had suffered new renal parenchymal defects or deterioration.[97]

Another study found that 91% of children developing new or progressive renal parenchymal defects had VUR, especially more severe VUR.[98]

Summary and interpretation of data on risk factors for renal scarring

Around 5% of children presenting with first-time UTI will have renal parenchymal defects on imaging. The rate is likely to be similar for boys and girls. The prevalence of reflux nephropathy in the community is greater in girls than boys as UTI is more common in girls. Rates calculated from three studies show that 1/200 to 1/750 girls in a community will develop reflux nephropathy in childhood, and 1/600 to 1/900 boys. The disparity in rates may reflect differences in imaging techniques and interpretation.

Boys may be much more susceptible to developing dysplasia or renal parenchymal defects *in utero*, whereas girls tend to acquire their renal parenchymal defects at a later age, and have a higher correlation with UTI episodes. Almost always, a history of acute pyelonephritis/upper

urinary tract infection was recorded prior to the discovery of renal scarring, although not every child who has episodes of acute pyelonephritis/upper urinary tract infection develops this complication. The effect of renal scarring *in utero* is poorly quantified.

Renal scarring is much more common in children with VUR, and almost universal in the most severe grades.

The association of VUR and febrile UTI suggests that VUR is both a cause of acute pyelonephritis/upper urinary tract infection and a compounder of its effects. Other risk factors are recurrent UTI and non-*E. coli* infection.

The situation on new and progressive renal scarring is not clear. In general, as children get older their risk of developing new renal scars reduces. Children with severe VUR remain at risk.

3.3.12 Long-term complications

Hypertension

The incidence of hypertension in the general paediatric population is less than 2%. Eight of the nine studies included in a 1990 critical review reported rates of 0–13% in children with a diagnosis of VUR and followed up for 18 months to 19 years. One small study of infants with gross VUR and followed up for a prolonged period of time (12–30 years) had much higher rates of hypertension of 38%.[99]

A systematic review collated the prevalence of hypertension following the development of reflux nephropathy. Of the under-20s, 5.6–27.9% had hypertension, and 5.6–24.7% of the over-20s. Three of the four studies reported no difference in risk between those with and those without renal parenchymal defects.[100] A small but good-quality retrospective cohort study showed no difference in mean 24 hour blood pressure in patients followed up for 16–26 years after a first UTI. Subgroup analysis for markers of severity did not alter the results.[101]

A second retrospective cohort study suggested that only those with severe renal parenchymal defects had an increased risk of hypertension over and above normal background risk.[102]

Another study found that the only predictor of hypertension was a positive family history.[103]

Two further cohort studies showed the relationship of hypertension to renal scarring. The first showed that hypertension only occurred in children with renal scarring or other renal problems.[67] The second in children who have had UTI and VUR found that hypertension in children and adults was found almost exclusively in those who had renal scarring.[104] There was one death in the latter group, from the consequences of uncontrolled hypertension.

A longitudinal study with matched controls showed that hypertension was associated with severe renal scarring.[105]

In another longitudinal study in Japan, the development of diastolic hypertension and albuminuria appeared to preface the development of established renal failure (ERF).[106] In contrast, another study suggested that albuminuria did not predict the degree of renal parenchymal defects.[102]

Other studies suggest that the risk of hypertension is large in the general population, and there is no significant increased risk with a history of UTI.

A USA study based in a regional centre (managing advanced renal disease) found that only 4% of children being treated for hypertension had a diagnosis of reflux nephropathy. None had severe VUR. Children younger than 15 years had predominantly renal hypertension, but older adolescents were more likely to have essential hypertension.[107]

Prevalence of hypertension in the general population

The World Health Organization (WHO) estimates that around 20% of the world's population have hypertension.[108] Age-standardised prevalence figures from the Royal College of General Practitioners (RCGP) annual returns suggest that around 7% of the population (2001–2005) have received a diagnosis of hypertension.[108]

Recent figures obtained from the Quality Outcomes Framework in English General Practice suggest that 11.3 % of registered patients have hypertension.[109]

Summary and interpretation of data on development of hypertension

Hypertension may be associated with UTI in childhood but the risk is likely to be small and associated only with more severe or bilateral renal scarring. In late adolescence and adulthood, the predominant cause in those with a history of childhood UTI appears to be essential hypertension. Most long-term studies are dominated by the presence of essential hypertension, even in at-risk groups. The prevalence of hypertension in adult populations is around 20%, about half of which may be undiagnosed. In adults with a history of childhood UTI, between 5.6% and 24.7% have diagnosed hypertension, but they are likely to be screened and monitored more closely than the general population. The development of renal hypertension may indicate a poor prognosis, although the evidence is limited.

Pregnancy

Two retrospective cohort studies, one in the UK and one in Sweden, have evaluated pregnancy complications. The Swedish study noted that bacteriuria was significantly increased in women with a history of childhood UTI. Hypertension was increased in pregnant women with severe renal scarring, but renal scarring conferred no extra risk if mild or moderate.[110] The UK study used a cohort of women screened for asymptomatic bacteriuria and subdivided them into groups with complications. Bacteriuria in pregnancy was more common than in controls. Hypertension and pre-eclampsia were both more common in women who had been found to have VUR and renal parenchymal defects (RR 1.3; 95% CI 0.9 to 2.0) compared with controls (RR 3.5; 95% CI 0.7 to 16.6).[102]

In a longitudinal study in Australia of women with reflux nephropathy, pre-eclampsia was increased in women with pre-existing hypertension (42%) compared with normotensive women (14%).[74] Women with mild or moderate renal impairment were at increased risk of renal function deterioration.

Summary and interpretation of data on pregnancy

Few women with a history of childhood UTI have been studied during pregnancy and recruiting sufficiently large samples of high-risk women is fraught with difficulty.

The limited evidence suggests that bacteriuria is more likely; renal scarring, especially more severe or bilateral renal scarring, may be associated with an increase in hypertension and pre-eclampsia during pregnancy. The GDG has not assessed outcomes such as caesarean section that are likely to be affected by confounding and biases.

Renal insufficiency and failure

The risk of ERF from pyelonephritic scarring/reflux nephropathy is published by several renal registries. England and Wales have a rate of 7.3% for 2003; Australia and Sweden both have rates of 4%. Some European countries give figures of over 15%, whereas the USA suggests 0.5%. These discrepancies are likely to reflect different diagnostic practices more than differences in epidemiology. The Australia and New Zealand register includes the diagnostic category of renal dysplasia separately, suggesting that a figure of 4% or slightly less may be a reasonable marker for ERF due to reflux nephropathy.

In one study, all 20 patients with renal scarring but no surgical intervention or ERF who were followed for 27 years had significantly lower glomerular filtration rate (GFR) and higher diastolic blood pressure and other markers of kidney function than 13 healthy age-matched controls. There was no correlation between recurrent UTI and renal damage, but children with extensive renal damage had the highest rate of ERF by age 30–40 years.[111]

The mean GFR in girls having their first episode of proven acute pyelonephritis/upper urinary tract infection before the age of 3 years was lower than controls. Girls with a later onset of acute pyelonephritis were no different than controls.[112]

GFR was well preserved in the patients who had not had bilateral renal scarring followed up for 16–26 years.[101]

In Italy, a register of children with chronic renal failure exists as well as one for ERF. Boys have more severe VUR in association with chronic renal failure (CRF), and it is usually bilateral. VUR is the principal cause of CRF in children even though it is not the most common cause of ERF.[113]

Another study suggests that boys and girls have equal rates of ERF caused by UTI.[114]

No child was registered in Sweden as having ERF as a result of pyelonephritic scarring/reflux nephropathy between 1986 and 1994.[38] However, in Australia and New Zealand, countries with high vigilance and equally low rates of ERF attributable to UTI, no improvement in rates had occurred between 1971 and 1998 after changes in diagnostic practice were accounted for.[86]

A study in the USA found that only 5% of children managed in a regional centre for advanced disease had a diagnosis of reflux nephropathy, although 9% with ERF had this diagnosis. All of these had VUR Grade III or worse and bilateral disease.[107]

Congenital renal dysplasia is suggested as a major cause of ERF and a study of kidneys removed operatively in children showed dysplasia in 63% of boys and no girls. Four times more boys had surgery than girls and at younger ages.[20]

Summary and interpretation of data on renal failure

It is difficult to be precise about the real lifetime risk of established renal failure (ERF) as a result of childhood UTI (see Section 6.4). There are concerns about the validity of diagnoses on the register: in developed countries the proportion of ERF attributed to acute pyelonephritis/upper urinary tract infection range from 0.5% to > 15%. There is also debate about whether active management has altered the incidence of ERF.[86] On the other hand, childhood UTI appears to be definitely associated with a small increased risk of ERF during childhood or early adulthood, so it seems logical that adult disease will also relate to childhood UTI. Chronic renal failure (CRF)/insufficiency without ERF, however, may be a much more common outcome.

Some studies suggest that congenital renal dysplasia, especially in boys, causes significant renal morbidity.

The conclusions on ERF rely on the findings of small studies but, since this outcome is otherwise very rare at a young age, it is likely that they are true reflections of the disease process in a small minority of children.

Compensatory growth of healthy kidneys

A study from Sweden identified a group of children who had unilateral renal parenchymal defects. Although the kidneys with renal parenchymal defects were smaller after 5–10 years, there was evidence of compensatory growth in the healthy kidneys, and it was estimated that after 15 years the mean renal area would be 98% of normal.[84]

Glomerular filtration rate was found to correlate with renal area in another study[102] but no significant differences were found between women with renal scarring from childhood UTI and those without.

Overall summary and interpretation of risk of long-term complications after UTI

There are no appropriate studies that accurately estimate the risks of long-term complications as a result of childhood UTI. There are problems in linking eventual outcomes to a disease process occurring many years before because progression of disease is slow and serious outcomes are infrequent or rare. The proportion of children that suffer from congenital renal dysplasia associated with VUR is difficult to determine, although it may be that many boys who progress to ERF have this problem.

Clinically significant adverse outcomes probably only occur in a few cases, predominantly in those with severe bilateral renal scarring. When investigating long-term complications, smaller studies do not produce statistically significant results, and any impact of renal disease in large population-based studies can be masked by common diseases, for example essential hypertension.

Research recommendation

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.

4 Diagnosis

4.1 Introduction

4.1.1 Aim

The aim of this section is to describe when and how to consider the diagnosis of UTI in infants and children and how to confirm the diagnosis. This requires awareness of the presenting symptoms, knowledge of how to carry out an appropriate and relevant history and examination, how to collect urine, how to test and interpret the results of urine testing and how to differentiate acute pyelonephritis/upper urinary tract infection from cystitis/lower urinary tract infection.

Establishing an accurate diagnosis is important to aid prompt antibiotic treatment, direct appropriate investigations and reduce both short- and long-term morbidity and mortality associated with the condition.

4.1.2 Background

Most children with a first-time UTI in the UK present to primary care or to an emergency department. The clinical presentation may be influenced by several factors including the age of the child, the anatomical location of the infection in the urinary tract, the extent of verbal skills in the child and the stage in their toilet-training. In infants and children the presentation is more likely to be with fever with or without other systemic symptoms but rarely with urinary symptoms. In older children the majority have typical urinary tract symptoms suggestive of acute pyelonephritis/upper urinary tract infection or cystitis/lower urinary tract infection. Presentation could include a septic neonate, a child with fever, vomiting and loin tenderness or a teenager with suprapubic pain, dysuria and frequency.

In addition to establishing a diagnosis of UTI it is necessary to identify whether the child is likely to have upper or lower urinary tract infection, or in pathological terms whether the child has acute pyelonephritis or cystitis. In practice the distinction between upper and lower urinary tract infection has to be made on clinical grounds in a child with evidence of UTI based on the presence or absence of symptoms, signs of systemic illness, and, in particular, fever.

The diagnosis can be confirmed by collecting a clean urine sample which should be tested appropriately.

The cost implications range from those associated with the use of various diagnostic modalities to direct future care and treatment, and the morbidities arising from the condition and its management.

4.1.3 Current practice

A guideline by the Royal College of Physicians (RCP) states that all infants and children with a non-specific fever should have a urine sample examined so that they can have appropriate treatment and follow-up.[21]

A national audit of the guideline reported that 746 children younger than 2 years with a fever in 31 hospitals were included. The report showed that 81% had a dipstick screening test but it was not clear what dipsticks had been used or what elements had been tested. Fifty-eight percent of hospitals used nitrite dipsticks.[23] Only 22% of urine dipstick results were clearly documented in the notes. Seventy-one percent had a documented urine sample sent to a laboratory for culture and/or microscopy. One hospital used direct microscopy of fresh urine at the bedside. A positive urine sample was obtained in 9.7% of cases sent to the laboratory. A second specimen was collected in almost half these children diagnosed with UTI. UTI was diagnosed and treatment and

follow-up arranged in 4.7% of children who had urine microscopy and culture. In addition a further 5% of these febrile infants and children had a positive urine on culture but were not given a diagnosis of UTI, did not receive any treatment, prophylaxis, imaging or follow-up, and there was no communication to the GP or patient about the positive urine culture. This means that half of the infants and children seen in secondary care with probable UTI did not receive the correct diagnosis or recommended treatment.

4.2 Predisposing factors

Clinical question
In infants and children, what are the predisposing factors for a UTI?

Review findings – host susceptibility factors (age, gender, race, underlying concomitant disease)
Eight studies were identified investigating host susceptibility factors in children.[47,116–122] All studies reported age and gender differences, but only one study reported race.[117] One study investigated phimosis.[122]

A case series study from the USA investigated 100 children aged 5 days to 8 months (mean age 2.1 months) who were hospitalised for first known UTI.[116] Male infants accounted for 75% of UTI cases within the first 3 months of life compared with 11% of infants who were 3 to 8 months of age. Of the 41 infants who were under 30 days old, 33 (81%) were boys. [EL = 3]

A cross-sectional US study investigated distribution of asymptomatic bacteriuria in 3057 school-aged children.[117] No boys were found to have bacteriuria and 12/1267 girls aged 6–15 years had first-time UTI (8/772 (1.0%) girls aged 6–10 years; 4/495 girls (0.8%) for 11–15 years age group). One school with black children only participated in the study. Again, no boys were found to have bacteriuria and 0.9% of 115 girls had UTI. [EL = 3]

A case series study from Turkey retrospectively investigated 71 neonates aged 18.1 days (± 11.2 days) in whom UTI was diagnosed during the first 4 weeks of life.[118] There were 54/71 (76.1%) boys and 17/71 (23.9%) girls with UTI, of which 40.8% (29/71) were preterm (gestational age range between 27 and 37 weeks). [EL = 3]

A case series study conducted in Sweden investigated 1177 children aged 10 years or younger with their first symptomatic UTI.[47] In boys 133/225 (59%) cases were detected before the age of 1 year and in girls 181/952 (19%) of UTIs were detected before the age of 1 year. [EL = 3]

A cross-sectional study conducted in the USA identified clinical and demographic factors associated with UTI in febrile infants who presented to an emergency department and were ≤ 60 days old.[119] Being uncircumcised (OR 11.6; 95% CI 5.0 to 26.6) and having a temperature > 39 °C (OR 2.5; 95% CI 1.6 to 4.0) was associated with an increased risk of UTI. In multivariable analysis, being uncircumcised ($P < 0.001$) and height of fever ($P < 0.001$) remained associated with UTI (see Table 4.1). [EL = 3]

A study conducted in Sao Paulo analysed the contribution of risk factors to the occurrence of UTI in 61 full-term neonates (26 boys, 35 girls) presenting with a positive bag culture and fever (> 37.8 ºC), weight loss (> 10% of birthweight) or non-specific symptoms (feeding intolerance, failure to thrive, hypoactivity, irritability).[120] On presentation, another urine sample was collected by suprapubic aspiration (SPA) to confirm diagnosis and 42 infants were found to be culture

Table 4.1 Associations between various risk factors and UTI

Risk factor	Factor present	Factor absent	Adjusted OR (95% CI)
Uncircumcised (versus circumcised male)	62/291	6/262	11.6 (5.0 to 26.6)
Maximum temperature > 39 °C (versus < 39 °C)	34/209	57/796	2.5 (1.6 to 4.0)
Female (versus circumcised male)	22/439	6/262	2.2 (0.9 to 5.5)
Age < 28 days (versus > 28 days)	37/334	54/671	1.4 (0.9 t 2.2)
Ill appearing (YOS > 10)	4/71	87/924	0.6 (0.2 to 1.6)

YOS = Yale Observation Scale.

negative (group I) and a diagnosis of UTI was confirmed in 19 (group II). There were no significant differences between groups for birthweight, sex, asphyxia or membrane rupture time. On presentation there were no differences between the groups for fever ($P = 0.31$), but there were significant differences for weight loss (> 10% of birthweight) ($P = 0.01$) and non-specific symptoms ($P < 0.001$).

Children who had UTI confirmed by SPA were significantly more likely to have associated infectious diseases (RR 3.27; 95% CI 1.15 to 7.04; $P < 0.001$), be using broad-spectrum antibiotics (RR 3.03; 95% CI 1.51 to 6.08; $P = 0.01$), have renal and urinary tract malformations (RR 2.97; 95% CI 1.57 to 5.64; $P = 0.007$), be on mechanical ventilation (RR 2.99; 95% CI 1.61 to 5.53; $P = 0.03$), be on parenteral nutrition (RR 5.05; 95% CI 2.72 to 9.39; $P < 0.001$) and to have an intravascular catheter (RR 3.27; 95% CI 1.84 to 5.83; $P = 0.009$). [EL = 3]

A case series study conducted in the Philippines evaluated whether unexplained and/or excessive jaundice was associated with UTI in 54 jaundiced infants (22 boys, 32 girls) younger than 8 weeks old.[121] Of the 54 included infants, five had UTI and 49 did not. There were no significant differences in demographic or historical characteristics between groups in terms of gender, age, place of birth, mode of delivery, birthweight, gestational age, neonatal infection or onset of jaundice. Similarly, there were no significant differences in maternal characteristics between groups in terms of maternal age, gravidity, presence of maternal infection or maternal illness. There were significant differences in total, direct and indirect bilirubin levels between infants who had and did not have UTI. [EL = 3]

One Japanese case–control study found that boys younger than 7 months with foreskins that could not be retracted to expose the external meatus were at 7.8 times higher risk for febrile UTI when compared with boys with foreskins that could be retracted to expose the external meatus (95% CI 3.99 to 15.31).[122] This study, however, suffers from a fundamental flaw due to the fact that phimosis is physiological at this age. Therefore this study should be interpreted with caution. Additionally, not all the results from the analysis were reported, making it difficult to assess quality. [EL = 2–]

No studies on blood group as a predisposing factor for UTI in children were identified.

Review findings – familial renal disease

VUR prevalence is covered in the epidemiology section and is also included in the section on recurrence. The following two studies were identified, which investigated the likelihood of VUR in siblings of children with VUR, the majority of whom did not have a history of UTI.[123,124]

Using an awake voiding cystogram, an American case series study assessed 104 siblings aged 3 months to 15 years of patients with VUR (irrespective of history of UTI).[123] Of the siblings, 34 (32.7%) were found to have VUR and among those with VUR, six (17.6%) had a history of UTI and 25 (73.5%) had no history of UTI. The remaining three were reported to have abnormal voiding patterns but their UTI history was not reported. [EL = 3]

A case series study conducted in Iran investigated the number of VUR cases in 40 children with siblings diagnosed with VUR.[124] Seventeen (43%) siblings of 34 patients with VUR (irrespective of history of UTI) had VUR. Of the 17 with VUR, five (29.4%) also had a history of symptomatic UTI. VUR was bilateral in 6/17 and unilateral in 11/17 of the siblings. [EL = 3]

No high-quality studies on kidney stones or genetics as predisposing factors for UTI in children were identified.

Review findings – circumcision

Seven studies have investigated the association between circumcision and risk of UTI.[125–132]

An Australian meta-analysis looked at the effect of circumcision on the risk of UTI in boys in twelve studies. The meta-analysis included one RCT, four cohort studies and seven case–control studies.[125]

The RCT was a study of recurrent UTI in 70 uncircumcised boys with proven UTI aged 3 months to 10 years who were randomised to circumcision or no circumcision and showed an OR of 0.13 (95% CI 0.01 to 2.63).

Four cohort studies were conducted in hospital settings in boys aged 1–3 years and showed benefit with a summary OR of 0.13 (95% CI 0.07 to 0.23), however there was significant heterogeneity between these studies ($\chi^2 = 82.48$; degrees of freedom (df) = 3; $P < 0.001$). When one outlying study was excluded, the heterogeneity was not significant ($P = 0.64$).

The seven case–control studies were conducted in secondary care settings. Six of the seven studies were in boys aged 1 month to 5 years in hospital care settings, and one study was in adults attending a community sexually transmitted disease clinic. The case–control studies included showed benefit with a combined OR of 0.13 (95% CI 0.07 to 0.23). There was no significant heterogeneity between these studies ($\chi^2 = 8.15$; df = 6; $P = 0.20$)

The summary OR across all study types was 0.13 (95% CI 0.08 to 0.20). There was no significant heterogeneity observed between study types ($\chi^2 = 0.16$; df = 2; $P = 0.90$), but significant heterogeneity was observed within the individual studies ($\chi^2 = 90.63$; df = 11; $P < 0.001$) owing to the inclusion of the cohort studies. Without the cohort studies, there was no significant heterogeneity ($\chi^2 = 10.92$; df = 10; $P < 0.4$).

The odds of a circumcised boy having a UTI are about 0.1 when compared with uncircumcised boys. While circumcision may be protective against UTI, the risk–benefit of circumcision is not easily quantifiable. The study concludes that while circumcision substantially reduces the risk of UTI, routine circumcision should not be considered. Circumcision has a potential role in boys with past history of recurrent UTI, or with high-grade VUR, as the benefits in these cases may outweigh the risk of complications. [EL = 2++]

A US cohort study of 28 812 infants found that the median age at diagnosis of UTI was 2.5 months for uncircumcised males, 4.5 months for circumcised males and 6.5 months for female infants.[126] The incidence of UTI in the first year of life was 1/47 for uncircumcised males, 1/455 for circumcised males and 1/49 for females. Circumcised males had significantly fewer episodes of first-time UTI (OR 9.1; 95% CI 5.2 to 15.7)[126] [EL = 2++]

In a retrospective cohort study of all 136 086 boys born in US army facilities from 1980 to 1985, medical records were examined to determine any association between UTI and circumcision during the first month of life.[127] Significantly more UTIs occurred in the boys who were not circumcised ($P = 0.001$) when compared with boys who were circumcised. [EL = 2+]

In a US cohort study of 5261 infants born at an army hospital from 1982 to 1983, 400 (7.6%) infants were evaluated for UTI in the first year of life and 41 of the infants (0.78%) were subsequently diagnosed with UTI.[128] Among the 41 with UTI, 13 were female, four were circumcised males and 24 were uncircumcised males. The incidence of UTI in males was higher than in females (28/2502 versus 13/2759; $P < 0.01$) and the incidence of UTI in uncircumcised males was higher than in circumcised males (24/583 versus 4/1919; $P < 0.001$). [EL = 2+] An evaluation of all infants born in army medical facilities from 1975 to 1984 ($n = 427\,698$) confirmed these findings.[129] Females were significantly more likely to have UTI in the first year of life when compared with males (0.51% versus 0.28%; $\chi^2 = 143.5$; $P < 0.001$) and circumcised males were less likely to have UTI in the first year of life when compared with uncircumcised males (0.09% versus 1.0%; $\chi^2 = 1086.4$; $P < 0.001$). [EL = 2+]

A Canadian cohort study identified 69 100 boys who had been circumcised within the first month of life. The risk of hospitalization for UTI decreased with age, but remained higher for boys who were uncircumcised.[130] At 1 month after birth, the probability of hospital admission for UTI (per 1000 person-years) was 4.5 times higher for uncircumcised boys when compared with circumcised boys (95% CI 2.4 to 8.4). Subsequent relative risk at 1 and 3 years was 3.7 (95% CI 2.8 to 4.9) and 3.0 (95% CI 2.4 to 3.8), respectively, with 195 circumcisions needed to prevent one hospital admission for UTI in the first year of life. [EL = 2++]

An Australian case–control study recruited boys younger than 5 years and compared 144 boys with UTI (median age 5.8 months) with 742 boys without UTI (median age 21.0 months).[131] Of the boys with UTI, two (1.4%) were circumcised compared with 47 (6.3%) of the controls ($P = 0.02$). There was no evidence that age was a confounder or modified the protective effect of circumcision. [EL = 2+]

A US case–control study compared 36 boys with UTI to 76 controls. Male infants younger than 1 year presenting with first-time UTI were significantly more likely to be uncircumcised when

compared with male infants without UTI.[132] This was true regardless of age (< 3 months and > 3 months; all $P < 0.0001$), ethnic group (white, black and Hispanic; all $P \leq 0.02$) and socioeconomic status (using type of medical insurance as a proxy; all $P \leq 0.02$). [EL = 2+]

Review findings – lifestyle considerations

Breastfeeding

A case–control study conducted in Sweden aimed to investigate the association between breastfeeding and the risk of first-time febrile UTI.[133] Cases ($n = 200$) and controls ($n = 336$) were recruited consecutively in two paediatric departments in Sweden and matched for gender and age. Of children aged 0–6 years, presenting for the first time with symptomatic UTI, exclusive breastfeeding was found to have a protective effect on the risk of UTI. The risk of UTI was 2.3 times higher in non-breastfed children when compared with exclusively breastfed children (95% CI 1.56 to 3.39). The protective effect of breastfeeding was dependent on the duration of breastfeeding as well as the gender of the child or infant. A longer duration of breastfeeding was associated with a lower risk of infection after weaning and the effect was stronger in girls (hazard ratio = 3.78) than in boys (hazard ratio = 1.63). [EL = 2+]

Use of nappies

A case–control study conducted in Finland compared disposable, superabsorbant and washable cotton nappies in children presenting with their first UTI.[134] No differences were found (disposable OR 0.95; 95% CI 0.62 to 1.46, superabsorbant OR 1.04; 95% CI 0.69 to 1.57, washable cotton OR 1.00; 95% CI 0.46 to 2.16). [EL = 2+]

Hygiene

In a case–control study from the Philippines, the association between UTI and urination, defecation, washing and bathing habits was investigated in children aged 6–12 years ($n = 23$ cases, $n = 23$ controls).[135] Bathing habits (daily versus less than daily), urinary frequency (fewer than 5 times per day or 5+ per day), holding urine during the day (yes or no), permission to urinate at school (during break versus whenever), washing after urination (yes or no), washing after defecation (yes or no), direction of washing (from behind versus from front), and use of soap during washing (yes or no) showed no association with risk of UTI. The study did not specify whether the controls were matched for age and gender, selection criteria were not explicit, withdrawals were not explained and the small sample size resulted in wide confidence intervals. [EL = 2–]

Voiding habits

In a Swedish cross-sectional study, 1557 children (aged 6–9 years) and their parents/carers responded to questionnaires (56% response rate) regarding voiding habits.[136] Nearly 10% of girls (75/823) and 3% of boys (20/728) reported a previous history of UTI. Although the number of boys with previous UTI was too small to draw any conclusions, symptoms suggesting emptying difficulties were seen significantly more often in girls with previous UTI when compared with girls with no history of UTI, including:

- bed wetting ($P = 0.002$)
- day wetting ($P < 0.001$)
- does not reach toilet ($P = 0.03$)
- prolonged voiding ($P < 0.002$)
- poor stream ($P < 0.003$)
- staccato voiding ($P < 0.006$)
- able to void again ($P < 0.002$)
- straining ($P = 0.02$)
- manual compression of abdomen ($P < 0.003$)
- encopresis ($P = 0.03$).

The daily frequency of micturition between children who reported a history of UTI was not statistically different from those who did not report a history of UTI. [EL = 3]

Evidence statement – predisposing factors

Being a male infant younger than 3 months and being a girl over 3 months are risk factors for UTI.

The risk of UTI is higher in uncircumcised boys than in circumcised boys (OR 9.1; CI 5.2 to 15.7). One hundred and ninety five male infants need to be circumcised to prevent one case of UTI requiring hospital admission.

Breastfeeding has a protective effect against UTI and this is more pronounced in female infants. This is dependent on the duration of breastfeeding and the effect appears to persist even after weaning.

No high-quality studies were identified evaluating the association between ethnicity, blood groups, type of nappy, familial susceptibility, phimosis or renal stones and risk of UTI in children. No good-quality studies were identified to link other personal hygiene, religious or social factors to risk of UTI in children.

4.3 Symptoms and signs

Clinical question
In infants or children, what signs or symptoms would give rise to the suspicion of UTI?

Review findings – symptoms and signs
Thirteen studies were identified reporting symptoms and signs in children presenting with UTI. The majority of studies reported symptoms in children treated for UTI in secondary care,[14,42,50,52,67,98,116,137–140] while two studies reported symptoms of children presenting to a GP.[45,141]

A case series study conducted in Australia described the clinical features of 305 children younger than 5 years who presented consecutively at an emergency department with first-time symptomatic UTI.[137] The most commonly reported symptoms were fever (80%), an axillary temperature higher than 37.5 °C (60%) irritability (52%), anorexia (49%), malaise (44%), vomiting (42%) and diarrhoea (21%). Less common symptoms in fewer than 20% of children were dysuria, offensive urine, abdominal pain, frequency and haematuria. [EL = 3]

A case series study from the USA reported symptoms and signs from 100 children aged 5 days to 8 months (mean age 2.1 months) who were hospitalised for first known UTI.[116] Fever was the most common symptom (63%) and irritability was reported in over half of the children (55%). Other symptoms included refused feeds (38%), vomiting (36%) and diarrhoea (31%). Less common symptoms were abdominal distension and jaundice, which were reported in 8% and 7% of the children, respectively. [EL = 3]

A case series study was conducted in the USA in 83 boys aged 2 weeks to 14 years presenting to a children's hospital with first-time UTI (25% were ≤ 1 year old and half were < 6 years old).[138] Fever was present in 40 (48%) of the children and was the only presenting sign in 25%. Other symptoms included overactive bladder syndromes in 23 (28%), abdominal or flank mass in 11 (13%), enuresis in seven (8%) and gross haematuria in six (7%). [EL = 3]

A case series study of children aged 0–14 years (64 children younger than 12 months) in Italy described 223 children presenting to a hospital with first-time UTI.[50] Presenting symptoms included fever in 144 (65%), dysuria and frequency in 91 (41%), gastrointestinal symptoms in 42 (19%), haematuria in 25 (11%), failure to thrive in 14 (6%) and jaundice in two (1%). [EL = 3]

A case series study in the UK investigated 120 children (aged 2 weeks to 12 years) who had a UTI and underwent an IVU.[98] Presenting symptoms were fever in 77% (57/74) and uncoordinated voiding with residual urine in 11% (8/74). [EL = 3]

A case series study in Finland presented population surveillance data of children aged 1 week to 9.5 years (median age 0.125 years) and reported on symptoms of UTI in 134 children with first-time bacteraemic UTI.[52] The most common presenting symptoms were fever (92%) and irritability (60%). Other symptoms included abnormal crying (34%), vomiting (16%), lethargy (26%), feeding problems (20%), abdominal pain (7%), dysuria (1%) and convulsions (4%). National Surveillance data were used to compare the results with 134 children with first-time non-bacteraemic UTI. The only significant difference reported was for feeding problems (20% versus 10%; $P = 0.02$). [EL = 3]

An RCT conducted in Turkey investigated the effectiveness of circumcision on recurrent UTI and described the presenting symptoms of 88 boys referred to a paediatric nephrology department with first-time UTI.[139] The most common presenting symptoms were fever < 38.5 °C (48%), dysuria/frequency (34%) and fever > 38.5 °C (24%). Other reported symptoms included vomiting and/or diarrhoea (22%), enuresis (7%), suprapubic discomfort (11%), abdominal pain (18%), flank pain (5%) and offensive urine (2%). [EL = 3]

A case series study conducted in the UK recruited 744 children with UTI aged 0–12 years treated in a hospital.[67] Fever was a presenting symptom in 42%. Other reported symptoms included abdominal or loin pain (31%) and enuresis (38%) which was only identified in children 5 years or older. A significantly greater proportion of children with VUR (141/246) presented with fever compared with children without VUR (173/498; 57.3% versus 34.7%; $P < 0.001$). [EL = 3]

A case series study from the UK reported symptoms of 14 children with UTI aged 15 years or younger in a semi-rural general practice.[45] Six children (40%) presented with dysuria and frequency, three (20%) with abdominal pain, two (13%) with enuresis and one each (7%) with loin pain, haematuria and failure to thrive. [EL = 3]

A case series study conducted in the UK reported the clinical and laboratory features of 49 boys aged 2–12 years presenting to primary care practices with UTI.[141] The most common presenting symptoms were dysuria/frequency (82%), abdominal pain (35%) and enuresis (45%). Other reported symptoms included fever (26%), haematuria (20%) and balanitis (20%). [EL = 3]

A study conducted in a general practice in the UK presented the clinical findings of 38 children (12 boys and 26 girls) younger than 15 years with culture-proven UTI (> 10^5 cfu/ml in a clean catch urine sample).[140] Dysuria was present in 27/38 children (71%) and was the most common symptom. Twelve children (32%) presented with abdominal pain, five (13%) presented with loin pain/tenderness, nine (24%) with enuresis, eight (21%) with fever, seven (18%) with offensive urine, two (5%) with daytime incontinence, one (3%) with haematuria and one (3%) with rigor. [EL = 3]

A case series study conducted in Sweden described fever (≥ 38 °C) as one of the clinical features of children aged 0–16 years presenting at a children's or maternity hospital for symptomatic UTI.[42] The number of children presenting with fever decreased with age. In infants younger than 12 months 179/186 (96%) presented with fever; in children 1 year or older but younger than 3 years 70/96 (73%) presented with fever; in children 3 years or older but younger than 10 years 120/200 (60%) presented with fever; in children 10 years or older but younger than 16 years 19/41 (46%) presented with fever. [EL = 3]

In a US prevalence study, UTI occurred in 50/945 (5.3%) febrile infants younger than 1 year presenting to the emergency department of a children's hospital. UTI was found to occur significantly more often among infants with no identified source of fever (34/454) when compared with infants with a condition identified as a possible source of fever (15/429; 3.5% versus 7.5%; $P = 0.02$).[14] UTI was least prevalent among infants with an unequivocal source of fever (1/62). [EL = 3]

Evidence statement – symptoms and signs

Limited evidence shows that the most common symptoms and signs of UTI in children diagnosed at primary care are frequency and dysuria.

The most common symptoms and signs of UTI in children diagnosed at hospital are fever, irritability, malaise and gastrointestinal symptoms. Other less common symptoms/signs include dysuria, frequency, abdominal pain, failure to thrive, smelly urine and haematuria, bed-wetting, problems with voiding and encopresis.

UTI is more frequent among infants with no obvious focus of fever compared with those in whom there is an obvious focus.

Table 4.2 Summary of included studies on symptoms and signs of UTI in children

Study	Craig (1998)[137]	Ginsburg (1982)[116]	Burbige (1984)[138]	Messi (1988)[50]	Smellie (1985)[98]	Honkinen (2000)[52]	Nayir (2001)[139]	Smellie (1981)[67]	Dickinson (1979)[45]	Hallett (1976)[141]	Brooks (1977)[140]
Age	< 5 years	5 days to 8 months	2 weeks to 14 years	< 14 years	2 weeks to 12 years	1 week to 9.5 years	3 months to 10 years	≤ 12 years	≤ 15 years	2–12 years	< 15 years
Study size (*n*)	305	100	83	223	120	134	88	744	14	49[a]	38
Setting	Hospital	Hospital	Hospital	Hospital	Hospital	Hospital	Hospital	Hospital	Primary care	Primary care	Primary care
Country	Australia	USA	USA	Italy	UK	Finland	Turkey	UK	UK	UK	UK
Symptom (%)											
Fever	60	63	48	65	77	92	72	42	—	26	21
Irritability	52	55	—	—	—	60	—	—	—	—	—
Vomiting	42	36	—	—	—	16	22[b]	—	—	—	—
Anorexia	49	—	—	—	—	—	*see vomiting*	—	—	—	—
Diarrhoea	21	31	—	—	—	—	—	—	—	—	—
Enuresis	—	—	8	—	—	—	7	38[c]	14	45	24
Dysuria	15	—	—	41[d]	—	1	34[d]	—	43[d]	82[d]	71
Frequency	10	—	—	*see dysuria*	—	—	*see dysuria*	—	*see dysuria*	*see dysuria*	—
Abdominal pain	13	—	—	—	46[e]	7	18	31	21	35	32
Smelly urine	13	—	—	—	—	—	2	—	—	—	18
Haematuria	7	—	7	10.8	—	—	—	—	7	20	3
Failure to thrive	—	—	—	6.3	—	—	—	—	7	—	—
Malaise	44	—	—	—	—	26	—	—	—		—
Poor feeding	—	38	—	—	—	20	—	—	—	—	—
Constipation	—	—	—	—	21	—	—	—	—	—	—

[a] All male.
[b] Reported with diarrhoea.
[c] In children 5 years or older (*n* = 355).
[d] Reported with frequency.
[e] Reported with loin pain.

4.4 Urine collection

Introduction

The aim of urine collection is to obtain a good-quality sample from which the diagnosis of UTI can be confidently confirmed or excluded.

Accurate diagnosis of UTI is essential to avoid inappropriate over- or undertreatment or investigation. This is most important in children who are not toilet-trained in whom obvious urinary tract symptoms are rarely present.

To establish an accurate diagnosis of UTI requires the collection of an appropriate urine sample. Since the majority of children presenting with a UTI in the UK are likely to present in primary care, the collection of a urine specimen needs to be simple, reliable, cost effective and acceptable to children, parents and carers.

Instructions to families need to include clear detailed information about the practicalities of the method used and advice about appropriate skin cleansing.

A variety of methods are used in primary care, predominantly 'clean catch', urine collection pads (Euron Uricol™) or urine collection bags. Collection by clean catch is difficult, particularly in children, and is not always successful. Other methods sometimes used to collect urine, including gauze, cotton wool balls, sanitary towels and panty-liners placed in the nappy, often lead to inaccurate results because of bactericidal agents incorporated in these materials, rendering them unsuitable.[34,142]

In hospitals, additional methods are available, including suprapubic aspiration (SPA) and samples taken using catheterisation. While being advocated in the literature as the 'reference standard' to collect urine, SPA is invasive and unpleasant for the child and is dependent upon skilled practitioners to perform. It is also not suitable as a method of urine collection in primary care. However, in a hospital environment, when a child is acutely unwell and commencement of antibiotics is urgent, it may be appropriate to use an invasive method such as urethral catheterisation or SPA.

The costs associated with urine collection include not only the costs of materials used and personnel time collecting and processing the urine, but also the costs of misdiagnosis. Failure to accurately diagnose a urine infection may result in treatment delay and may increase the likelihood of renal parenchymal defects.

All urine collection methods have a risk of contamination by organisms not present in the bladder. This may lead to misdiagnosis and unnecessary treatment or investigation if current guidelines are followed. Children who are not toilet-trained are particularly prone to yield contaminated samples, as they are unable to pass urine to order or to cooperate with the process. In addition urine often flushes the vagina in infant girls and the prepuce in infant boys. Thus contamination of samples occurs after leaving the bladder but before it can be retrieved for diagnostic purposes.

The clean catch method tends to provide fewer contaminated samples than bags or pads. Urine collection bags are unpleasant for the child, costly and not environmentally friendly. Pads may be useful – if used correctly they are inexpensive and user friendly. The material cost of a clean catch specimen is negligible but it may be time-consuming; nevertheless, some parents/carers have expressed a preference for this method.

Current practice

In the RCP guideline it was stated that clean catch urine in an infant or a mid-stream urine specimen in an older child is the ideal. If a clean catch urine is not available then use a bag.[21]

In the national audit of the RCP guideline, specimen types recorded were: bag urine 32%, mid-stream urint (MSU) 22%, clean catch 11%, SPA and catheter specimen of uring (CSU) 4.1%. There was no record of urine specimen type in 27%. It was unclear what MSU meant in this age group. Contamination was found in 0–75% of samples from different units (mean contamination rate 34%).[23]

Clinical question

In infants and children with suspected UTI, which method of urine collection is most effective?

Review findings – clean catch urine samples

A systematic review[143] [EL = II] identified five studies (with seven data sets) that assessed the diagnostic accuracy of a clean catch urine sample, with SPA urine sample as the reference standard. All studies were judged to be of reasonable quality. Half of the studies were in children aged 0–12 years and half were in children aged younger than 3 years with a mean age of around 4 months. There was no study that directly compared diagnostic accuracy of this urine sampling between different age groups.

Sensitivity ranged from 75% (specificity 96%) to 100% (specificity 100%) and specificity ranged from 57% (sensitivity 83%) to 100% (sensitivity 100%). The positive likelihood ratio (LR+) values ranged from 1.9 (negative likelihood ratio (LR–) of 0.30) to 47.7 (LR– = 0.08). The LR– values ranged from 0.08 (LR+ = 47.7) to 0.36 (LR+ = 3.57). Although there was considerable heterogeneity all studies were clustered towards the top left of the receiver operating characteristic (ROC) curve suggesting that acceptable diagnostic performance is obtained from clean catch urine samples.

There was considerable heterogeneity in pooled LR+ values ($P < 0.0001$) but the LR– values were statistically homogeneous ($P = 0.50$). The pooled LR+ was 7.7 (95% CI 2.5 to 23.5) and the pooled LR– was 0.23 (interquartile range (IQR) 0.18 to 0.30).

Review findings – early compared with mid-stream samples

No studies were found comparing early to mid- or late stream samples for any urine collection method in children.

Review findings – pad/nappy samples

A systematic review found four studies that examined the accuracy of specimens collected from pads/nappies. Three studies compared pad/nappy samples with culture of bag specimens, although bag collection was not considered likely to be the best method of urine sample collection, limiting the value of these studies. The remaining study was found to have compared the pad/nappy specimens to SPA samples, and reported 100% sensitivity and 94% specificity between the two methods. The LR+ was 12.5 and the LR– was 0.09. Limited data made it difficult to draw firm conclusions.[143] [EL = II] An RCT conducted in the UK evaluated a modified urine collection pad method for its ability to reduce heavy mixed growth bacterial contamination of urine collection pad samples in 68 children (37 single pads, 31 replaced pads) younger than 2 years with suspected UTI.[144] Eighty children were recruited (42 in the single urine collection pad and 38 in the replaced urine collection pad), and urine collection failed in 12 children (five single pad, seven replaced pad) mainly because of faecal soiling of the pad and were excluded from the analysis. Sixty-eight children were randomised into two groups: a single urine collection pad that was left in the nappy until a sample had been obtained; or a urine collection pad that was replaced every 30 minutes until a sample was obtained. Alarm sensors were placed in all urine collection pads.

Baseline characteristics of the groups were similar with respect to age but there were significantly more boys in the single pad group (25/37 versus 13/31; $P = 0.03$). Three of the 68 (4%) children had a UTI. Of the remaining 65 who did not have a UTI, heavy mixed growth was significantly higher in the single pad (10/35), compared with the replaced pad (1/30), $P = 0.008$. [EL = 1+]

Review findings – bag samples

A systematic review[143] and three cohort studies[145–147] investigated urine collection bags.

A systematic review found three studies examining bag specimens. One study compared culture and microscopy results of bag specimens to catheter specimens in two age groups, in children younger than 5 years and in the whole sample (children aged 9 days to 11 years). In children younger than 5 years, sensitivity was 81%, specificity 87%, LR+ 5.5 and LR– 0.24. In children aged up to 11 years, the sensitivity was 77%, specificity 82%, LR+ 3.9 and LR– 0.30. The other two studies compared culture of bag samples with culture of SPA samples, with considerable difference in results – one reported a sensitivity of 100% and specificity of 89%, with an LR+ of 7.7 and a LR– of

0.04; the other reported a sensitivity of 50%, specificity of 92%, LR+ of 5.4 and LR– of 0.55. There were insufficient data for drawing firm conclusions about bag specimens.[143] [EL = II]

A cohort study conducted in the UK evaluated the ease of application and reliability of two different urine collection bags, the Hollister U-bags and the Urinicol bag (Euron Uricol™), in 50 children (33 boys, 17 girls) attending a children's clinic.[145] The nurses first cleaned the genital area with warm tap water and cotton wool balls before applying the bag. Hollister U-bags were used in 18 boys and seven girls, while Urinicol bags were used in 15 boys and ten girls. Eight out of 25 Hollister U-bags leaked compared with 0/25 Urinicol bags ($P < 0.01$). [EL = 2+]

A cohort study conducted in Canada compared the risks of contaminated culture results in urine specimens obtained by urine collection bag with those obtained by catheterisation in 7584 urine samples collected from 4632 children aged up to 24 months at an emergency department or outpatient unit.[146] Bag urine cultures were obtained by Hollister U-bag after the perineum was cleansed with antibacterial soap and tap water. In the outpatient centre the bag was replaced after 30 minutes, while in the emergency department it was not. Catheter specimens were only collected in the emergency department after cleansing with iodinated soap and sterile water.

Of the 7584 urine cultures, 42.1% were obtained in infants younger than 6 months, 25.9% in infants between 6 and 11 months and 31.9% from infants between 12 and 24 months. Of the bag specimens, 2597 were collected at the emergency department and 2530 at the outpatient unit. 2457 catheter specimens were collected at the emergency department. Bag collection (54.4% bag versus 9.0% catheter ($P < 0.001$)); male gender (38.7% male versus 29.2% female ($P < 0.001$)); and age over 12 months (31.4% < 12 months versus 38.7% 12–24 months ($P < 0.001$)) were significantly more likely to be contaminated. The odds ratio (adjusted for age, sex and leucocyte esterase test) was 13.3 (95% CI 11.3 to 15.6) and when limited to the first urine culture in each child was OR 13.6 (95% CI 11.1 to 16.7). [EL = 2+]

A study conducted in the UK compared the contamination rates between bag and clean catch urine collection methods in children younger than 2 years in one of two inpatient wards.[147] In Ward A, the child's genitalia was washed with soap and water and urine samples were collected in a sterile foil bowl. In ward B soap and water was used, followed by cleansing with sterile water and drying with cotton wool balls and urine collection bags, either Hollister U-bags or Simcare bags, were applied.

Forty-six urine samples (23 from each ward) were obtained; in ward A 44 attempts were made to obtain 23 urine samples, 18 of which were obtained in 1 hour or less. A parent/carer was involved in 33 of the 44 attempts. Of the 11 times a nurse was involved, total time taken was 3 hours and 25 minutes, but for 2 hours and 15 minutes nurses were also feeding the infants, therefore extra time taken overall was 1 hour and 10 minutes. No specimens were contaminated.

In ward B 28 attempts were made to obtain 23 samples. The urine collection bags were in place for 15 minutes to 4 hours and 10 minutes, with an average time of 1 hour and 25 minutes. Eleven specimens were contaminated with faecal bacteria. [EL = 3]

Review findings – catheter and SPA samples

An RCT conducted in Israel compared the severity of pain during SPA with pain during transurethral catheterisation in 51 infants (31 boys, 20 girls) younger than 2 months.[148] Pain during urine collection was assessed on a 100 mm visual analogue scale by a nurse and a parent/carer. Additionally, the infants' upper body was videotaped during the procedure and an investigator assigned a point score based on the Douleur Aigue du Nouveaune (DAN) neonatal pain scale.

There were no baseline differences between children undergoing SPA and those who were catheterised in terms of age or weight, but those who were catheterised were older than those undergoing SPA (27.7 ± 14.8 days versus 36.5 ± 12.3; $P = 0.007$). On the visual analogue scale recorded by a nurse, the mean pain recorded for SPA was 63 ± 18 compared with 43 ± 25 for catheter. When parents/carers used the visual analogue scale, they recorded a mean of 63 ± 27 in children undergoing SPA compared with 46 ± 26 in children who were catheterised. Similarly, DAN scores and duration of cry were higher and longer for children randomised to SPA (7.0 ± 1.9 and 62.9 ± 26 seconds, respectively) compared with infants randomised to catheter (4.5 ± 2.1 and 49.7 ± 35.7 seconds, respectively). [EL = 1+]

Review findings – ultrasound-guided SPA versus conventional SPA

It is difficult to obtain a good-quality urine sample from infants because they are unable to cooperate. SPA has been regarded as the reference standard for urine collection in babies younger than 12 months, but it is an invasive procedure with attendant risks and inexperienced clinicians can find this method difficult. Ultrasound-guided SPA involves either scanning for the presence of urine before attempting an SPA, or scanning while aspirating the urine.

Four RCTs[149–152] were identified comparing ultrasound-guided SPA with conventional blind SPA. A summary of the results is presented in Table 4.3.

An RCT conducted in Hong Kong investigated the optimal method of SPA in 60 infants, the success rate of real-time ultrasound-guided SPA (30 infants: 19 boys and 11 girls) compared with conventional SPA (30 infants: 8 boys and 22 girls) and factors associated with success.[149] The overall success rates were 26/30 (87%) in the ultrasound-guided group and 24/30 (80%) in the control group ($P < 0.05$). The first attempts in both groups were equally successful 18/30 (60%). In the ultrasound-guided group, compared with failed attempts, successful SPA was associated with a greater bladder depth (28 ± 11 mm versus 21 ± 5 mm; $P < 0.01$), length (32 ± 12 mm versus 23 ± 9 mm; $P < 0.05$) and volume (17 ± 13 ml versus 8 ± 6 ml; $P < 0.01$) but similar width ($P > 0.05$). In the control group, successful attempts were associated with the presence of bladder dullness demonstrated by light percussion (23/24 versus 8/18; OR 29.0; $P < 0.001$) compared with failed attempts. [EL = 1+]

An RCT conducted in the USA investigated whether ultrasound guidance was useful to localise the position of the bladder and to increase the amount of urine obtained by SPA in 53 neonates.[150] Twenty-eight were randomised to the ultrasound-guided group and 25 to the control group. Ultrasound-guided SPA was more likely to be successful on the first attempt (26/28 versus 7/25; $P = 0.001$), more successful overall – with one or more attempt (27/28 versus 15/25; $P = 0.003$), have a greater volume of urine obtained (2.1 ± 1.2 ml versus 1.3 ± 0.9 ml; $P = 0.03$) and require fewer passes (1.7 ± 1.0 versus 4.4 ± 2.0; $P = 0.001$). There were no differences with respect to procedure time (53 ± 59 seconds versus 60 ± 40 seconds; $P = 0.60$). [EL = 1+]

An RCT conducted in the USA investigated whether portable ultrasound could improve the success rate of SPA in 66 children aged 0–15 months (median age 1 month) presenting to a paediatric emergency department.[151] Fifteen of 19 (79%) SPA attempts were successful in the ultrasound group compared with 16/31 (52%) in the control group ($P = 0.04$). In 3/4 SPA attempts in the ultrasound group and in 11/15 SPA attempts in the control group, aspiration yielded ≥ 5 ml of urine. Operator efficiencies showed an increasing success rate over time ($P = 0.03$). [EL = 1+]

In children younger than 1 month, there were no differences in success rates between ultrasound-guided (75%) and controls (74%) ($P > 0.05$). Additionally, the volume of urine obtained was approximately 6 ml for both groups ($P > 0.05$). [EL = 1+]

Review findings – early compared with late stream samples

A systematic review[143] [EL = II] found one study showing good agreement between the results of culture from the early part of a catheter sample when compared with the later part of the same sample, with sensitivity of 100%, specificity of 95%, LR+ of 16.7 and LR– of 0.08. The limited data available means no firm conclusions can be drawn.

No other studies were found comparing early with late stream samples for any other urine collection method in children.

Table 4.3 Summary results for included studies comparing ultrasound-guided SPA with conventional methods

	Chu (2002)[149]		**Kiernan (1993)[150]**		**Gochman (1991)[151]**	
n	140		53		66	
Allocation	Ultrasound	Control	Ultrasound	Control	Ultrasound	Control
Numbers randomised	30	30	28	25	35 (SPA attempted in 19)	31
Success rate	87%	80%	96%	60%	79%	52%
Significance	$P > 0.05$		$P = 0.003$		$P = 0.04$	

Review findings – other comparisons of urine collection methods

Four studies investigated other combinations of urine collection methods.[153–155]

A prospective cross-sectional study compared the validity of the urinalysis on clean catch and bag versus catheter urine specimens using catheter culture as the reference standard in non-toilet-trained children younger than 3 years who presented to a children's emergency hospital in the USA between June 2000 and December 2001.[153]

The sensitivity of the bag dipstick was greater than the catheter dipstick (85% (95% CI 78% to 93%) versus 71% (95% CI 61% to 81%); $P = 0.03$) and sensitivity was highest in children older than 90 days. However, specificity of the bag dipstick for all ages was low compared with the catheter specimens (62% (95% CI 56% to 69%) versus 97% (95% CI 94% to 99%); $P < 0.001$). The LR+ of the bag dipstick was 2.24, while for the catheter dipstick it was 23.67. LR– values were 0.24 for the bag dipstick and 0.30 for the catheter dipstick. In the combined dipstick and microscopy urinalysis, sensitivity of both bag and catheter specimens increased, and specificity decreased compared with dipstick alone.

The dipstick sensitivity in both bag and catheter samples did not differ according to sex. However, specificity was higher in boys than in girls for all ages and could not be explained by the fact that circumcision had been performed. Sensitivity rose with higher cut-off values for defining positive UTI, while specificity dropped. [EL = III]

A study conducted in the USA compared urine collected by bag and by catheter test performance characteristics in children younger than 93 days with temperature of 38 °C or higher who underwent urinalysis and urine culture.[154] A summary of the results is presented in Table 4.4.

Of the 1482 infants who had urinalysis and urine culture, 1384 had samples obtained by bag or catheter. Overall, leucocyte esterase had higher sensitivity, while nitrites had higher specificity. The only significant difference between bag and catheter was the comparison of specificity of leucocyte esterase. There were no significant differences when the cut-off values for a positive result were changed.

Further analysis was carried out on 54 patients who had false positive results for leucocyte esterase on bag urinalysis. Of the children who were also tested for nitrites, 4/15 (8%) had positive results. Of children who were also tested for urine white blood cell counts (WBC) 9/47 (19%) had more than 10 WBC/hpf. If children who had urine samples with positive leucocyte esterase and positive nitrite results, more than 10 WBC/hpf, or ambiguous culture results are considered to have a UTI, the difference between the methods in specificity for leucocyte esterase was still significant (bag 89%, catheter 95%; $P < 0.001$).

The area under the ROC curve for urine WBC counts and UTI was higher in children with catheter samples than in those with bag samples (0.86 versus 0.71; $P = 0.01$). [EL = III]

A study conducted in the UK assessed 44 parents'/carers' preferences for collecting urine at home from 29 boys and 15 girls aged 1–18 months and examined contamination rates.[155] Pads were placed inside the nappy and checked every 10 minutes until wet, then urine aspirated with a syringe. Bags were applied and inspected every 10 minutes and removed to decant urine. Parents/carers preferred using the pad first, the bag second and the clean catch method third. Seven samples from pads, eight from bags and one from clean catch had contamination.

Table 4.4 Summary of the study by Schroeder *et al*.[154] comparing non-invasively collected urine and catheterised urine test performance

Collection method		Bag	Pad	*P* value
Leucocyte esterase	Sensitivity	76%	86%	0.19
	Specificity	84%	94%	< 0.001
	LR+	4.75	14.33	
	LR–	0.29	0.15	
Nitrite	Sensitivity	25%	43%	0.07
	Specificity	98%	99%	0.59
	LR+	12.50	0.77	
	LR–	43.00	0.58	

Nine samples from five children grew > 10^5 cfu/ml, suggesting infection. However, these were excluded by sterile samples collected on the same day in hospital.

Parents/carers found pads and bags easy to use and preferred them to the clean catch method. The pad was considered comfortable, whereas the bag was distressing, particularly on removal often leaking and leaving red marks. Some found extracting the urine from the pad or emptying the bag awkward. Most parents/carers complained that the clean catch method was time-consuming and often messy and nine parents/carers gave up after prolonged attempts. [EL = 2+]

Evidence statement – urine collection

Limited available evidence showed that the urine collection methods that produce a most diagnostically accurate sample for testing are clean catch and SPA.

The only urine collection method for which there was adequate data was the comparison of clean catch urine to SPA. There were five studies, two of which used different criteria for being positive. When both samples were cultured the agreement between the methods was reasonable for diagnostic values. One outlying study showed poor performance of clean catch urine. The reasons for this are unclear.

Ultrasound-guided SPA is a more successful method of obtaining urine from the bladder than conventional SPA. Three of four studies found that the use of ultrasound to detect urine in the bladder immediately before SPA increases the success rate of SPA.

There is insufficient data to draw conclusions about urine collection bags and urine collection pads. There is low-level evidence that showed that the accuracy of urine collection pads was greatly improved if the pads were not used for longer than 30 minutes.

None of the routine methods for urine collection (clean catch, pad or bag) are costly in terms of equipment or clinician time. Urine collection bags cost between £0.65 and £3.25 each, while urine collection pads cost around £0.55 per pack of two pads (May 2007 prices, see Chapter 8). The evidence for choosing urine collection bags or pads is insufficient, so the least costly method should be preferred. The GDG consensus was that ultrasound-guided SPA was likely to a cost-effective alternative where it is not possible to obtain a urine sample through non-invasive methods.

4.5 Urine preservation

Introduction

Urine readily supports bacterial growth and specimens of urine are frequently contaminated. It is well recognised that time delay in culturing urine allows contaminants to multiply and produce inaccurate results. The addition of preservatives, usually boric acid, to the urine samples can be an alternative to lowering the temperature. Currently, boric acid is used in various commercially available transportation tubes.

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.

Clinical question

How should a urine sample be transported to ensure its reliability?

4.5.1 Chemical preservation

Review findings – chemical preservation of urine

Six studies were found that evaluated chemical preservation of urine.[156–161]

One study in Sweden evaluated a commercial tube prepared with boric acid, sodium formate and sorbitol. One conventional tube was sent to the laboratory by ordinary chilled transport. Another conventional tube and one HG tube were transported to the laboratory without chilling. Cultures were performed upon arrival at the laboratory and then 24, 48 and 72 hours after primary sampling.

Of the 154 consecutive outpatients with suspected UTI, 144 had positive cultures, defined as > 10^3 cfu/ml. Twenty-four hours after sampling there were no significant differences in bacterial

counts between the chilled conventional tubes and the HG tubes at room temperature. However, in the HG tubes a significant change in enterococcal counts were noted after 48 hours.[156] [EL = 2+]

One study in the USA evaluated whether or not chemical preservatives in the Becton-Dickinson urine culture kit had an effect on urinalysis, microscopy or Gram stain. Of the 304 clean catch urine specimens obtained from pregnant women, 2% had significant bacteriuria (10^5 cfu/ml). There was complete agreement between preserved and unpreserved split samples in the detection of glucose, ketones, bilirubin and blood. Of the 388 women with symptoms of UTI seen in the emergency room or outpatient department, 198 (51%) had significant bacteriuria.

Urine microscopy revealed a tendency for erythrocyte counts to be diminished after 24 hours at room temperature in unpreserved specimens. Gram stain results of preserved and unpreserved split samples were comparable; staining characteristics were not altered by the preservative.[157] [EL = III]

One study in the UK compared methods of preservation with simulated specimens of pooled urine seeded with known five parallel comparisons of six species.[158] One strain each of *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella aerogenes*, *Proteus mirabilis*, *Micrococcus* and *Streptococcus faecalis* were isolated from infected urine. An overnight culture of each test strain in pooled urine was serially diluted to give six simulated specimens of 10, 10^3, 10^4, 10^5, 10^6 and 10^7. In unpreserved specimens at room temperature each test strain multiplied rapidly and the surface viable counts showed concentrations of between 10^7 and 10^8 cfu/ml within 72 hours in every specimen. In refrigerated specimens the surface viable counts for all the specimens remained constant for 72 hours. In specimens preserved with 1.8% boric acid, the surface viable counts remained constant for 24 hours, but the viable counts of specimens infected with *P. aeruginosa* fell markedly. After 24 hours the viable counts of the *E. coli* specimens, except for the most heavily infected specimen, declined. The viable counts of specimens in the *K. aerogenes*, *P. mirabilis*, *Micrococcus* and *S. faecalis* and the specimen that was most heavily infected with *E. coli* remained constant for 72 hours. In specimens with 9% sodium chloride (NaCl)–0.9% polyvinyl-pyrrolidone there were no differences between the results obtained with polyvinyl-pyrrolidone of the two molecular weights. The surface viable counts of all specimens of *E. coli* fell markedly within 24 hours, except the viable count of the most heavily infected specimen, which fell more slowly. The viable counts of the most heavily infected *K. aerogenes* remained constant while the other specimens fell more slowly. The strain of *Micrococcus* grew in the specimens but after 24 hours the viable counts remained in the same range that they were in at time zero. The viable counts of *S. faecalis* specimens remained constant for 72 hours, but the viable counts of all specimens in the *P. mirabilis* and *P. aeruginosa* specimens fell markedly within 24 hours. [EL = 3]

One study in the USA evaluated the efficacy of collecting urine specimens in Becton-Dickinson tubes and subsequently screening them for bacteriuria with the Abbott MS-2.[159] Following collection, urine samples were immediately placed in the Becton-Dickinson tube and another in a screw-cap tube routinely used for transporting urine from the hospital to the laboratory. If samples could not be transported within 20 minutes, the conventional tube was refrigerated.

Of the 312 mid-stream urine specimens collected from obstetric outpatients receiving prenatal care, 124 were positive for bacteriuria. The median time required for urine specimens to be judged positive by the MS-2 was similar for conventional tube and for Becton-Dickinson tubes (95 and 105 minutes, respectively). Bacterial specimen results from conventional tubes did not differ significantly from those from Becton-Dickinson tubes. Culture results from 24 hour delayed samples from the Becton-Dickinson tubes were significantly different in that 40 of the 188 specimens had colony counts in excess of 10^5 cfu/ml. [EL = III]

One study in the USA aimed to determine whether boric acid interferes with the reactions of the Chemstrip LN dipstick.[160] A preliminary study of specimens negative for leucocyte esterase and nitrite were obtained by multiple mid-stream urine collections into disposable non-sterile urine cups from one asymptomatic volunteer male. Specimens positive for leucocyte esterase and nitrite were prepared by placing Chek-Stix urinalysis control strips in 12 ml deionised water, following the manufacturer's instructions. The positive and negative samples were then transferred to numbered Sage collection tubes containing boric acid. Twenty-one samples (12 negative and 9 positive) were tested immediately following preparation and tested again after 2 hours. Preliminary studies with the LN+ and LN– samples preserved in boric acid demonstrated no evidence of interference with the LN strips immediately after preparation, or after the 2 hour incubation.

Following the preliminary study, 177 consecutive clinical urine specimens from inpatients, outpatients and residents of a nursing centre preserved in boric acid were evaluated before routine culturing. The dipstick correctly indicated the presence or absence of leucocyte esterase and nitrite in all cases. [EL = 2+]

One study in the USA evaluated the boric acid-glycerol-sodium formate preservative in the Becton-Dickinson urine culture kit and the use of ordinary paper cups for collection of urine.[161] Of 1000 urine samples from children and adults with symptoms suggesting UTI and from pregnant women being screened for asymptomatic bacteriuria, 88 of the initial reference cultures were positive (pure growth of 10^5 cfu/ml). Eighty-two (93.2%) of the 88 specimens on reference culture were also positive after refrigeration or holding at room temperature in the transport tube for 24 hours. There was one false positive culture from refrigerated urine but none from the transport tube. Mixing urine in the non-sterile container did not introduce detectable contamination. [EL = 3]

4.5.2 Time

Review findings– effect of time

Two studies were identified that investigated the effect of time on the multiplication of bacteria in urine samples.[162,163]

One study from the UK investigated the multiplication of contaminant bacteria in urine and attempted to define the duration of delay during which bacterial culture can be expected to give a reliable indication of the presence or absence of urinary infection.[162] Samples were collected from 106 patients attending a health centre and members of the hospital staff and cultures were performed within 1 hour of voiding and successive cultures were carried out at 2, 4, 8, 12 and 24 hours after voiding. Throughout the period of sampling, specimens were kept between 19 °C and 23 °C. In the freshly voided urine, 14 of the 41 urine samples from males (34%) and five of 65 from females (7.7%) had bacterial populations of less than 10^2 cfu/ml. None of the urine samples from males had bacterial counts in excess of 10^5 cfu/ml, while four urine samples from females (6.2%) had counts exceeding 10^5 cfu/ml. In subsequent cultures enterococci, *E. coli, Staphylococcus albus* and group B streptococci were the organisms which most commonly multiplied in urine to give counts in excess of 10^5 cfu/ml within 24 hours of voiding. The lag phase was usually short and frequently undetectable. Enterobacteria other than *E. coli* were rarely isolated more than 10^2 cfu/ml when sampling was carried out but at later samplings showed growth patterns similar to *E. coli*. All isolates grew exponentially after approximately 8 hours, and most had a lag time of approximately 4 hours. [EL = 3]

One study in the USA evaluated the effect of transport delay on the microflora of clinical specimens collected for microbiological analysis.[163] Clean catch urine specimens were collected from patients on medical wards and proportions of these specimens were cultured approximately 10 minutes after collection for aerobic organisms. The remainder of each specimen was kept at room temperature until collected by the transportation service. The time necessary for transportation of the urine specimens ranged from 2 to 5 hours with an average of 4 hours. The results from 100 urine specimens cultured immediately after collection indicated that 71% had colony counts of less than 10^2 cfu/ml; 14% between 10^4 and 10^5 cfu/ml; and 15% more than 10^6 cfu/ml. After transportation, 71% maintained colony counts of less than 10^2 cfu/ml, 9% between 10^4 and 10^5 cfu/ml, and 20% more than10^6 cfu/ml. [EL = 3]

4.5.3 Temperature and refrigeration

Review findings – temperature

Two studies were found that evaluated temperature for urine samples.[164,165]

One study in Costa Rica evaluated the effect of time, temperature and glucose content on the growth of two initial populations of either *E. coli* or *P. vulgaris* in sterile urine samples.[164] In urine containing no glucose, the original number of bacteria both in the urines and the controls showed little or no change over time. Populations of *P. vulgaris* remained unchanged at all three temperatures while *E. coli* showed a slight increase over time. In urine containing glucose all bacterial strains studied showed reductions in the populations after 2 hours of incubation at –10 °C and continued to decline at 4 hours and 8 hours. However, there was a steady increase in bacterial

numbers with time in the samples incubated at room temperature (25 °C), which showed at least 10^5 cfu/ml organisms within 4 hours. The bacterial populations showed almost no change when the incubation temperature was 4 °C, regardless of bacterial strain. [EL = 3]

One study in the USA evaluated the minimum amount of urine necessary to obtain accurate results with the Sage urine culture tube and the Becton-Dickinson culture tube system.[165] Both tubes were injected with 1, 2, 3 and 4–5 ml (tube capacity) of urine containing each culture. Specimens were held at 22 °C and cultured at 0, 4 and 24 hours. The Becton-Dickinson urine culture kits were toxic to *E. coli* and *K. pneumoniae* in specimens containing up to 2 ml of urine. The minimum useable amount of urine for reliable results was 3 ml. The Sage urine culture tube maintained the number of bacteria in 1 to 4.5 ml of urine in 83% of the specimens. However the Sage tube was toxic to *E. coli* when held for 24 hours. Quantitative counts of enterococci tended to significantly increase in specimens that contained 2 ml or more of urine in either system. [EL = 3]

Review findings – refrigeration

Two studies investigated the effect of refrigeration on bacterial growth in urine samples.[166,167]

One study from the USA assessed the validity of overnight refrigeration for quantitative bacteriological evaluation and compared initial urine cultures (less than 2 hours old) with refrigerated urine cultures.[166] Of 414 urine cultures, there were 109 cultures with colony counts of 10^4 cfu/ml or higher. Four cultures changed from sterile to significant colony count (10^5 cfu/ml or greater), all of which were *Staphylococcus aureus*. There was also a single culture which changed from 10^5 cfu/ml to sterile where the organism involved was *E. coli*. Nine other cultures exhibited some change in colony count in which a number of organisms were involved in the discrepancies. [EL = 3]

One study in the USA evaluated whether bacterial concentrations generally considered insignificant (less than 10^4 cfu/ml) become significant as a result of bacterial multiplication in the urine during refrigeration.[167] Clean catch specimens obtained from 'normal' males and females were refrigerated at 5 °C for approximately 24 hours. The urine was then pooled, sterilised by pressure filtration and stored at 5 °C in 100 ml aliquots in sterile bottles. Two bottles were inoculated for each of the bacteria employed and the bottles were placed at 0.5, 5, 10 and 15 °C. Every 24 hours for 4 days samples of urine from each bottle were cultured. At 0.5, 5 and 10 °C, *E. coli* remained largely unchanged.

At 15 °C, *E. coli* grew from 12 000 cfu/ml immediately after collection to 16 000 cfu/ml at 24 hours, 370 000 cfu/ml at 48 hours and reached 800 000 cfu/ml by 72 hours. Bacterial counts overall remained the most stable in the 5 °C group. [EL = 3]

Evidence statement – urine preservation

The studies included confirm the need for a method of preserving urine specimens when they cannot be examined immediately.

Culture of urine within 4 hours of voiding is likely to give a true indication of the presence or absence of bacteria. With further delay the interpretation of a heavy growth of bacteria in urine becomes progressively more unreliable. Where it is impractical to culture urine within 4 hours, urine specimens which are to be used to detect bacteriuria should be refrigerated immediately following collection.

There is evidence to suggest that culture kits containing boric acid, sodium formate and sodium borate maintain a stable bacterial population in urine for up to 24 hours. However, prolonged storage (more than 24 hours) may alter subsequent bacterial counts. Potential toxicity against bacteria in the specimen from boric acid can occur if the manufacturer's recommendations about the volume of urine required are not followed. There is no evidence that commercially available urine collection kits offer any advantage.

4.6 Urine testing

Introduction

Prompt and accurate diagnosis of UTI is essential if this condition is to be managed correctly. The first step in making a diagnosis is to identify whether children presenting to the healthcare

system, often but not exclusively via primary care, have a UTI. The initial assessment will usually involve a combination of clinical assessment and diagnostic testing.

Diagnostic tests fall functionally into two groups: firstly, those which give immediate results and, secondly, those in which, due to the nature of the test, there is a delay. There are obvious practical advantages in tests which give an immediate answer. Dipstick testing and microscopy fall into the first group and as such can assist in making an immediate assessment. Investigations involving bacterial culture fall into the second as an overnight incubation is required to allow bacteria to grow. The aim of this chapter is to review the evidence for the use of each test and make recommendations on how best to investigate a patient presenting with symptoms of UTI.

At present there is wide variation in practice. At one end of the spectrum all patients with possible UTI may be tested with a combination of dipstick and formal urine microscopy and culture. At the other end diagnostic testing might not be used until the patient has failed to improve following a course of empirical therapy. There is also wide variation both in the type of dipstick used as a near-patient test and in how microbiology laboratories perform microscopy and culture.

The cut-off value of 10^5 cfu/ml was proposed by Kass[41,168] as it enabled 96% of UTI cases to be identified correctly when applied to adult women with asymptomatic bacteriuria and acute pyelonephritis/upper urinary tract infection.

Bacterial counts as low as 1000 cfu/ml can, in certain unusual clinical situations, represent a true UTI but when bacterial numbers are lower than 10^5 cfu/ml the chance of the identified bacteria representing contamination increases. Mixed growth can also represent a real infection, for example when the infecting bacteria are 'hidden' among a larger number of contaminating bacteria or in children with severe malformations in whom multi-bacterial infections occur.

The results from urine culture can therefore not be interpreted in isolation, but should be done in relation to the clinical setting, symptoms and findings. The results of other diagnostic tests should also be considered.

Clinical questions

In infants and children with suspected UTI, which is the most diagnostically accurate urine test for detecting UTI?

In infants and children with suspected UTI, which is the most effective diagnostic test?

4.6.1 Dipstick urine tests

Introduction

Dipstick tests are a group of tests which involve dipping reagent strips into collected urine.

Review findings – dipstick uring tests

A systematic review identified 38 studies that evaluated dipstick tests for the diagnosis of UTI. The studies included dipstick tests for nitrite, leucocyte esterase, protein, glucose and blood.[143] [EL = II] A further meta-analysis identified 70 studies[169] and two additional studies were identified from the literature search.[170,171]

Nitrite

A systematic review reported 27 data sets from 23 studies investigating nitrite dipstick tests.[143] Culture was used as the reference standard in all but two studies, where a combination of culture and microscopy was used as the reference standard. The majority of studies used 10^5 cfu/ml as a positive reference standard. The studies reported poor sensitivity, ranging from 16.2 (specificity 97.6%) to 88.1% (specificity 100%), and high specificity, ranging from 75.6% (sensitivity 61.1%) to 100% (sensitivity 16.7–88.1%). Only two specificity estimates were below 90%. LR+ values ranged from 2.5 (LR– = 0.51) to 439.6 (LR– = 0.63). LR– values ranged from 0.12 (LR+ = 157) to 0.86 (LR+ = 6.7). The pooled LR+ was 15.9 (95% CI 10.7 to 23.7) and the pooled LR– was 0.51 (95% CI 0.43 to 0.60), but there was considerable heterogeneity in terms of LRs ($P < 0.001$).[143] [EL = II]

Leucocyte esterase

A systematic review identified 14 studies reporting 16 data sets which investigated leucocyte esterase dipstick tests.[143] Twelve studies used culture as the reference standard and two used a combination of culture and microscopy.

Sensitivity ranged from 37.5% (specificity 96.4%) to 100% (specificity 92%). Specificity ranged from 69.3% (sensitivity 93.5%) to 97.8% (sensitivity 70%). LR+ values ranged from 2.6 (LR– = 0.39) to 32.2 (LR– = 0.31). LR– values ranged from 0.02 (LR+ = 12.5) to 0.66 (LR+ = 6.97). There was considerable heterogeneity in both positive and negative LRs ($P < 0.001$). The pooled LR+ was 5.5 (95% CI 4.1 to 7.3) and the pooled LR– was 0.26 (95% CI 0.18 to 0.36).[143] [EL = II]

Protein

A systematic review identified two studies reporting three data sets that examined protein dipstick tests.[143] One study used culture and the other used a combination of culture and microscopy as the reference standard. The systematic review concluded that these studies did not use an appropriate spectrum of patients or adequately report the criteria used to select the patients. The studies did not report sufficient information to assess the avoidance of review bias. The sensitivity was estimated to range from 8.1% (specificity 95.1%) to 53.3% (specificity 83.9%). Both studies found protein dipstick was a poor test for the identification of UTI. [EL = II]

Glucose

A systematic review identified four studies containing five data sets investigating biochemical test strips for glucose using culture as the reference standard.[143] The studies identified investigated glucose strips which are not currently commercially available in the UK, as currently available glucose strips are optimised to detect abnormally high urinary glucose levels. Sensitivity ranged from 64% to 98% while specificity ranged from 96.4% to 100%. LR+ values ranged from 27.8 (LR– = 0.07) to 166.2 (LR– = 0.02) while LR– values ranged from 0.02 (LR+ = 166.2 and 113.7) to 0.36 (LR+ = 32.5). The pooled LR+ was 66.3 (95% CI 20.0 to 219.6) and the pooled LR– was 0.07 (95% CI 0.01 to 0.83). There was significant heterogeneity in both the positive and negative LRs ($P < 0.001$). [EL = II]

Blood

A systematic review identified one study investigating the accuracy of dipstick tests for blood using culture as the reference standard.[143] The study reported that dipstick testing with blood is not a useful tool for diagnosing UTI in children, with estimated sensitivities of 25.4% for visual examination and 53.3% for automated examination, and specificities of around 85%. [EL = II]

Leucocyte esterase or nitrite positive

A systematic review identified 15 studies containing 20 data sets examining the use of a combination test where either a positive leucocyte esterase dipstick or a positive nitrite dipstick was considered a positive UTI result.[143] All studies used culture as the reference standard. Sensitivity ranged from 69.4% (specificity 78.5%) to 100% (specificity 88.4%). Specificity ranged from 69.2% (sensitivity 94.1%) to 97.8% (sensitivity 70%). LR+ values ranged from 3.0 (LR– = 0.23) to 32.2 (LR– = 3.1) while LR– values ranged from 0.03 (LR+ = 5.6) to 0.39 (LR+ = 3.2). However, LRs showed considerable heterogeneity ($P < 0.001$). The pooled LR+ was 6.1 (95% CI 4.3 to 8.6) and the pooled LR– was 0.20 (95% CI 0.16 to 0.26). [EL = II]

Leucocyte esterase and nitrite positive

A systematic review identified nine studies containing 12 data sets examining the use of a combination test where a positive results from both leucocyte esterase and nitrite dipstick was considered a positive UTI result.[143] All studies used culture as the reference standard. Sensitivity ranged from 30% (specificity 100%) to 89.2% (specificity 97.6%). Specificity ranged from 89.2% (sensitivity 87%) to 100% (sensitivity 30–88%). LR+ values ranged from 8.0 (LR– = 0.15) to 197.1 (LR– = 0.17) while LR– values ranged from 0.11 (LR+ = 36.7) to 0.7 (LR+ = 107.7). Both pooled positive and negative LRs were heterogeneous ($P < 0.037$ and $P < 0.001$, respectively). The pooled LR+ was 28.2 (95% CI 15.5 to 43.4) and the pooled LR– was 0.37 (95% CI 0.26 to 0.52). [EL = II]

Leucocyte esterase and protein positive

A systematic review identified one study investigating the use of a combination test where a positive result from both leucocyte esterase and protein dipstick was considered a positive UTI result.[143] A combination of microscopy and culture was used as the reference standard. The study

reported a sensitivity of 89% and a specificity of 95%; an LR+ of 17.4 and LR– of 0.12 were calculated. [EL = II]

Combinations of three dipsticks

A systematic review identified five studies reporting a total of ten data sets investigating various combinations of three dipsticks.[143] Four studies evaluated one combination of tests (nitrite, blood or protein positive; nitrite, blood or leucocyte esterase positive; nitrite, blood and leucocyte esterase positive; nitrite, leucocyte esterase or protein positive) and two further studies investigated the same combination (nitrite, leucocyte esterase and protein positive). All studies used culture as the reference standard.

Insufficient information was available to draw any overall conclusions, but one combination (nitrite, leucocyte esterase and protein positive) investigated by two studies appeared to be potentially useful for diagnosing UTI. One study reported a sensitivity of 96% and a specificity of 99%, LR+ of 69.2, LR– of 0.04, while the second study reported a sensitivity of 89% and a specificity of 72%, LR+ of 3.1 and an LR– of 0.17. [EL = II]

A meta-analysis of urine dipstick tests to rule out infection identified 70 studies.[169] Accuracy of nitrites was higher in pregnant women (diagnostic odds ratio (DOR) = 165) and in elderly people (DOR = 108). Subgroup analysis of diagnostic accuracy found ten studies of nitrite dipstick tests in children. Sensitivity was 50% (42% to 60%), specificity 92% (87% to 98%) with DOR 34 (12 to 97). Accuracy of leucocyte esterase was high in studies in urology patients (DOR = 267). The combination of both test results showed an increase in sensitivity. Accuracy was high in studies in urology patients (DOR = 52), in children (DOR = 46) and if clinical information was present (DOR = 28). Subgroup analysis of accuracy of leucocyte esterase and nitrite dipsticks in combination found nine studies of nitrite dipstick tests in children. Sensitivity ranged from 78% to 89% and specificity ranged from 79% to 91% with DOR 46 (23 to 95). [EL = II]

One study investigated whether dipstick urinalysis for leucocyte esterase, nitrites, blood and protein in the paediatric population is an adequate screening tool to exclude UTI.[170] Prevalence of UTI overall was calculated to be 10.7% in a paediatric population with a higher prevalence (15%) in children younger than 2 years, and lower prevalence in children 2 years or older but younger than 10 years (7%). The sensitivity of the dipstick in all cases was 92.5% (95% CI 84.3% to 100%), specificity 39.4% (95% CI 34.2% to 44.6%), LR+ of 1.52 and an LR– of 0.18. The sensitivity of the dipstick in children aged 0–2 years was 87.5% (95% CI 74.3 to 100%), specificity 39.7% (95% CI 31.5 to 47.9%), LR+ of 1.47 and LR– of 0.30. The sensitivity of the dipstick in children 2 years or older but younger than 10 years was 100% (95% CI 100% to 100%), specificity 39.2% (95% CI 32.4% to 46%), and LR+ 1.64. The LR– was not estimable. [EL = II]

One study assessed the clinical utility of pathogen-specific tests to be applied with widely used dipsticks.[171] The false negative rate for leucocyte esterase or nitrite dipstick tests was 5% (80/1743), false positive rate 17% (304), true positive rate 15% (262) and true negative rate 63% (1097).

The false negative rate for the immuno-chromatography strip was 10% (168/1743), false positive rate 2% (42), true positive rate 10% (174) and true negative rate 78% (1359). The false negative rate for combination leucocyte esterase, nitrite dipstick and immuno-chromatography tests was 11% (190/1743), false positive rate 1% (19), true positive rate 9% (152) and true negative rate 79% (1382). [EL = II]

Further analysis on dipstick urine testing by the NCC-WCH

A further analysis using data included in the systematic review[143] was conducted to explore differences in diagnostic values between age and parameters (e.g. leucocyte esterase and nitrite).

Age

When compared within the same studies, the same trend for leucocyte esterase and nitrite was found in both children younger and older than 2 years. However, in children younger than 2 years, the diagnostic performance of the leucocyte esterase and nitrite dipstick, in particular the LR–, is poorer. (Table 4.5)

To examine this further, a meta-analysis was conducted to obtain both summary positive and negative LRs stratified by age for the performance of dipsticks compared with culture. The first set of figures examines the situation where both leucocyte esterase *and* nitrite are positive. Figure 4.1 shows the

Table 4.5 Comparison of diagnostic values of various combinations of urine dipstick test between infants and children

Study	Age	Nitrite only		Leucocyte esterase only		leucocyte esterase or nitrite		leucocyte esterase and nitrite	
		Sensitivity Specificity	LR+ LR–	Sensitivity Specificity	LR+ LR–	Sensitivity Specificity	LR+ LR–	Sensitivity Specificity	LR+ LR–
Sharief (1998)	< 1 year	12.5% 98.3%	7.8 0.85	75.0% 74.1%	2.8 0.38	75.0% 73.3%	2.7 0.38	12.5% 99.1%	13.0 0.84
	1–16 years	55.6% 95.8%	13.3 0.46	80.0% 81.3%	4.3 0.25	80.0% 78.6%	3.8 0.25	55.6% 98.4%	35.6 0.45
Shaw (1991)	< 2 years					71.4% 92.4%	9.4 0.31	14.3% 97.7%	6.24 0.88
	2–19 years					87.1% 77.8%	3.9 0.17	51.6% 98.1%	27.1 0.49

summary LR+. There was a clear divergence in performance with a summary LR+ for younger children of 7.74 (95% CI 1.88 to 31.93), while that for older children was 28.79 (95% CI 13.92 to 59.52).

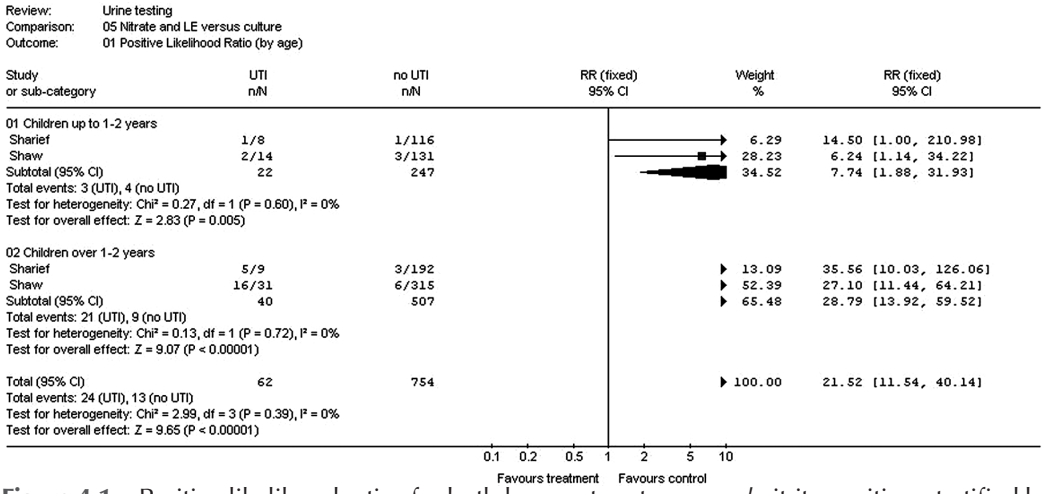


Figure 4.1 Positive likelihood ratios for both leucocyte esterase *and* nitrite positive, stratified by age

The next analysis (Figure 4.2) shows the summary LR– when both leucocyte esterase *and* nitrite are negative. The summary LR– for younger children was 0.32 (95% CI 0.16 to 0.63). For children over 2 years the summary LR– was 0.19 (95% CI 0.09 to 0.40).

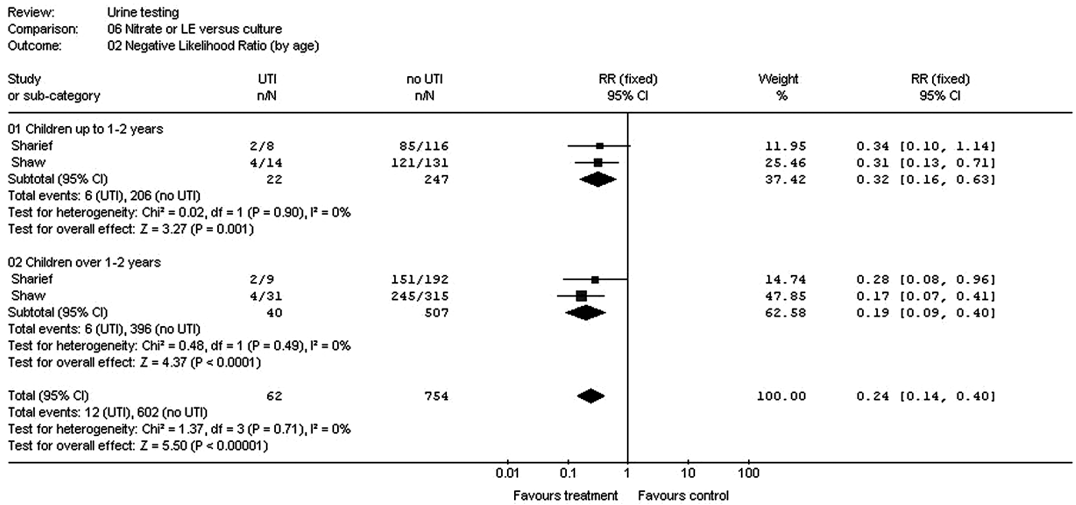


Figure 4.2 Negative likelihood ratio for both leucocyte esterase *and* nitrite negative, stratified by age

Leucocyte esterase versus nitrite

When compared within the same studies, there was a tendency for LR+ to be higher for nitrite and LR– was lower for leucocyte esterase (Table 4.6).

Evidence statement – dipstick urine tests

It is clear that leucocyte esterase and nitrite dipsticks are more valuable in diagnosing UTI when used in combination than when used alone. There is general agreement among studies that a combination of a positive leucocyte esterase with positive nitrite has the highest LR+ and is the most useful dipstick test for ruling in UTI. However, a negative result for either leucocyte esterase or nitrite has the highest LR– and will be most useful in excluding UTI. It is important to note that in children younger than 2 years the dipsticks are less reliable in both scenarios.

Table 4.6 Comparison of diagnostic values of dipstick urine tests for children (leucocyte esterase versus nitrite)

Study	Country	Age	Manufacturer	Reference test	Nitrite only		Leucocyte esterase only	
					Sensitivity Specificity	LR+ LR–	Sensitivity Specificity	LR+ LR–
Dayan (2002)	USA	< 2 months	Super UA	SPA 10^3 cfu/ml	35.0%	15.1	80.0%	13.8
				Clean catch 10^5 cfu/ml	97.7%	0.67	94.2%	0.21
Sharief (1998)	UK	< 1 year	Multistix (Bayer)	10^5 cfu/ml	12.5%	7.8	75.0%	2.8
					98.3%	0.85	74.1%	0.38
		1–16 years			55.6%	13.3	80.0%	4.3
					95.8%	0.46	81.3%	0.25
Wiggelinkhuizen (1988)	South Africa		Combur9 (BM)	Not clear	62.7%	46.1	94.1%	3.0
					98.9%	0.38	68.9%	0.09
			Multistix (Ames)		62.7%	44.1	93.5%	3.0
					98.6%	0.38	69.3%	0.09

Only studies including diagnostic values of both parameters, leucocyte esterase and nitrite.

Table 4.7 Comparison of diagnostic values of dipstick urine tests for children (leucocyte esterase and/or nitrite)

Study	Country	Age	Manufacturer	Reference test	Leucocyte esterase or nitrite		Leucocyte esterase and nitrite	
					Sensitivity Specificity	LR+ LR–	Sensitivity Specificity	LR+ LR–
Sharief (1998)	UK	< 1 year			75.0%	2.7	12.5%	13.0
		n = 124			73.3%	0.38	99.1%	0.84
		1–16 years			80.0%	3.8	55.6%	35.6
		n = 209			78.6%	0.25	98.4%	0.45
Shaw (1991)	USA	< 2 years			71.4%	9.4	14.3%	6.24
		n = 145			92.4%	0.31	97.7%	0.88
		2–19 years			87.1%	3.9	51.6%	27.1
		n = 346			77.8%	0.17	98.1%	0.49
Dayan (2002)	USA	< 2 months	Super UA	SPA 10^3 cfu/ml	85.0%	10.5	30.0%	
		n = 193		Clean catch 10^5 cfu/ml	91.9%	0.16	100.0%	
Wiggelinkhuizen (1988)	South Africa		Combur9 (BM)		95.4%	3.0	61.4%	58.5
					68.7%	0.07	99.0%	0.39
			Multistix (Ames)		94.1%	3.1	62.0%	47.8
					69.2%	0.08	98.7%	0.38
Marsik (1986)	USA	≤ 21 years	Chemstrip (Biodynamics)	SPA any bacteria	88.7%	3.1	62.3%	27.2
		n = 601		Catheter 10^3 cfu/ml	71.5%	0.16	97.8%	0.39
				Clean catch 10^5 cfu/ml				
Woodward (1993)	UK	≤ 15 years	Multistix (Bayer)	10^5 cfu/ml and WBC 20/ml	100.0%	8.6	83.3%	
		n = 134			88.4%	0.04	100.0%	

Glucose dipstick tests may be useful for both ruling in and ruling out UTI, but evidence is limited.

There is not enough evidence to draw conclusions about dipstick tests for protein or blood, or for combinations of three or more dipstick tests.

Nitrite has a higher LR+ but a higher LR– than leucocyte esterase. When both leucocyte esterase and nitrite are positive the dipstick test is useful to rule in a diagnosis of UTI in patients 2 years or older (LR+ = 28.79). When both leucocyte esterase and nitrite are negative the dipstick test is useful to rule out a diagnosis of UTI in patients over 2 years of age (LR– = 0.19).

4.6.2 Microscopy

Introduction

The performance and interpretation of microscopy is more demanding than dipsticks. A variety of cellular elements can be identified in urine (e.g. white cells, red cells, bacteria and casts) by a number of different microscopic methods including inverted microscopy, Gram stain and centrifuged deposit.

Review findings – pyuria

A systematic review reported 27 studies (49 data sets) investigating the microscopic detection of pyuria. Twenty-four studies used culture as the reference standard and three studies used culture and automated microscopy. Only half the studies included an appropriate spectrum of patients and ten studies did not provide an adequate description of patient selection. Most studies did not provide enough information to assess the avoidance of review bias. One-third did not provide an adequate description of the test and/or the reference standard. Several studies reported results for different cut-off points.

Sensitivity ranged from 37% (specificity 93%) to 96% (specificity 96%). Specificity ranged from 32% (sensitivity 89%) to 100% (sensitivity 50%).

LR+ values ranged from 1.3 (LR– = 0.33) to 27.7 (LR– = 0.09). LR– values ranged from 0.04 (LR+ = 24.0) to 0.68 (LR+ = 5.3). Likelihood ratios showed considerable heterogeneity ($P < 0.001$). The pooled LR+ was 5.9 (95% CI 4.1 to 8.5) and the pooled LR– was 0.27 (95% CI 0.20 to 0.37).

ROC curves suggested that the considerable heterogeneity between studies was not just the result of different cut-off values but was likely to be caused by other factors. Regression analysis indicated that centrifugation of the sample, description of selection criteria, test bias, review bias, description of study withdrawals and age were significantly associated with the heterogeneity observed. Multivariate analysis showed that only two items remained significant; centrifugation of the sample and reporting selection criteria. The DOR was 20% less in samples centrifuged compared with non-centrifuged samples and three times greater in studies that provided an adequate description of selection criteria.[143] [EL = II]

Review findings – bacteriuria

A systematic review reported 22 studies (including 34 data sets) evaluating the microscopic detection of bacteriuria. Nineteen studies used culture as the reference standard. One study used culture and microscopy as the reference standard and a further two studies used culture and automated microscopy as the reference standard. Approximately half did not include an appropriate spectrum of patients, eight studies did not provide selection criteria, and only four studies reported blinding. One-third of studies did not provide adequate descriptions of the test and/or reference standard.

Sensitivity ranged from 52.4% (specificity 99%) to 100% (specificity 98%) and specificity ranged from 40% (sensitivity 93%) to 99.7% (sensitivity 96%). LR+ values ranged from 1.6 (LR– = 0.17) to 304.8 (LR– = 0.04) and LR– values ranged from 0.01 (LR+ = 3.4) to 0.48 (LR+ = 3.5). Likelihood ratios showed considerable heterogeneity ($P < 0.001$). The pooled LR+ was 14.7 (95% CI 8.7 to 24.9) and the pooled LR– was 0.19 (95% CI 0.14 to 0.24). ROC curves indicated that although different cut-off points may account for some of the heterogeneity, it is likely that other factors may be contributing to test performance. In univariate regression analysis, Gram stain and

incorporation bias were shown to be significant and both remained significant in multivariate analysis. The DOR was 5.5 times greater in samples that were Gram stained, and in studies where incorporation bias was not present the DOR was 100 times greater.[143] [EL = II]

One study compared the accuracy in diagnosing significant bacteriuria between quantitative unspun-urine microscopy and the Gram stain method.[172] Significant bacteriuria was detected by urine culture in 37 out of 325 urine samples.

Unspun-urine microscopy samples in cell-counting chambers were negative in 248 samples, positive in 33 and ambiguous in 44. Ambiguous samples were subjected to oil-immersion microscopy, which made it possible to identify rods, cocci, salts or other particles. Overall, unspun-urine microscopy was able to detect bacteriuria in 35 of 37 urine samples with culture-proven significant bacteriuria (sensitivity 94.6%), failing to identify bacilli in two urine samples. Unspun-urine microscopy identified 286 of 288 urine samples with negative culture results (specificity 99.3%). Gram stain method was able to detect bacteriuria in 33 of 37 urine samples with culture-proven significant bacteriuria (sensitivity 89.2%). The Gram stain method identified 284 of 288 urine samples with negative culture results (specificity 98.6%). Both the unspun-urine microscopy and the Gram stain methods were similarly reliable when compared with culture. [EL = II]

One study compared the accuracy of the differential fluorescent staining method and the Gram stain method in screening for bacteriuria with conventional culture.[173] A total of 1487 urine samples were tested: 289 were found to have colony counts greater than 10^4 cfu/ml, 237 yielded a single organism and 52 a mix of two or more organisms.

Of the 237 yielding a single organism, 224 were detected by the differential fluorescent staining method and 162 by the Gram stain (13 undetected by the differential fluorescent staining method and 75 undetected by the Gram stain).

The sensitivity of the differential fluorescent staining method was 95%, specificity 92%, LR+ 11.8 and LR– 0.05. The sensitivity of the Gram stain was 68.3%, specificity 76%, LR+ 2.83 and LR– 0.42. The specificity of the differential fluorescent staining method was 91.6% and the Gram stain 75.8%. [EL = III]

Review findings – pyuria or bacteriuria

A systematic review reported eight studies (including ten data sets) investigating pyuria or bacteriuria where a positive result from either test was taken as a positive result for UTI.[143] The majority did not provide adequate information to assess the avoidance of test review bias (blinding). Sensitivity ranged from 75% (specificity 93%) to 100% (specificity 32%) and specificity ranged from 32.3% (sensitivity 100%) to 92.9% (sensitivity 75%). LR+ values ranged from 1.5 (LR– = 0.05) to 12.9 (LR– = 0.05). LR– values ranged from 0.02 (LR+ = 2.8) to 0.27 (LR+ = 4.1 and 10.5). Likelihood ratios showed considerable heterogeneity ($P < 0.001$). The pooled LR+ was 4.2 (95% CI 2.3 to 7.6) and the pooled LR– was 0.11 (95% CI 0.05 to 0.23). ROC curves indicated that the considerable heterogeneity between studies was not just the result of different cut-off points but was likely to be caused by other factors. There was insufficient data to investigate heterogeneity further using regression analysis. [EL = II]

Review findings – pyuria and bacteriuria

A systematic review reported eight studies (including ten data sets) investigating combinations of pyuria and bacteriuria where a positive results from both tests was taken as a positive result for UTI.[143] All studies used culture as the reference standard. The majority of studies included an appropriate spectrum of patients, although they did not provide adequate information to assess test review bias (blinding).

Sensitivity ranged from 46.7% (specificity 96%) to 93.1% (specificity 98%) and specificity ranged from 73.6% (sensitivity 71%) to 99.7% (sensitivity 84%). LR+ values ranged from 2.7 (LR– = 0.04) to 281 (LR– = 0.16). LR– values ranged from 0.07 (LR+ = 41) to 0.56 (LR+ = 11). Likelihood ratios showed considerable heterogeneity ($P < 0.001$). The pooled LR+ was 37.0 (95% CI 10.9 to 125.9) and the pooled LR– was 0.21 (95% CI 0.13 to 0.36). ROC curves indicated that the considerable heterogeneity between studies was not just the result of different cut-off points but was likely to be caused by other factors. [EL = II]

Evidence statement – microscopy

Given the heterogeneity between studies and the lack of data for combinations of microscopy tests, it is difficult to draw overall conclusions about the diagnostic accuracy of microscopy for detecting UTI. However, the pooled likelihood ratios show that a negative result for either pyuria or bacteriuria (LR– = 0.11; 95% CI 0.05 to 0.230) is better at ruling out UTI than dipstick testing.

A systematic review concluded that presence or absence of bacteriuria is considerably better than presence or absence of pyuria for ruling in or ruling out UTI. The diagnostic performance of bacteriuria may be improved when combined with pyuria, but there is insufficient evidence to provide certainty in these estimates.

4.6.3 Culture

Review findings – dipslide culture

A systematic review reported eight studies investigating the accuracy of dipslide culture for the diagnosis of UTI.[143] More than half did not use an appropriate spectrum of patients, did not report selection criteria and did not provide an adequate description of the test and/or reference standard. The majority of studies did not provide adequate information to assess test review bias (blinding).

Reported diagnostic values for dipslide culture compared with standard culture are as follows: sensitivity ranged from 56.3% (specificity 97%) to 100% (specificity 92%) and specificity ranged from 70.7% (sensitivity 78%) to 100% (sensitivity 83%). LR+ values ranged from 2.7 (LR– = 0.31) to 135.4 (LR– = 0.17) and LR– values ranged from 0.02 (LR+ = 12.18) to 0.46 (LR+ = 7.8). There was considerable statistical heterogeneity in both positive and negative LRs ($P < 0.001$). The pooled LR+ was 14.6 (95% CI 6.7 to 31.8) and the pooled LR– was 0.23 (95% CI 0.14 to 0.39). ROC curves indicated considerable heterogeneity across the studies with no clear outliers. There were not enough studies to investigate heterogeneity further using regression analysis. [EL = II]

One study assessed the validity of urine dipslides performed under daily practice conditions and assessed the influence of the incubation period (24 versus 48 hours) on validity.[174] The nitrite test was the initial test in all practices. For the 268 urine samples a sensitivity of 42% (95% CI 34% to 49%) and a specificity of 95% (95% CI 89% to 98%) was reported. The LR+ was 8.40 and the LR– was 0.61. The sensitivity of the dipslide in general practice after 24 hours incubation was 73% (95% CI 66% to 80%) and specificity was 94% (95% CI 88% to 98%). The LR+ was 12.17 and the LR– was 0.29. Overall, the dipslide read under practice conditions performed less well than when performed under optimal conditions. [EL = II]

One study evaluated the diagnostic performance of the DipStreak device (using two different medium formulations) compared with Uriselect 3 plates and the reference streak method (calibrated loop).[175] In the study comparing DipStreak (CHROMagar and MacConkey media), Uriselect 3 plates and calibrated loop culture, 2000 urine samples were processed and 511 cultures were found to be positive. The CHR DipStreak device, the Uriselect 3 and calibrated loop cultures gave the same detection rate (99.7%). For the direct identification of *E. coli*, *Proteus* and *Enterococcus* isolates, the DipStreak device and Uriselect showed overall sensitivities of 97% and 93.4%, respectively. In a second study comparing DipStreak, Uriselect 3 and MacConkey media, 3000 urine samples were processed and 714 cultures were found to be positive. The DipStreak device, the Uriselect 3 and calibrated loop cultures gave detection rates of 99.4%, 99.9% and 99.2%, respectively. For the direct identification of *E. coli*, *Proteus* and *Enterococcus* isolates, the DipStreak device and Uriselect plates showed overall sensitivities of 88.7% and 94.4%, respectively. [EL = III]

Evidence statement – dipslide culture

There is not enough evidence to draw conclusions about different methods of dipslide culture for detecting UTI in children. The pooled LR– for dipslide culture was 0.23 (see Figure 4.3 in Section 4.8).

4.6.4 Combinations of two or more methods

Review findings – combinations of tests

A meta-analysis of urine screening tests for UTI in children concluded that rapid dipstick tests could not be definitively assessed because of the small number of studies assessing their effectiveness. Bivariate summary ROC (SROC) curves showed that pyuria more than 10/hpf *and* bacteriuria more than 10/hpf had the best diagnostic performance. In multivariate analysis, both remained significant.[176] [EL = II]

One study evaluated the diagnostic properties of urine Gram stain and urine microscopic examination for screening UTI. The prevalence of UTI from culture was 54.7% (52 cases).[177] The sensitivity of the Gram stain was 96.2%, specificity 93.0%, LR+ 13.71 and LR– 0.04. The sensitivity of the microscopic examination was 65.4%, specificity 74.4%, LR+ 2.50 and LR– 0.47. Combining the Gram stain and the microscopic examination, the sensitivity was 98.1%, specificity 74.4%, LR+ 3.77 and LR– 0.03. [EL = Ib]

One study aimed to determine which method best identified UTI in children younger than 5 years presenting to a paediatric emergency department.[178] Twenty-five cases (17.6%) of UTI were diagnosed by culture, 48% were younger than 12 months and 16% were male. Positive leucocyte esterase dipstick had an overall sensitivity of 48%. In children younger than 12 months, sensitivity was 42% while in children 12 months or older, sensitivity was 53%. Positive nitrite dipstick had an overall sensitivity of 20%. In children younger than 12 months, sensitivity was 17% while in children 12 months or older, sensitivity was 23%. Positive blood dipstick had an overall sensitivity of 44%. In children younger than 12 months, sensitivity was 33% while in children 12 months or older, sensitivity was 53%. Positive unspun leucocyte count > 10/μl had an overall sensitivity of 68%. In children younger than 12 months, sensitivity was 67% while in children 12 months or older, sensitivity was 69%. Positive cyto-centrifuge Gram stain had an overall sensitivity of 60%. There was a statistically significant difference between children younger than 12 months (sensitivity 42%) and children 12 months or older (sensitivity 76%) ($P < 0.05$). 2 to 5 or more leucocytes/hpf in sediment had an overall sensitivity of 48%. In children younger than 12 months, sensitivity was 42% while in children 12 months or older, sensitivity was 53%. [EL = II]

One study compared the performance of leucocyte esterase and nitrite dipstick with the assessment of pyuria by microscopic examination and culture of urine samples in patients with symptoms of UTI.[179] The sensitivity of the leucocyte esterase dipstick was 68.4% and specificity 73.4%, LR+ 2.52 and LR– 0.44. The sensitivity of the nitrite dipstick was 58.9%, specificity 77.8% LR+ 2.68 and LR– 0.53. The sensitivity of the microscopic pyuria count was 34%, specificity 86.5%, LR+ 2.62 and LR– 0.76. There was a significant correlation between dipstick results, microscopic examination and urine culture ($P < 0.001$). [EL = III]

One study investigated the validity of the urinary Gram stain compared with a combination of pyuria plus Gram stain and overall urinalysis.[180] Of the 100 children, 70% had a positive urine culture. The sensitivity of the Gram stain was 80%, specificity 83%, LR+ 4.71 and LR– 0.24. The sensitivity of the combination of Gram stain and pyuria was 42%, specificity 90%, LR+ 4.20 and LR– 0.64.

The sensitivity of the overall urinalysis was 74%, specificity 3.5%, LR+ 0.77 and LR– 6.50. The study concluded that neither method (Gram stain, or the combination of Gram stain plus pyuria) should substitute for urine culture in symptomatic children. [EL = III]

Evidence statement – combinations of tests

There is not enough evidence to draw conclusions about combinations of different methods for detecting UTI in children and they cannot be considered cost-effective.

4.6.5 Other tests

Review findings – other tests

A study published in 1968 examined the triphenyltetrazolium chloride reduction (TCC) test and the nitrite test.[143] One study evaluated three laboratory-based blood tests (peripheral WBC, erythrocyte sedimentation rate (ESR) and C-reactive proteins) in which all were found to be poor tests for diagnosing UTI. Other tests included FiltraCheck-UTI for bacteriuria, quantitative estimation

of proteinuria and two studies of Uriscreen (reporting contrasting results). Only one study used an appropriate spectrum of patients and only two reported an adequate description of the test and/or the reference standard. Because of the small number of studies that examined these tests, there was insufficient information to assess their usefulness in diagnosing UTI. [EL = II]

One study evaluated the analytical performance of the Sysmex UF-100 cytometer compared with culture for diagnosing UTI.[181] Of the 2010 patients considered, 529 (26.3%) had a UTI. Of the dipstick screening tests (leucocyte esterase and nitrite dipstick tests), 171 (8.5%) false negatives were observed and 184 (9.2%) false positives. Sensitivity was 64% and specificity 88%, with an LR+ of 5.33 and LR– of 0.41. Of the culture tests (bacterial growth on CLED agar), 56 (2.8%) false negatives were observed and 35 (1.7%) false positives, sensitivity was 89% and specificity 98%, with an LR+ of 44.50 and LR– of 0.11. Of the UF-100 tests, 29 (1.4%) false negatives were observed and 102 (5.1%) false positives. Sensitivity was 94% and specificity 93%, LR+ 13.43 and LR– 0.06. The Sysmex UF-100 performed more accurately than both the dipstick testing and culture. [EL = II]

Evidence statement – other tests

There is not enough evidence to draw conclusions about alternative diagnostic tests for identifying UTI in children.

4.6.6 Dipstick urine testing versus culture

Review findings

One study conducted in a laboratory aimed to determine whether the biochemical results of the urine dipstick could be used to eliminate unnecessary urine cultures.[182]

Of the 6192 urine samples processed, 64% (3932) had cultures performed. These were samples which showed positive dipstick and were ordered on physician request, or were not cancelled. Thirty-six percent (2260) had a negative dipstick and were cancelled. The rate of cancellation appeared consistent at approximately one-third when tracked month by month. Of the 3932 samples cultured, 22.4% (883) were true positives (positive dipstick and positive culture), while 31.8% (1248) had a positive dipstick but grew organisms that were considered contaminants. False positive results were observed in 1558 (39.6%). Of the samples that showed negative dipstick and were cultured, 11 (0.3%) grew a clinically significant pathogen. The study concluded that the urine dipstick testing can be used as a screen to determine whether or not a urine culture should be performed and implementation of this policy has resulted in the elimination of up to one-third of the urine cultures performed in one laboratory. [EL = III]

One study investigated the sensitivity of standard urinalysis as a screening test for UTI in 11 089 patients who had urine cultured to determine how it varies with age and to determine the clinical situation that necessitates the sending of urine for culture regardless of the urinalysis result.[183] In this study, a urinalysis was considered positive if the presence of one of the following was detected: leucocyte esterase, nitrite or pyuria. The study found that sensitivity of urinalysis was 82% (95% CI 79% to 84%) and did not vary with age. The specificity of urinalysis was 92% (95% CI 91% to 92%). The LR+ was 10.6 (95% CI 10.0 to 11.2) and the LR– was 0.19 (95% CI 0.18 to 0.20). [EL = III]

A study conducted in China evaluated the usefulness of culture of urine samples obtained by urethral catheterisation in diagnosing UTI in 492 uncircumcised boys compared with 460 girls aged 1–18 months (mean age 0.49 years) who had catheter urine cultures performed between July 1999 and June 2002 at a paediatric hospital and to test whether a single cut-off bacterial count has high sensitivity and specificity.[184] Children were classified as group A if they had a positive culture of a urine sample obtained by urethral catheterisation, acute fever, positive leucocyte esterase and nitrite dipstick and leucocytes on microscopy, and a definite response to antibiotic treatment; and group B if they had cultures yielding no growth, urine culture positive but asymptomatic and had negative urinalysis results. Group A were used as the gold standard.

There were significantly higher counts in group A children than group B ($P < 0.001$) and group B had significantly more cases of mixed growth ($P < 0.001$). The probability of UTI was increased when cfu/ml was $> 10^5$ for uncircumcised boys (LR 20.2) and $> 10^5$ (LR 18.8) or 10^4–10^5 (LR 8.95)

for girls. UTI was unlikely when cfu/ml were 10–10^3 (LR 0.11) or 10^3–10^4 (LR 0.45) for boys or if mixed growth was found (LR 0.21; 95% CI 0.12 to 0.37). [EL = III]

4.6.7 Dipstick urine testing versus microscopy

Further analysis shows that the diagnostic performance for dipstick urine testing varies with age. To examine which is the most appropriate test for each age group (infants and older children), studies that examined diagnostic values of both urine dipstick testing and microscopy compared with culture were extracted from the identified studies. Among these studies, only studies that examined results that were stratified by age group were used so only one study could be included.

Diagnostic values of both microscopy and dipstick urine testing are presented in Table 4.8. Two values are used as criteria for a positive microscopy, one used a cut-off value of 10 WBC counts/hpf for pyuria and moderate bacteriuria and the other used a cut-off value of 5 WBC counts/hpf for pyuria and few bacteriuria.

Children younger than 2 years

In children younger than 2 years where a cut-off of 5 WBC/hpf was used neither test performed well but dipstick testing again had a higher LR+ than microscopy: 6.24 versus 1.63 (95% CI 1.14 to 34.22 versus 1.24 to 2.13]. Where a cut-off of 10 WBC/hpf was used microscopy had a higher LR+ than dipstick testing at 27.10 versus 10.84 (95% CI 4.16 to 58.44 versus 1.14 to 34.22).

In children younger than 2 years where a cut-off of 5 WBC/hpf was used microscopy had a lower LR– than dipstick urine testing at 0.27 (95% CI 0.07 to 0.99) versus 0.31 (95% CI 0.13 to 0.71). Where a cut-off of 10 WBC/hpf was used microscopy had a higher LR+ than dipstick urine testing at 15.6 (95% CI 4.16 to 58.44) versus 6.24 (95% CI 1.14 to 34.22).

Children 2 years or older

When the use of microscopy, compared with dipstick testing, was examined for making a positive diagnosis of UTI in children 2 years or older where a cut-off of 5 WBC/hpf was used, dipstick testing had a higher LR+ than microscopy: 27.10 versus 1.69 (95% CI 11.44 to 64.21 versus 1.52 to 1.87). Where a cut-off of 10 WBC/hpf was used, dipstick testing again had a higher LR+ than microscopy at 27.10 versus 10.84 (95% CI 11.44 to 64.21 versus 5.95 to 19.75).

When the use of microscopy, compared with dipstick testing, was examined for ruling out a diagnosis of UTI in children 2 years or older where a cut-off of 5 WBC/hpf was used, microscopy had a lower LR– than dipstick testing at 0.04 versus 0.17 (95% CI 0.00 to 0.59 versus 0.07 to 0.41). Where a cut-off of 10 WBC/hpf was used, dipstick testing had a lower LR– than microscopy at 0.17 versus 0.51 (95% CI 0.07 to 0.41 versus 0.35 to 0.73).

The results of these analyses are presented in Table 4.8.

Overall, the evidence shows that to make a rapid diagnosis of UTI, the dipstick test has the highest LR+ in children aged 2 years or older, with microscopy using a cut-off of > 10 WBC/hpf having the highest LR+ for those younger than 2 years. To exclude a diagnosis of UTI in children younger than 2 years, microscopy with a cut-off of 5 WBC/hpf has a marginally better LR– than dipstick testing: 0.27 versus 0.31.

Table 4.8 Likelihood ratios of diagnosing UTI by age group

	Microscopy (> 5 WBC/hpf for pyuria and few bacteria for bacteriuria)		Microscopy (> 10 WBC/hpf for pyuria and moderate bacteria for bacteriuria)		Dipstick urine testing (both leucocyte esterase and nitrite)	
Children	**Younger than 2 years**	**2 years or older**	**Younger than 2 years**	**2 years or older**	**Younger than 2 years**	**2 years or older**
LR+	1.63	1.69	15.6	10.84	6.24	27.1
(95% CI)	(1.24 to 2.13)	(1.52 to 1.87)	(4.16 to 58.44)	(5.95 to 19.75)	(1.14 to 34.22)	(11.44 to 64.21)
LR–	0.27	0.04	0.66	0.51	0.31	0.17
(95% CI)	(0.07 to 0.99)	(0.00 to 0.59)	(0.44 to 0.97)	(0.35 to 0.73	(0.13 to 0.71)	(0.07 to 0.41)

4.7 Localisation of UTI

Clinical question
In infants and children with suspected UTI, what is the most effective test for assessing the localisation of UTI?

4.7.1 Localisation of UTI by symptoms and signs

Review findings – localising UTI by symptoms and signs
A systematic review identified five studies assessing various clinical features for the localisation of UTI in children.[143] A summary of the results is presented in Table 4.9. [EL = II]

Two studies compared body temperature with the reference standard of dimercaptosuccinic acid (DMSA) scintigraphy for diagnosing acute pyelonephritis/upper urinary tract infection. Test performance was poor in both studies, with one reporting sensitivity of 64% and specificity of 40%, an LR+ of 1.1 and LR– of 0.89 for a cut-off value of 39.1 °C, and the other reporting sensitivity of 87% and specificity of 64%, LR+ of 2.4 and LR– of 0.23 for a cut-off value of 38 °C.

Two studies evaluated the diagnostic accuracy of symptoms of acute pyelonephritis/upper urinary tract infection using DMSA scintigraphy as the reference standard. Sensitivities of 57% and 71% were found, with specificities of 100% in both studies. LR+ values were 4.5 and 26.6 while LR– values were 0.49 and 0.31, respectively.

One study assessed the presence of physical symptoms or positive laboratory findings for the diagnosis of acute pyelonephritis/upper urinary tract infection using DMSA scintigraphy as the reference standard. Sensitivity was 98%, specificity 33%, with an LR+ of 1.5 and an LR– 0.09.

Evidence statement – localising UTI by symptoms and signs
Clinical features used and the methods of determination were diverse and poorly described. They cannot used to predict pyelonephritic changes on acute DMSA.

Table 4.9 Clinical features compared with DMSA carried out during the acute illness for detecting UTI – results of included studies

Study	Test details	Definition of positive result	Reference standard; definition of positive result	Unit of analysis	Sensitivity	Specificity	LR+	LR–
Biggi (2001)[143]	Temperature	≥ 39.1 °C	Scintigraphy (Tc-99m-DMSA); renal changes indicative of APN	Patients	64.3%	40.0%	1.1	0.89
Buyan (1993)[143]	Flank pain, chills, nausea, vomiting, fever, tenderness of the costovertebral angle	Presence of any symptoms	Scintigraphy (Tc-99m-DMSA); renal changes indicative of APN	Patients	57.1%	100.0%	4.5	0.49
Everaert (1998)[143]	Not stated	Symptoms of APN; acute	Scintigraphy (Tc-99m-DMSA); renal changes indicative of APN	Patients	70.5%	100.0%	26.6	0.31
Fretzayas (2000)[143]	Temperature	≥ 38 °C	Scintigraphy (Tc-99m-DMSA); renal changes indicative of APN	Patients	86.7%	64.2%	2.4	0.23
Landau (1994)[143]	Physical examination, blood WBC, band forms, urinalysis, WBC in stool (when diarrhoea present)	Presence of any symptoms	Scintigraphy (Tc-99m-DMSA); renal changes indicative of APN	Patients	98.0%	32.9%	1.5	0.09

APN = acute pyelonephritis; DMSA = dimercaptosuccinic acid.

4.7.2 Localisation of UTI by laboratory tests

Introduction

Attempts have been made to distinguish acute pyelonephritis/upper urinary tract infection from cystitis/lower urinary tract infection by using some laboratory investigations including C-reactive protein (CRP) and procalcitonin. The purpose of this review was to evaluate diagnostic values of these biochemical markers to differentiate upper and lower UTI. Results of DMSA scintigraphy were considered as the reference standard.

Review findings – localisation of UTI by laboratory tests

A systematic review identified seven studies which evaluated the accuracy of circulatory CRP for diagnosing acute pyelonephritis/upper urinary tract infection, all using DMSA scintigraphy as a reference standard (Table 4.10).[143] Five additional studies were identified.[185–189]

In the systematic review it was reported that three studies using a concentration of 20 mg/ml to define a positive result reported sensitivity above 85%, while specificity ranged from 19% to 60%. The remaining four studies used varying concentrations (20 µg/l to 880 mg/l) and reported poor diagnostic performance. For the higher concentrations, sensitivity ranged from 65% to 70% and specificity from 55% to 86%. One study with very low concentration (20 µg/l) reported sensitivity of 14% and specificity of 100%.

The systematic review reported other laboratory analyses, but the small number of studies and the diverse methodologies and cut-off points make it difficult to draw any conclusions about the value of these laboratory-based tests for diagnosing UTI. [EL = II]

An Italian study investigating markers for localising UTI and renal damage reported values for procalcitonin and CRP at various levels.[185] Children found to have moderate to severe acute pyelonephritis/upper urinary tract infection were significantly more likely to have longer duration of fever ($P = 0.002$), higher procalcitonin level (4.48 ± 5.84 ng/ml versus 0.44 ± 0.30 ng/ml;

Table 4.10 Summary CRP results from the included studies

Positive CRP (cut-off)	Sensitivity	Specificity	LR+	LR–
> 880 mg/l	64%	68%	2.0	0.53
≥ 400 mg/l	68%	55%	1.5	0.58
> 200 mg/l	70%	57%	1.6	0.53
> 20 mg/l	86%	60%	2.2	0.23
≥ 20 mg/l	100%	19%	1.2	N/A
> 20 mg/l	95%	28%	1.3	0.18
> 20 µg/l	14%	100%	N/A	N/A

Table 4.11 Summary CRP and procalcitonin measures[185]

Parameters	Sensitivity	Specificity	LR+	LR–
≥ 0.8 ng/ml procalcitonin	83%	94%	13.8	0.18
≥ 0.5 ng/ml procalcitonin	91%	70%	3.0	0.13
≥ 1 0 ng/ml procalcitonin	81%	94%	13.5	0.20
≥ 20 mg/l CRP	94%	32%	1.4	0.19
≥ 50 mg/l CRP	74%	77%	3.2	0.34

Table 4.12 Summary diagnostic measures[186]

Diagnostic value	Haemocytometer WBC counts (≥ 10 WBC/µl)	Pyuria (≥ 5 WBC/hpf)	CRP (> 20 mg/l)	ESR (> 30 mm/hour)	Peripheral WBC (> 15 000 WBC/µl)
Sensitivity	82%	59%	59%	73%	36%
Specificity	94%	93%	90%	78%	80%
LR+	12.7	8.3	5.9	3.3	1.8
LR–	0.19	0.44	0.45	0.35	0.80
ROC area	0.909 ± 0.045	0.791 ± 0.065	0.822 ± 0.036	0.787 ± 0.060	0.544 ± 0.074

$P < 0.001$), higher CRP level (106.0 ± 68.8 mg/l versus 36.4 ± 26.0 mg/l; $P < 0.001$) and higher erythrocyte sedimentation rate (ESR) (79.1 ± 33.0 mm/hour versus 58.5 ± 33.1 mm/hour; $P = 0.03$) than the children with mild or no acute pyelonephritis/upper urinary tract infection. There were no differences between the groups in terms of age ($P = 0.40$), gender ($P = 0.78$) or leucocyte esterase count ($P = 0.15$). For the children with acute pyelonephritis/upper urinary tract infection, Table 4.11 shows the varying sensitivities, specificities and likelihood ratios for various levels of procalcitonin or CRP.

When inflammatory markers were correlated with the severity of renal lesions (on DMSA), a significant correlation was shown with both procalcitonin and CRP levels. However, when correlated in follow-up scans, only procalcitonin remained significant. [EL = II]

A study conducted in Taiwan assessed the usefulness of laboratory parameters for identifying UTI in 162 febrile infants younger than 8 weeks presenting to a hospital emergency department.[186] (Table 4.12)

There were no significant differences in the areas under the ROC curves for the standard urinalysis, CRP or ESR, but the area under the curve for haemocytometer WBC counts was significantly better than the other laboratory parameters ($P < 0.05$) and total WBC count was significantly smaller ($P < 0.05$).

The most sensitive indicator to UTI was pyuria ≥ 10 WBC/µl (< 0.05). Pyuria ≥ 5 WBC/hpf had poor sensitivity but high specificity. The combination of pyuria ≥ 10 WBC/µl and CRP > 20 mg/l increased the specificity to 98%, while sensitivity decreased to 54%. The specificity of pyuria ≥ 10 WBC/µl combined with a positive ESR increased to 97%, while the sensitivity decreased significantly to 72%. UTI was significantly more likely when the urine had ≥ 5 WBC/hpf or ≥ 10 WBC/µl. [EL = II]

A study conducted in Switzerland measured procalcitonin levels in children aged 1 month to 16 years (mean age lower UTI 36 months, mean age acute pyelonephritis/upper urinary tract infection 42 months) with clinical signs of acute pyelonephritis/upper urinary tract infection, compared with other inflammatory markers, and evaluated its ability to predict renal involvement as assessed by DMSA.[187]

There were no differences in mean age ($P = 0.35$) or sex ($P = 0.14$) between groups. There were significant differences between children with cystitis/lower urinary tract infection and those with acute pyelonephritis/upper urinary tract infection in the leucocyte count (10 939 ± 834 mg/l versus 17 429 ± 994 mg/l; $P < 0.001$), procalcitonin level (0.38 ± 0.19 mg/l versus 5.37 ± 1.9 mg/l; $P < 0.001$) and CRP (30.3 ± 7.6 mg/l versus 120.8 ± 8.9 mg/l; $P < 0.0001$). For predicting renal involvement, CRP had a sensitivity of 100% and a specificity of 26.1%, and LR+ of 1.35 (the LR– was not estimable). Procalcitonin had a sensitivity of 70.3% and a specificity of 82.6%%, LR+ of 4.12 and an LR– of 0.36. [EL = III]

One study conducted in Turkey and one study from Israel were identified investigating clinical findings compared with DMSA for localising UTI in children.[188,189] Neither of these studies reported raw numbers for sensitivity or specificity and were generally of poor quality. They should be interpreted with caution.

A study conducted in Turkey evaluated 76 patients (48 girls and 28 boys) aged 2 months to 12 years to investigate whether serum levels of pro-inflammatory cytokines and procalcitonin in children with UTI could be used as markers in distinguishing acute pyelonephritis/upper urinary tract infection.[188] Significantly higher procalcitonin and pro-inflammatory cytokine levels were detected in children with acute pyelonephritis/upper urinary tract infection ($P < 0.001$). Using a cut-off value of 0.5 ng/ml, procalcitonin showed a sensitivity of 58% and a specificity of 76%, LR+ of 2.42 and LR– of 0.55. Using a cut-off value of 20 mg/l, CRP showed a sensitivity of 94% and a specificity of 58%, LR+ of 2.24 and LR– of 0.10. For the inflammatory cytokines using cut-off values of 6.9 pg/ml, 18 pg/ml and 2.2 pg/ml, respectively, interleukin 1 beta (IL-1β) showed a sensitivity of 97% and specificity of 59%, LR+ of 2.37 and LR– of 0.05, interleukin 6 (IL-6) showed a sensitivity of 88% and a specificity of 74%, LR+ of 3.38 and LR– of 0.16, and tumour necrosis factor alpha (TNF-α) showed a sensitivity of 88% and a specificity of 80%, LR+ of 4.40 and LR– of 0.15. [EL = III–]

A study conducted in Israel evaluated the ability of procalcitonin level to predict renal involvement assessed by DMSA in 64 children (44 girls and 20 boys) aged 2 weeks to 3 years (mean

age 16.7 ± 8.6 months).[189] CRP at a cut-off value of 20 mg/l showed a sensitivity of 100% and specificity of 18.5%, and an LR+ of 0.12 (LR– not estimable), while procalcitonin at a cut-off value of 0.5 µg/l showed a sensitivity of 94.1%, a specificity of 89.7%, an LR+ of 9.40 and an LR– of 0.07. [EL = III–]

Evidence statement – localisation of UTI by laboratory tests

Both CRP levels and other laboratory analyses show variable diagnostic performance in localising UTI. The small number of studies and the diverse cut-off points make it difficult to draw any conclusions about the value of these laboratory-based tests for differentiating upper from lower UTI.

Procalcitonin appears to be significantly correlated with a diagnosis of UTI, but more studies are needed to confirm this association.

There is an absence of evidence from which to draw clear conclusions about the clinical and cost-effectiveness of CRP and procalcitonin to differentiate between acute pyelonephritis/upper urinary tract infection and cystitis/lower urinary tract infections.

4.7.3 Localising UTI by imaging tests

Introduction

It may very occasionally be important to attempt to differentiate by imaging infection confined to the lower urinary tract (urinary bladder) from upper urinary tract infection (renal parenchyma – acute pyelonephritis) to guide management. Ultrasound may give some indication of renal parenchymal involvement but DMSA scintigraphy is considered to be the gold standard.

The following section comprises a comprehensive evaluation of the accuracy of the various imaging tests available to assess the urinary tract following UTI in children.

Imaging modalities that have been used as markers to identify involvement of the upper urinary tract include ultrasound (with and without Doppler), DMSA and other forms of static renal scintigraphy, micturating cystourethrogram (MCUG), magnetic resonance imaging (MRI) and intravenous urogram (IVU). The use of power Doppler ultrasound permits a qualitative assessment of regional perfusion and may provide information about renal parenchymal involvement by acute infection.

Previous guideline

The localisation of infection (to the kidneys) by imaging was not a part of the RCP's 1991 guidelines on imaging in childhood UTI.[190] In UK clinical practice, differentiation of acute pyelonephritis/upper urinary tract infection from cystitis/lower urinary tract infection is usually made using a combination of clinical and laboratory features.[23]

Review findings – ultrasound compared with DMSA scan

A total of 20 studies were included in this review, of which 18 were identified in the HTA[143] and the others were from the literature search (Table 4.13).

A systematic review assessed the diagnostic accuracy of ultrasound in 18 studies where renal scintigraphy was the reference standard.[143] In 14 of the 18 studies the scintigraphic standard was DMSA. Of the 18 studies, ten did not use an appropriate spectrum of patients and four did not describe criteria used to select patients. Six of the 18 studies provided an adequate description of both the index test and the reference standard.

Of the 18 studies, sensitivity ranged from 9.2% (specificity 100%) to 93.6% (specificity 50%). However, all but three studies reported sensitivities of below 60%. Specificity ranged from 50% (sensitivity 93.6%) to 100% (sensitivity 9.2% to 50%); all but four studies were above 80%.

Likelihood ratios showed considerable heterogeneity ($P < 0.0001$), with LR+ values ranging from 1.6 (LR– = 0.68) to 55.0 (LR+ = 12.7) and LR– values ranging from 0.10 (LR+ = 2.5) to 0.91 (LR+ = 12.7). The pooled LR+ was 3.1 (95% CI 2.3 to 4.3) and the pooled LR– was 0.62 (95% CI 0.53 to 0.73). ROC plots show considerable heterogeneity between studies, suggesting that conventional ultrasound is a poor test for the localisation of UTI.

Table 4.13 Ultrasound compared with DMSA scan for localising UTI

Study details	Test details; time	Definition of positive result	Reference standard; definition of positive result; time	Unit of analysis	Sensitivity	Specificity	LR+	LR−
Andrich (1992)[143]	Standard; not stated	Not stated	Scintigraphy (Tc-99m-DMSA); not stated; not stated	Patients	11.5%	100.0%	6.5	0.88
Benador (1994)[143]	Standard; acute phase	Renal changes indicative of APN	Scintigraphy (Tc-99m-DMSA); renal changes indicative of APN; acute phase	Patients				
≥ 1 year, any UTI					38.7%	66.7%	1.1	0.94
≥ 1 year, 1st UTI					27.8%	33.3%	0.5	1.89
≥ 1 year, multiple UTI					53.8%	83.3%	2.5	0.59
< 1 year, any UTI					46.5%	85.7%	3.0	0.63
< 1 year, 1st UTI					45.0%	84.6%	2.7	0.66
< 1 year, multiple UTI					66.7%	100.0%	3.8	0.45
All ages, any UTI					43.2%	81.1%	2.3	0.70
All ages, 1st UTI					39.7%	79.3%	1.8	0.77
All ages, multiple UTI					56.3%	87.5%	3.4	0.53
Biggi (2001)[143]	Standard; not stated	Renal changes indicative of APN	Scintigraphy (Tc-99m-DMSA); renal changes indicative of APN; acute phase	Renal units	27.1%	88.9%	2.4	0.82
Bircan (1995)[143]	Standard; acute phase	Renal changes indicative of APN and presence of congenital abnormalities	Scintigraphy (Tc-99m-DMSA); renal changes indicative of APN; acute phase	Patients	24.4%	100.0%	9.5	0.76
Boudailliez (1998)[143]	Doppler; not stated	Not stated	Scintigraphy (Tc-99m-DMSA); not stated; acute phase	Renal units	33.3%	88.2%	2.8	0.76
Girona (1995)[143]	Standard; not stated	Abnormal kidney size	Scintigraphy (Tc-99m-DMSA); renal changes indicative of APN; not stated	Renal units	45.9%	72.9%	1.7	0.74
Guermazi (1993)[143]	Standard; not stated	Renal changes indicative of APN or renal parenchymal defect	Scintigraphy (Tc-99m-DMSA); presence of acute or chronic lesions; not stated	Patients	42.4%	92.8%	5.9	0.62
Hajjar (2002)[143]	Doppler; acute phase	Renal changes indicative of APN	Scintigraphy (Tc-99m-DMSA); renal changes indicative of APN; acute phase	Patients	53.6%	95.2%	11.3	0.49
Hitzel (2002)[143]	Doppler; acute phase	Renal changes indicative of APN	Scintigraphy (Tc-99m-DMSA); renal changes indicative of APN; acute phase	Patients	93.6%	50.0%	1.9	0.13
				Renal units	79.6%	81.4%	4.1	0.26
Hitzel (2000)[143]	Colour Doppler; not stated	Not stated	Scintigraphy (Tc-99m-DMSA); not stated; acute phase	Renal units	84.3%	81.7%	4.6	0.19
Ilyas (2002)[143]	Standard; acute phase	Renal changes indicative of APN	Scintigraphy (Tc-99m-DMSA); renal changes indicative of APN; acute phase	Patients	9.2%	100.0%	12.7	0.91
Jakobsson (1992)[143]	Standard; acute phase	Renal changes indicative of APN	Scintigraphy (Tc-99m-DMSA); renal changes indicative of APN; acute phase	Renal units	56.5%	63.9%	1.6	0.69
Jequier (1998)[143]	Standard; acute phase	Renal changes indicative of APN	Scintigraphy (Tc-99m-DMSA); renal changes indicative of APN; acute phase	Patients	40.6%	84.3%	2.6	0.70
	Doppler; acute phase			Patients	19.8%	98.4%	8.4	0.82
Krzemien (2002)[143]	Doppler; acute phase	Renal changes indicative of APN	Scintigraphy (Tc-99m-DMSA); renal changes indicative of APN; acute phase	Renal units	46.9%	92.3%	6.1	0.58
Lavocat (1997)[143]	Standard; acute phase	Renal changes indicative of APN	Scintigraphy (Tc-99m-DMSA); renal changes indicative of APN; acute phase	Renal units	50.0%	100.0%	55.0	0.50
Morin (1999)[143]	Standard; acute phase	Renal changes indicative of APN	Scintigraphy (Tc-99m-DMSA); renal changes indicative of APN; acute phase	Patients	93.5%	62.5%	2.5	0.10
Sfakianakis (1989)[143]	Standard; not stated	Not stated	Scintigraphy (Tc-99m-glucoheptonate); not stated; not stated	Patients	48.0%	100.0%	23.1	0.52
Sreenarasimhalah (1995)[143]	Standard; acute phase	Not stated	Scintigraphy (Tc-99m-DMSA); renal changes indicative of APN; acute phase	Renal units	39.6%	95.3%	8.5	0.63
Wang (2005)[191]	Standard; acute phase	Not stated	Scintigraphy (Tc-99m-DMSA); renal changes indicative of APN; acute phase	Patients	49.0%	88.0%	4.1	0.58
Ilyas (2002)[192]	Standard; acute phase	Not stated	Scintigraphy (Tc-99m-DMSA); renal changes indicative of APN; acute phase	Patients	9.0%	100.0%	N/A	N/A
Halevy (2004)[193]	Doppler; acute phase	Renal changes indicative of APN	Scintigraphy (Tc-99m-DMSA); renal changes indicative of APN; acute phase	Patients	87.0%	92.0%	10.9	0.14
Bykov (2003)[194]	Doppler; acute phase	Renal changes indicative of APN	Scintigraphy (Tc-99m-DMSA); renal changes indicative of APN; acute phase	Patients	74.0%	94.0%	12.3	0.28

APN = acute pyelonephritis; DMSA = dimercaptosuccinic acid.

A study conducted in Taiwan evaluated the use of ultrasonography in 45 children (31 boys and 14 girls) aged 9 days to 10 years (mean age 1.5 ± 0.2 years, median age 0.3 years) with febrile UTI who fulfilled criteria for acute pyelonephritis/upper urinary tract infection.[191] The reported sensitivity and specificity were 49.0% and 88.0%, respectively. [EL = III]

A study conducted in the USA compared DMSA renal ultrasonography and MCUG, using DMSA scintigraphy as the gold standard, in 222 children (47 boys, 175 girls) aged 2 to 228 months (median age 55 months).[192] The sensitivity of renal ultrasound to detect renal involvement was 9% and specificity was 100%. [EL = III]

Two additional studies were identified from our search.

A study conducted in Israel investigated power Doppler ultrasonography (PDU) in children with UTI (n = 57 children with a mean age of 22 months).[193] Baseline characteristics showed that the mean CRP level was significantly higher in children with acute pyelonephritis/upper urinary tract infection than in children with cystitis/lower urinary tract infection (48.1 ± 39.2 mg/l versus 114.9 ± 48.1 mg/l; $P < 0.001$). There were no differences in age ($P = 0.66$), gender ($P = 0.47$), WBC count ($P = 0.06$) or ESR ($P = 0.46$). For detecting acute pyelonephritis/upper urinary tract infection, PDU showed a sensitivity of 87% and a specificity of 92%. [EL = III]

A second Israeli study of 40 infants (78 kidneys evaluated) assessed the role of renal PDU to identify acute pyelonephritis/upper urinary tract infection.[194] The PDU showed a sensitivity of 74% and a specificity of 94%. The study went on to compare PDU with DMSA scintigraphy for identifying renal lesions in children who showed acute pyelonephritis/upper urinary tract infection on DMSA. The sensitivity of the PDU decreased to 58%. [EL = Ib]

All included studies are summarised in Table 4.13.

Review findings – MRI/CT scans compared with DMSA scan

Two studies were identified from the HTA[143] (Table 4.14).

One study assessed the accuracy of gadolinium-enhanced MRI and found sensitivity to be 92% and specificity 44%. A second study assessed the accuracy of CT for diagnosing acute pyelonephritis/upper urinary tract infection and reported a sensitivity of 56% and a specificity of 100%. Both studies used DMSA as the reference standard, although because there was only one of each of these studies, conclusions cannot be drawn about their usefulness in localising UTI.

Evidence statement – localising UTI by imaging tests

Overall, none of the tests above was considered to add clinical value in the acute phase of the infection.

Conventional ultrasound appears to be a poor diagnostic test for localising infection. Use of power Doppler may increase its diagnostic values.

No conclusions can be drawn about the effectiveness or cost-effectiveness of MRI, CT or IVU in localising UTI owing to there only being a small number of poor-quality studies.

DMSA is considered the gold standard for the localisation of infection to the renal parenchyma.

Table 4.14 MRI/CT scans versus DMSA scan

Study	Test details; time	Definition of positive result	Reference standard; definition of positive result; time	Unit of analysis	Sensitivity	Specificity	LR+	LR–
Lavocat (1997)[143]	CT scan (sodium meglumine ioxitalamate); acute phase	Renal changes indicative of APN	Scintigraphy (Tc-99m-DMSA); renal changes indicative of APN; acute phase	Patients	56.0%	100.0%	13.4	0.46
Lonergan (1998)[143]	MRI (gadolinium enhanced); not stated	Renal changes indicative of APN	Scintigraphy (Tc-99m-DMSA or Tc-99m-glucoheptonate); renal changes indicative of APN; not stated	Patients	92.0%	44.4%	1.6	0.21
				Renal units	86.7%	69.4%	2.8	0.21

APN = acute pyelonephritis; CT = computed tomography; DMSA = dimercaptosuccinic acid; MRI = magnetic resonance imaging.

4.8 GDG translation and recommendations

GDG translation

Predisposing factors

A number of factors were identified that increase or decrease the likelihood of an infant or child having a UTI. These risk factors should be evaluated during the history and examination so that they can help to inform the diagnostic process.

The reviewed evidence shows that there is a lower incidence of UTI in boys who are circumcised. The evidence for risks and benefits of circumcision has not been evaluated by this guideline.

The review showed that breastfeeding is associated with a reduced risk of UTI in infants. In addition to recording the feeding method and duration of breastfeeding in the history, mothers could be made aware of the protective effect of breastfeeding when they are making plans about how to feed their baby. Any future NICE guideline on breastfeeding should consider including this as a recommendation.

First UTI is most common in infancy and affects boys most often in the first 3 months of life while in girls the peak incidence is after 6 months. Infants are often systemically unwell and have acute pyelonephritis/upper urinary tract infection while older children more often have lower urinary tract infection and typical symptoms of cystitis. The incidence of first UTI falls with age in both sexes but UTI is less common in boys than in girls after the first 6 months. Recurrent infections in boys are relatively uncommon whereas they are very common in girls. These represent a high proportion of the infections seen in primary care. UTI seems to be less common in children with Afro-Caribbean origins in the USA.

Symptoms and signs

The majority of the included studies are of infants and children treated in secondary care centres and do not represent the majority of infants and children who present with a UTI in primary care. Furthermore, some of the studies from primary care only looked at children with symptoms localised to the urinary tract and therefore do not provide comprehensive data because of the lack of localising signs in infants.

Reported symptoms/signs in infants and children with UTI include fever, irritability, lethargy, vomiting, anorexia, diarrhoea, enuresis, dysuria, frequency, abdominal pain, loin tenderness, offensive urine, haematuria and failure to thrive. UTI is more likely to be the cause of fever when there is no obvious source of infection and there is no alternative diagnosis.

Presenting symptoms combined with findings on examination, urine testing and knowledge of the risk factors should all be taken into account when considering a diagnosis of UTI.

Some features in history and examination are important for assessing the probability of UTI as well as the risk of serious underlying abnormality and will aid the diagnostic process as well as informing the most appropriate imaging strategy.

Urine collection

In children able to cooperate, clean catch urine collection provides a good-quality sample. In children unable to cooperate, urine collection is more difficult and time-consuming. It may be impossible to obtain a sample and there is a high possibility of the sample being contaminated. In this situation, urine collection pads are a preferable alternative to urine collection bags. They are less costly and are not unpleasant for the child.

Although diarrhoea can be associated with UTI it is not usually the main symptom. It is often difficult to get a good-quality urine sample for testing for UTI in the presence of diarrhoea. There should be a high threshold for urine collection in infants and children when the cause is most likely to be due to acute viral or bacterial gastroenteritis.

Urine testing

Which test to choose

When all diagnostic methods are plotted in ROC space it is clear that there is a wide variation in reported methods for all performance and all have strengths and potential drawbacks (Figure 4.3).

There are two groups of urine tests, those providing immediate information on which to base therapeutic intervention, i.e. dipstick testing and microscopy, and culture, which provides information on sensitivity and identification of the pathogen but whose results are not available for at least 24 hours.

Age cut-off

The GDG considered that age was an important factor to be taken into consideration when choosing the most appropriate tests to diagnose UTI. Tests for UTI were considered separately for infants and children younger than 3 years and children 3 years or older since the majority of children 3 years or older are able to provide a good-quality urine sample on request. It was considered that reasons for poorer reliability of dipstick testing for infants and children younger than 2 years include urine sample contamination, differences between urine collection methods, small capacity of the bladder and frequent emptying.

No study examined the age as a continuous variable to enable evaluation of optimum age cut-off. Two studies looked at urine testing stratified by age. One study presented the results for children younger than 1 year and 1 year or older separately, and the other did so for those younger than 2 years and those 2 years or older. The rationale for each decision in the two age groups is discussed below in more detail.

Rapid testing (decision making on acute management)

Infants and children younger than 3 years

Table 4.8 shows that, in infants and children younger than 2 years, the best performing rapid test to support a clinical diagnosis of UTI is microscopy using a threshold of 10 WBC/hpf. However, in terms of ruling out a UTI, no test performs particularly well, with only marginal differences between dipstick and microscopy.

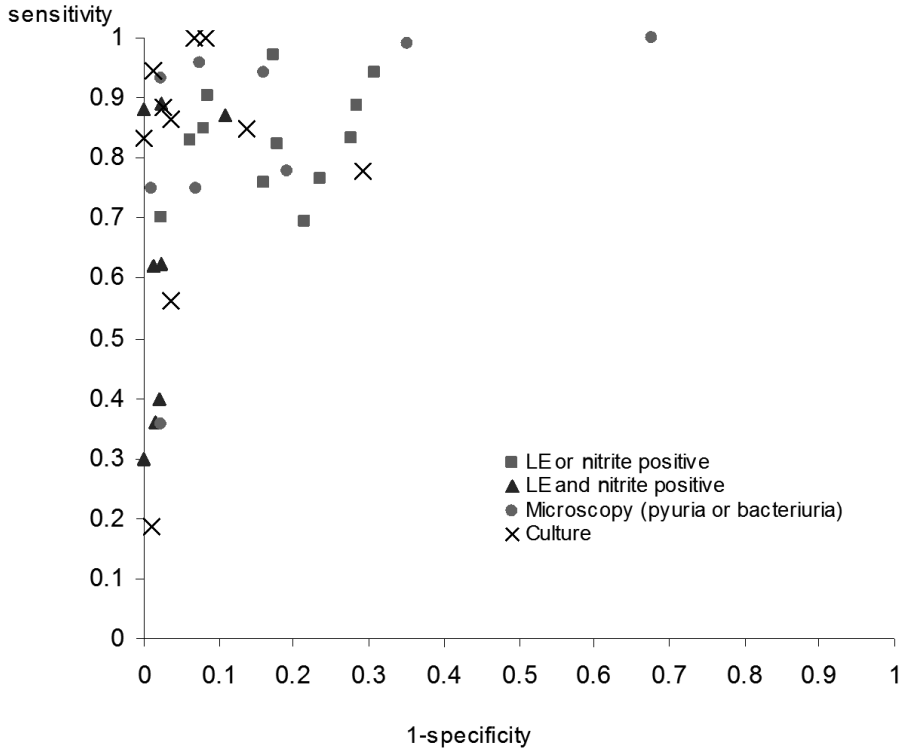


Figure 4.3 Leucocyte esterase (LE) or nitrite dipstick, microscopy and dipslide culture plotted in ROC space

Therefore the GDG suggests using urgent microscopy to make a decision on acute management, although, considering the marginal difference in ruling out UTI and practicality in primary care settings, dipstick urine testing may be used for infants and children younger than 3 years with non-specific symptoms and low or moderate risk of serious illness where urgent microscopy is not possible. The GDG considers that infants and children younger than 3 years with high risk of serious illness should be sent to a paediatric specialist where urgent microscopy should be available. The GDG also considers that infants and children younger than 3 years with non-specific symptoms and low risk of serious illness can be observed without antibiotic treatment until results of standard (not urgent) microscopy are available. This decision takes into consideration the risks and benefits of blind treatment and the very low risk of having acute pyelonephritis/upper urinary tract infection in this group. However, urine for microscopy and culture should be sent from all infants and children younger than 3 years to confirm the diagnosis, and appropriate treatment can be started when the results are available after 24–48 hours if the diagnosis is in doubt.

Children 3 years or older

It is clear from Table 4.8 that dipstick testing with both leucocyte esterase and nitrite is the best performing rapid test to support a clinical diagnosis of UTI in children 2 years or older. However, the position for ruling out UTI is more complex. In absolute diagnostic terms, microscopy using a cut-off of 5 WBC/hpf is the most reliable test to rule out UTI. However, there was no statistical evidence of difference between microscopy and urine dipstick testing to rule out UTI, as the confidence interval in the available study for LR– for microscopy is wide. Microscopy is more complicated to perform, needs a higher level of training and, with regulatory demands to ensure quality of near-patient testing, would require the development of local or national EQA and IQA schemes to ensure that performance is maintained. This is achievable in the setting of hospital laboratories but may be more difficult or impossible in primary care. The following factors were taken into account when considering the best test to use in this age group:

1. the difficulty of organising urgent laboratory tests in primary care
2. the training required to perform microscopy in the surgery
3. the need for quality assurance
4. the difference in LR– values between microscopy and urine dipstick testing in children 2 years or older was not statistically significant
5. the available studies showed that dipstick urine testing has a more favourable LR+ than microscopy in children 2 years or older
6. the cost of performing microscopy is significantly higher than urine dipstick testing.

Consequently, the GDG considers that urine dipstick testing is the most appropriate test to make a decision on diagnosis and acute management in children 3 years or older.

The role of culture (confirmation of diagnosis)

Both dipstick urine testing and microscopy may give false negative and false positive results which will give rise to both under- and over-diagnosis of UTI in infants and children. Therefore, confirmation of UTI using urine culture is recommended as this is regarded as the gold standard. Urine culture should be carried out in selected higher risk cases where there is evidence of a risk of acute pyelonephritis/upper urinary tract infection, recurrent UTI or atypical features, since in these cases there is the greatest risk of renal damage or underlying abnormality. The risk of acute pyelonephritis/upper urinary tract infection is greatest in the youngest infants and children and therefore culture is recommended in all infants and children under 3 years.

Implication for current practice and cost-effectiveness

Current practice recommends routine use of microscopy and culture of urine for the diagnosis of UTI in infants and children. In positive cases, confirmation of UTI is recommended using a second sample for culture collected by clean catch or SPA. Dipsticks were considered acceptable for ruling in but not for ruling out UTIs.[21]

The national audit showed that 71% of infants and children younger than 2 years with a fever or other symptoms of UTI admitted to hospital had urine culture and microscopy and 100% of infants and children diagnosed with UTI. Fifty-seven percent had a second sample taken for culture and microscopy. Dipsticks were used in some hospitals but results were poorly documented.[23]

Based on clinical evidence, the GDG proposes that the first line of investigation should be to use dipstick urine testing for children 3 years or older and microscopy and culture in infants and children younger than 3 years. Infants and children younger than 3 years, infants and children with signs and symptoms suggesting acute pyelonephritis/upper urinary tract infection and infants and children with recurrent UTI should have a urine sample sent for culture. In the younger age group dipsticks are only recommended for use as a substitute for microscopy when transport of a sample to the laboratory is impossible and the child has a low to intermediate risk of serious illness.

In addition to being more clinically effective and evidence based, the new proposals in this guideline for children 3 years or older are more cost-effective since, for older children, the shift is from microscopy to dipstick testing, which is both more effective and better use of NHS resources.

Laboratory tests for localisation of UTI

CRP and procalcitonin can be used to help with the diagnosis or exclusion of acute pyelonephritis/upper urinary tract infection in an appropriate clinical setting. In particular, a CRP of < 20 mg/l reduces the risk that an infant or child has a serious bacterial infection and may be useful in ruling out acute pyelonephritis/upper urinary tract infection in infants and children with fever and pyuria who often have a viral infection. In the context of UTI, a CRP of < 20 mg/l makes the diagnosis of acute pyelonephritis/upper urinary tract infection unlikely.

Imaging tests for localisation of UTI

In the majority of infants and children with UTI who respond promptly to treatment, differentiation of acute pyelonephritis/upper urinary tract infection from cystitis/lower urinary tract infection by imaging is unnecessary and would represent a poor use of NHS resources. DMSA scanning has been regarded as the most sensitive imaging test for the diagnosis of acute pyelonephritis/upper urinary tract infection.

If localisation of UTI by imaging tests is required, it would be good practice to utilise ultrasound with power Doppler prior to DMSA scan as a positive finding may obviate the need for DMSA scan.

Recommendations

Symptoms and signs

Infants and children presenting with unexplained fever of 38 °C or higher should have a urine sample tested after 24 hours at the latest.

Infants and children with an alternative site of infection should not have a urine sample tested. When infants and children with an alternative site of infection remain unwell, urine testing should be considered after 24 hours at the latest.

Infants and children with symptoms and signs suggestive of UTI should have a urine sample tested for infection. Table 4.15 is a guide to the symptoms and signs that infants and children present with.

Table 4.15 Presenting symptoms and signs in infants and children with UTI

Age group		Symptoms and signs Most common ⟷ Least common		
Infants younger than 3 months		Fever Vomiting Lethargy Irritability	Poor feeding Failure to thrive	Abdominal pain Jaundice Haematuria Offensive urine
Infants and children, 3 months or older	Preverbal	Fever	Abdominal pain Loin tenderness Vomiting Poor feeding	Lethargy Irritability Haematuria Offensive urine Failure to thrive
	Verbal	Frequency Dysuria	Dysfunctional voiding Changes to continence Abdominal pain Loin tenderness	Fever Malaise Vomiting Haematuria Offensive urine Cloudy urine

Assessment of risk of serious illness

The illness level in infants and children should be assessed in accordance with recommendations in 'Feverish illness in children' (NICE clinical guideline 47).

Urine collection

A clean catch urine sample is the recommended method for urine collection. If a clean catch urine sample is unobtainable:

- Other non-invasive methods such as urine collection pads should be used. It is important to follow the manufacturer's instructions when using urine collection pads. Cotton wool balls, gauze and sanitary towels should not be used to collect urine in infants and children.
- When it is not possible or practical to collect urine by non invasive methods, catheter samples or suprapubic aspiration (SPA) should be used.
- Before SPA is attempted, ultrasound guidance should be used to demonstrate the presence of urine in the bladder.

In an infant or child with a high risk of serious illness it is highly preferable that a urine sample is obtained; however, treatment should not be delayed if a urine sample is unobtainable.

Urine preservation

If urine is to be cultured but cannot be cultured within 4 hours of collection, the sample should be refrigerated or preserved with boric acid immediately.

The manufacturer's instructions should be followed when boric acid is used to ensure the correct specimen volume to avoid potential toxicity against bacteria in the specimen.

Urine testing

The urine-testing strategies shown in Tables 4.16–4.19 are recommended.*

As with all diagnostic tests there will be a small number of false negative results; therefore clinicians should use clinical criteria for their decisions in cases where urine testing does not support the findings.

Table 4.16 Urine-testing strategy for infants younger than 3 months

All infants younger than 3 months with suspected UTI (see Table 4.15) should be referred to paediatric specialist care and a urine sample should be sent for urgent microscopy and culture. These infants should be managed in accordance with the recommendations for this age group in 'Feverish illness in children' (NICE clinical guideline 47).

Table 4.17 Urine-testing strategies for infants and children 3 months or older but younger than 3 years

Urgent microscopy and culture is the preferred method for diagnosing UTI in this age group; this should be used where possible.	
If the infant or child has specific urinary symptoms	Urgent microscopy and culture should be arranged and antibiotic treatment should be started. When urgent microscopy is not available, a urine sample should be sent for microscopy and culture, and antibiotic treatment should be started.
If the symptoms are non-specific to UTI	• For an infant or child with a high risk of serious illness: the infant or child should be urgently referred to a paediatric specialist where a urine sample should be sent for urgent microscopy and culture. Such infants and children should be managed in line with 'Feverish illness in children' (NICE clinical guideline 47). • For an infant or child with an intermediate risk of serious illness: if the situation demands, the infant or child may be referred urgently to a paediatric specialist. For infants and children who do not require paediatric specialist referral, urgent microscopy and culture should be arranged. Antibiotic treatment should be started if microscopy is positive (see Table 4.19). When urgent microscopy is not available, dipstick testing may act as a substitute. The presence of nitrites suggests the possibility of infection and antibiotic treatment should be started (see Table 4.18). In all cases, a urine sample should be sent for microscopy and culture. • For an infant or child with a low risk of serious illness: microscopy and culture should be arranged. Antibiotic treatment should only be started if microscopy or culture is positive.

* Assess the risk of serious illness in line with 'Feverish illness in children' (NICE clinical guideline 47) to ensure appropriate urine tests and interpretation, both of which depend on the child's age and risk of serious illness.

Table 4.18 Urine-testing strategies for children 3 years or older

Dipstick testing for leucocyte esterase and nitrite is diagnostically as useful as microscopy and culture, and can safely be used.	
If both leucocyte esterase and nitrite are positive	The child should be regarded as having UTI and antibiotic treatment should be started. If a child has a high or intermediate risk of serious illness and/or a history of previous UTI, a urine sample should be sent for culture.
If leucocyte esterase is negative and nitrite is positive	Antibiotic treatment should be started if the urine test was carried out on a fresh sample of urine. A urine sample should be sent for culture. Subsequent management will depend upon the result of urine culture.
If leucocyte esterase is positive and nitrite is negative	A urine sample should be sent for microscopy and culture. Antibiotic treatment for UTI should not be started unless there is good clinical evidence of UTI (for example, obvious urinary symptoms). Leucocyte esterase may be indicative of an infection outside the urinary tract which may need to be managed differently.
If both leucocyte esterase and nitrite are negative	The child should not be regarded as having UTI. Antibiotic treatment for UTI should not be started, and a urine sample should not be sent for culture. Other causes of illness should be explored.

Table 4.19 Guidance on the interpretation of microscopy results

Microscopy results	**Pyuria positive**	**Pyuria negative**
Bacteriuria positive	The infant or child should be regarded as having UTI	The infant or child should be regarded as having UTI
Bacteriuria negative	Antibiotic treatment should be started if clinically UTI	The infant or child should be regarded as not having UTI

Indication for culture

Urine samples should be sent for culture:

- in infants and children who have a diagnosis of acute pyelonephritis/upper urinary tract infection
- in infants and children with a high to intermediate risk of serious illness
- in infants and children younger than 3 years
- in infants and children with a single positive result for leucocyte esterase or nitrite
- in infants and children with recurrent UTI
- in infants and children with an infection that does not respond to treatment within 24–48 hours, if no sample has already been sent
- when clinical symptoms and dipstick tests do not correlate.

History and examination on confirmed UTI

The following risk factors for UTI and serious underlying pathology should be recorded:

- poor urine flow
- history suggesting previous UTI or confirmed previous UTI
- recurrent fever of uncertain origin
- antenatally diagnosed renal abnormality
- family history of vesicoureteric reflux (VUR) or renal disease
- constipation
- dysfunctional voiding
- enlarged bladder
- abdominal mass
- evidence of spinal lesion
- poor growth
- high blood pressure.

Clinical differentiation between acute pyelonephritis/upper urinary tract infection and cystitis/ lower urinary tract infection

Infants and children who have bacteriuria and fever of 38 °C or higher should be considered to have acute pyelonephritis/upper urinary tract infection. Infants and children presenting with fever lower than 38 °C with loin pain/tenderness and bacteriuria should be considered to have acute pyelonephritis/upper urinary tract infection. All other infants and children who have bacteriuria but no systemic symptoms or signs should be considered to have cystitis/lower urinary tract infection.

Laboratory tests for localising UTI

C-reactive protein alone should not be used to differentiate acute pyelonephritis/upper urinary tract infection from cystitis/lower urinary tract infection in infants and children.

Imaging tests for localising UTI

The routine use of imaging in the localisation of a UTI is not recommended.

In the rare instances when it is clinically important to confirm or exclude acute pyelonephritis/ upper urinary tract infection, power Doppler ultrasound is recommended. When this is not available or the diagnosis still cannot be confirmed, a dimercaptosuccinic acid (DMSA) scintigraphy scan is recommended.

Research recommendations

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

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.

Further investigation of leucocyte esterase and nitrite dipstick tests alone and in combination, stratified by age and method of urine collection, is required to determine their accuracy in diagnosing UTI.

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

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

5 Acute management

5.1 Antibiotic treatment for symptomatic UTI

Introduction

A variety of antibiotics are used in the UK to treat acute UTI in infants and children. The choice of antibiotic, route of administration and the duration of treatment depend upon on a combination of clinical presentation and local sensitivity patterns. The aim is to eradicate the infection, relieve symptoms and minimise the development of renal parenchymal defects. Oral antibiotics and shorter courses are generally more convenient for patients, have fewer risks and adverse effects and are less costly. In addition, appropriate use of antibiotics is likely to result in the development of less resistance to antibiotics in the community. This chapter aims to summarise the different considerations underlying the administration of antibiotics for the management of a first-time urinary tract infection and to develop the best possible advice on safe and effective treatment for infants and children based the points above.

Studies that were published more than 20 years ago have not been included as evidence in this chapter as antibiotics then used and sensitivities do not reflect the current UK practice.

Previous guideline

In the RCP guideline, it was stated that after an appropriate urine specimen has been collected treatment should be started immediately, especially in infants and children younger than 2 years.[190]

In a national audit of the guideline, 89% of 422 infants and children younger than 2 years diagnosed with a UTI in hospital received appropriate treatment with a suitable antibiotic, which generally started within a few hours of urine collection. However, 11% had no record of any treatment or follow-up. Additionally, the diagnosis of UTI was not made in 50% of infants and children with positive urine culture.[23] These infants and children also did not receive appropriate treatment.

Clinical questions

In infants and children with UTI, which is the most effective antibiotic treatment?

In infants and children with suspected UTI, how does oral antibiotic treatment compare with intravenous antibiotic treatment?

5.1.1 Oral antibiotic treatment for cystitis/lower urinary tract infection

Review findings – various antibiotics

Three RCTs were identified comparing various oral antibiotic treatments for children with UTI.[195–197]

An RCT conducted in Israel randomised 94 children aged 6 months to 13 years with symptoms of UTI to oral cefixime (8 mg/kg/day) or oral trimethoprim/sulfamethoxazole (8/40 mg/kg/day), for 7 to 10 days.[195] Peripheral white blood cell (WBC) counts, erythrocyte sedimentation rate (ESR), body temperature and urinalysis returned to normal at the same rate in both groups. [EL = 1+]

Two other RCTs, albeit at EL 1–, reached the same conclusions. The two RCTs were graded 1– owing to large numbers of children lost to follow-up. One in the USA randomised 125 children aged 6 months to 12 years with uncomplicated UTI to receive oral trimethoprim (10 mg/kg/day) or oral trimethoprim/sulfamethoxazole (8/40 mg/kg/day) for 10 days. Fewer than 50% of children were evaluated,[196] but there were no differences in bacteriological outcome ($P = 0.55$) or clinical response (equivalent) between the treatments. [EL = 1–]

Review findings – various durations

A Cochrane review included ten RCTs comparing short (2–4 days) with standard (7–14 days) duration of the same oral antibiotic in infants and children aged 3 months to 18 years with mild to moderate UTI. Overall, no significant differences were found in persistence of clinical symptoms, persistence of bacteriuria, recurrent UTI, compliance with medication or development of resistance.[198] [EL = 1+]

Persistence of clinical symptoms

One study comparing cefuroxime 125 mg twice daily for 2 days versus 10 days reported the outcome of symptomatic UTI. Symptoms persisted in three of 12 children after 2 days of treatment and none of 13 children following 10 days. However, the authors did not state on what day assessment of symptoms was made.

Persistence of significant bacteriuria

There were no significant differences in the frequency of bacteriuria at 0–10 days after completing treatment (RR 1.06; 95% CI 0.64 to 1.76). Subgroup analysis revealed that the treatment effects of antibiotics containing sulphonamides (alone or in combination with trimethoprim) did not differ (RR 0.80; 95% CI 0.45 to 1.41), nor did other antibiotics not containing sulphonamides (RR 1.72; 95% CI 0.64 to 3.80). Two studies included 60/159 children with abnormal imaging on IVU or MCUG. Children with abnormal imaging did not differ in their response (RR 0.71; 95% CI 0.38 to 1.32) when compared with children with normal imaging (RR 0.99; 95% CI 0.12 to 8.56).

Recurrent UTI and development of resistant organisms

Overall, there were no significant differences in the number of UTIs at 1–15 months of follow-up (RR 0.95; 95% CI 0.70 to 1.29). Subgroup analysis revealed that recurrence of UTI did not differ between antibiotic groups for antibiotics containing sulphonamides (RR 0.96; 95% CI 0.64 to 1.44), nor other antibiotics not containing sulphonamides (RR 0.93; 95% CI 0.53 to 1.61). One study found no significant differences between short and standard duration therapy for urinary pathogens resistant to the treating antibiotic (RR 0.57; 95% CI 0.32 to 1.01) and three studies found no significant difference for recurrent UTI (RR 0.39; 95% CI0.12 to 1.29).

Evidence statement – oral antibiotic treatment for cystitis/lower urinary tract infection

There are no differences between short duration (2–4 days) and longer duration (7–14 days) of antibiotic treatment for children with cystitis/lower urinary tract infection. Few studies, small sample sizes and wide confidence intervals could indicate imprecision.

5.1.2 Antibiotic treatment for acute pyelonephritis/upper urinary tract infection

Review findings – choice of antibiotic

A systematic review[199] identified four RCTs comparing the effectiveness of various IV antibiotic treatments for children with acute pyelonephritis/upper urinary tract infection. These studies were unable to be pooled as they each investigated different IV antibiotics, and so are reported individually. [EL = 1+]

The first RCT involved 20 children and compared 14 day IV cefotaxime (25 mg/kg/day) to 7 day IV amoxicillin/clavulanic acid (25 mg/kg/day) followed by 7 day oral amoxicillin/clavulanic acid (50 mg/kg/day).[200] The study numbers were small but showed no significant differences between the treatment groups for bacteriuria, recurrent infection, persistent fever or gastrointestinal adverse events. Two children treated with cefotaxime had persistent bacteriuria at 48 hours. Two children treated with cefotaxime had persistent fever at 48 hours. Three children treated with amoxicillin/clavulanic acid had adverse gastrointestinal effects.

The second RCT involved 299 children and compared IV cefepime (50 mg/kg/day) till afebrile for 48 hours with IV ceftazidime (50 mg/kg/day) till afebrile for 48 hours, both followed by oral trimethoprim/sulfamethoxazole for 10–14 days.[201] There were no significant differences between the treatment groups in the number of children with persistent bacteriuria (RR 3.05; 95% CI 0.13 to 74.16), the occurrence of an unsatisfactory clinical response (RR 0.68; 95% CI 0.12 to 4.02), or in adverse events (RR 1.12; 95% CI 0.76 to 1.63).

The third RCT involved 100 children and compared IV cefotaxime with IV ceftriaxone in children 24 months or older.[202] There were no significant differences between the treatment groups for bacteriuria at the end of treatment (RR 0.87; 95% CI 0.37 to 2.03), recurrent infection at 1 month (RR 0.68; 95% CI 0.30 to 1.50) or adverse events (RR 0.67; 95% CI 0.12 to 3.82). *Post hoc* analysis revealed no differences between children with and without abnormalities on imaging studies of the urinary tract at 1 month after the therapy.

The fourth RCT involved 16 children and compared the aminoglycosides isepamicin and amikacin.[203] There were no significant differences between the treatment groups for bacteriuria or resolution of fever.

Review findings – duration of antibiotic therapy (IV followed by oral)

The same review[199] identified a number of studies which examined the duration of IV therapy. Four trials involving 480 children compared oral with IV administration after an initial 3–4 days of IV therapy for both groups. Two trials compared IV ceftriaxone (3–4 days) followed by oral cefixime or ceftibuten with IV ceftriaxone (10 days). [EL = 1+]

One trial compared IV temocillin (3 days) followed by oral amoxicillin or amoxicillin/clavulanic acid with IV temocillin (7 days). The fourth trial compared IV cefotaxime (4 days) followed by oral amoxicillin/clavulanic acid with IV cefotaxime (14 days).

Two of these trials also converted the IV group to oral therapy after 7–10 days to complete 15–21 days of treatment. In the three trials where persistent bacteriuria was reported, only one patient had persistent bacteriuria.

There was no significant difference between the two groups for recurrent UTI within 6–12 months (four trials: RR 1.15; 95% CI 0.52 to 2.51) or in the number of persisting renal parenchymal defects seen on DMSA scan at 3–6 months (three trials: RR 0.99; 95% CI 0.72 to 1.37).

Post hoc subgroup analysis showed that the number of children with persisting renal parenchymal defects on DMSA scan did not differ between those with VUR (two trials: RR 0.99; 95% CI 0.56 to 1.74) and without VUR (two trials: RR 1.19; 95% CI 0.81 to 1.76) and those younger than 1 year (one trial: RR 1.46; 95% CI 0.71 to 3.01) and 1 year or older (one trial: RR 0.89; 95% CI 0.59 to 1.34).

Duration of hospitalisation was 4.9 days for the IV and oral group compared with 9.8 days for the IV group.

Three studies comparing single-dose IV antibiotics with oral antibiotics were also included. Two studies used antibiotics licensed for children in the UK and compared single-dose IV antibiotics (one trial IV gentamicin, one trial IV cefotaxime) with oral antibiotics given for 7–10 days in 61 children. There were no significant differences in persistent bacteriuria following treatment (RR 1.73; 95% CI 0.18 to 16.30) or recurrent UTI within 6 weeks (RR 0.24; 95% CI 0.03 to 1.97)

Review findings – IV versus oral

A systematic review[199] identified two studies comparing 10–14 days of oral antibiotics (cefixime or amoxicillin/clavulanic acid) with IV ceftriaxone for 3 days until defervescence, followed by oral antibiotics in 693 children with acute pyelonephritis/upper urinary tract infection. [EL = 1+]

Overall, there were no significant differences between the groups in the time to fever resolution (WMD (hours) 1.54; 95% CI –1.67 to 4.76), the rate of symptomatic recurrences within 6 months (RR 0.67; 95% CI 0.27 to 1.67) or the rate (RR 1.45; 95% CI 0.63 to 3.03). [EL = 1++]

Review findings – switch therapy

Switch therapy most often consists of IV therapy initially, followed by a switch to oral antibiotics as quickly as possible. The rationale behind switch therapy is considerable cost savings both to the patients and to the healthcare system, including decreasing the complications of IV therapy and decreasing the costs of administering antibiotics. Initiation of IV antibiotic therapy when patients are admitted to the hospital assures maximal care for those with serious infection. However, as the antibiotics takes effect and symptoms subside, usually within 72 hours, most patients are able to take oral medications.

A systematic review[199] identified four RCTs investigating short-duration IV antibiotics followed by oral therapy compared with longer duration IV antibiotics. [EL = 1+]

The first RCT involved 36 children and compared IV ceftriaxone followed by oral ceftibuten 24–48 hours after defervescence (total duration 10 days) with 10 day IV ceftriaxone (the children in the first group were discharged after switching to oral antibiotics).[204] There were no significant differences between the treatment groups in persistent renal damage, recurrence, persistence of bacteriuria or adverse events.

The second RCT involved 229 children and compared 3 day IV ceftriaxone followed by 12 day oral cefixime with 10 day IV ceftriaxone followed by 5 day oral cefixime.[205] There were no significant differences between the treatment groups in persistent renal damage or recurrence.

The third RCT involved 147 children and compared 4 day IV ceftriaxone and IV netilmicin followed by oral cefixime alone for 6 days with 4 day IV ceftriaxone and IV netilmicin followed by IV ceftriaxone alone for 6 days.[206] There were no significant differences between the treatment groups in persistence of bacteriuria, recurrence or adverse effects.

The fourth RCT involved 87 children and compared 3 day IV temocillin followed by 18 day oral treatment (amoxicillin or amoxicillin plus clavulanic acid) with 7 day IV temocillin followed by 14 day oral treatment.[207] Both groups remained in hospital for the initial 7 days. There were no significant differences between the treatment groups in persistence of bacteriuria, recurrence or persistent renal damage. Temocillin is not licensed for use in children in the UK.[208]

Overall, the systematic review found no significant differences between the treatment groups for recurrent UTI within 6–12 months (RR 1.15; 95% CI 0.52 to 2.51), persisting renal parenchymal defects seen on DMSA at 3–6 months (RR 0.99; 95% CI 0.72 to 1.37) or adverse effects (gastrointestinal upset) (RR 1.29; 95% CI 0.55 to 3.05).

An additional RCT[209] was identified comparing IV amikacin or gentamicin with ampicillin for 7–10 days with IV ceftriaxone for 2 days followed by oral cefixime for 8 days. There was no significant difference between the groups for the rate of response clinically or microbiologically.

Review findings – intramuscular antibiotics versus oral antibiotics

A systematic review[199] identified one RCT investigating one dose of intramuscular (IM) antibiotic therapy and oral therapy compared with oral antibiotic therapy alone. One additional RCT was identified[210] that investigated one dose IM amikacin compared with 10 days of oral antibiotic therapy. [EL = 1+]

A systematic review[199] identified one trial involving 69 febrile children with acute pyelonephritis/upper urinary tract infection and compared one dose IM ceftriaxone and 10 day oral trimethoprim/sulfamethoxazole with 10 day oral trimethoprim/sulfamethoxazole alone.[211] There were no significant differences in persistence of bacteriuria at 48 hours (RR 0.77; 95% CI 0.19 to 3.20), persistence of symptoms (RR 0.82; 95% CI 0.24 to 2.81) or adverse events (RR 1.37; 95% CI 0.33 to 5.86).

Review findings – dosing regimens

Aminoglycosides are antibiotics that are administered parenterally to treat serious bacterial infections including UTI in children. Single daily dosing of aminoglycosides is possible because of their rapid concentration-dependent killing and post-antibiotic effect and has the potential for decreased toxicity.

A systematic review[199] identified three studies investigating dosing regimens of IV aminoglycoside therapy in 495 children with acute pyelonephritis/upper urinary tract infection. [EL = 1+] Two studies investigated once-daily dosing compared with eight-hourly dosing of IV gentamicin[212,213] [EL = 1+] and one study investigated IM netilimicin.[214] [EL = 1+]

Overall, the systematic review found no significant differences between the treatment groups for persisting bacteriuria 1–3 days after commencing treatment (RR 1.98; 95% CI 0.37 to 10.53), increase in serum creatinine during treatment (RR 0.75; 95% CI 0.20 to 2.82) or hearing impairment following treatment (RR 2.83; 95% CI 0.33 to 24.56).

The first RCT involving 172 children compared once-daily IV gentamicin with IV gentamicin administered three times daily.[212] In addition to the pooled results, there were no significant differences between the treatment groups in time to defervescence (WMD (hours) 2.40; 95% CI −7.2 to 12.72) or renal parenchymal damage at 3 months (OR 0.66; 95% CI 0.32 to 1.36).

The second RCT involving 179 children compared once-daily IV gentamicin with IV gentamicin three times a day.[213] In addition to the pooled results, there were no significant differences between the treatment groups in persistent bacteriuria 3 days following treatment (RR 1.98; 95% CI 0.37 to 10.53) or time to defervescence ($P = 0.6$). Mean time to defervescence was 27 hours (IQR 15 to 48 hours) with daily dosing and 33 hours (IQR 12 to 48 hours) with eight-hourly dosing.

The third RCT involving 144 children compared once-daily IM netilmicin with IM netilmicin three times a day.[214] In addition to the pooled results, there were no significant differences between the groups in persistent bacteriuria 1 week after treatment (RR 2.84; 95% CI 0.12 to 68.57) or re-infection 1 month following treatment (RR 1.18; 95% CI 0.33 to 4.23).

Evidence statement – antibiotic treatment for acute pyelonephritis/upper urinary tract infection

IV and oral antibiotics
The evidence suggests that all antibiotics compared were equivalent.

IM
The available evidence indicates no difference between 1 or 2 day therapy with IM aminoglycosides or cephalosporins compared with oral antibiotics for treating children with acute pyelonephritis/upper urinary tract infection.

Switch
Short duration of IV antibiotics followed by oral therapy (switch therapy) is safe and as effective as longer duration of IV antibiotics for treating severe UTI.

Dosage
There appears to be no difference between once or three times daily dosing of IV gentamicin and IM netilmicin for treating children with UTI.

5.2 Symptomatic treatment

Clinical question
In infants and children with UTI, which is the most effective symptomatic treatment in addition to antibiotics?

5.2.1 Cranberry

Overview of available evidence
A systematic review[215] did not identify any studies evaluating cranberry products in any age group for treating UTI. No further studies were identified investigating cranberry juice or cranberry products for treating first-time UTI in infants or children.

5.2.2 Other symptomatic treatment

Overview of available evidence
No studies were identified that investigated other symptomatic treatment as a monotherapy or in addition to antibiotics in infants or children with UTI.

5.3 GDG translation on antibiotic treatment during acute phase and recommendations

There appear to be no differences between individual antibiotics. This could be due to the limited data available or because all antibiotics included in studies were appropriate for treating UTI and showed equivalent outcomes. Clinicians have been guided by local policies and guidance from the local microbiology laboratory where resistance patterns have been monitored. Some of the older studies have used antibiotics that are no longer available.

Conventional treatment for children with acute pyelonephritis/upper urinary tract infection in some countries has been a 7–14 day course of antibiotics, although, in the UK, duration of 7–10 days of antibiotics is currently the most common. The theoretical benefits of shorter courses of antibiotics, in children who are systemically well, include improved compliance, decreased antibiotic-related adverse effects and diminished emergence of resistant organisms, although none of these benefits was observed in any of the above studies. There was no study that investigated optimal duration of antibiotic treatment for acute pyelonephritis/upper urinary tract infection, and the available evidence is not sufficient to make concrete recommendations for duration of antibiotics. In the light of balance between possible risks and benefits described above, the GDG chose the current UK practice of 7–10 days.

There is no difference in outcomes for children treated for cystitis/lower urinary tract infection with short-duration antibiotics compared with long-duration antibiotics, so short-duration treatment should be used for the treatment of cystitis/lower urinary tract infection. The evidence does not provide guidance as to which antibiotics are most useful but a choice from trimethoprim, nitrofurantoin, a first-generation cephalosporin or amoxicillin for oral use would be supported by available evidence and current clinical practice.

For acute pyelonephritis/upper urinary tract infection, IV co-amoxiclav or a third-generation cephalosporin such as cefotaxime or ceftriaxone would be supported by available evidence and current clinical practice.

In the UK, IM injections are rarely used in current practice but have a role in circumstances where oral or IV therapy is not tolerated.

Recommendations on acute management

Note that the antibiotic requirements for infants and children with conditions that are outside the scope of this guideline (for example, children already known to have significant pre-existing uropathies) have not been addressed and may be different from those given here.

Infants and children with a high risk of serious illness should be referred urgently to the care of a paediatric specialist.

Infants younger than 3 months with a possible UTI should be referred immediately to the care of a paediatric specialist. Treatment should be with parenteral antibiotics in line with 'Feverish illness in children' (NICE clinical guideline 47).

For infants and children 3 months or older with acute pyelonephritis/upper urinary tract infection:

- Consider referral to secondary care.
- Treat with oral antibiotics for 7–10 days. The use of an oral antibiotic with low resistance patterns is recommended, for example cephalosporin or co-amoxiclav.
- If oral antibiotics cannot be used, treat with an intravenous (IV) antibiotic agent such as cefotaxime or ceftriaxone for 2–4 days followed by oral antibiotics for a total duration of 10 days.

For infants and children 3 months or older with cystitis/lower urinary tract infection:

- Treat with oral antibiotics for 3 days. The choice of antibiotics should be directed by locally developed multidisciplinary guidance. Trimethoprim, nitrofurantoin, cephalosporin or amoxicillin may be suitable.
- The parents or carers should be advised to bring the infant or child for reassessment if the infant or child is still unwell after 24–48 hours. If an alternative diagnosis is not made, a urine sample should be sent for culture to identify the presence of bacteria and determine antibiotic sensitivity if urine culture has not already been carried out.

For infants and children who receive aminoglycosides (gentamicin or amikacin), once-daily dosing is recommended.

If parenteral treatment is required and IV treatment is not possible, intramuscular treatment should be considered.

If an infant or child is receiving prophylactic medication and develops an infection, treatment should be with a different antibiotic, not a higher dose of the same antibiotic.

Asymptomatic bacteriuria in infants and children should not be treated with antibiotics.

Laboratories should monitor resistance patterns of urinary pathogens and make this information routinely available to prescribers.

6 Long-term management

6.1 Long-term impact of UTI

Introduction

The aim of long-term management is to reduce the risk of further UTIs and any renal damage that might occur as a result. This section evaluates the risk of serious consequences and the effectiveness of long-term strategies in achieving these aims.

Clinical question

In infants and children who have or develop a renal scar, what is the risk of future renal-related morbidity?

Review findings – UTI and established renal failure

Six case series studies of future renal damage in children were identified, but the quality and study design were not sufficient to answer the question. The studies identified are summarised below.[38,72,84,94,112,216]

A Swedish study[38] found that non-obstructive pyelonephritis was not the cause of chronic renal failure in any children studied and a similar study carried out in the USA[216] showed that 1.9% of children with established renal failure (ERF) had a previous UTI. An additional Swedish study[94] investigating radiological progression of kidney damage as assessed by renal parenchymal defects from childhood to adulthood found that one-third of kidneys had progressed.

Two Swedish studies investigated kidney growth. One study[112] found that children with early onset of pyelonephritis (before 3 years of age) had a low capacity for early compensatory hypertrophy compared with patients with late-onset pyelonephritis and the second study[84] found that in children with unilateral renal parenchymal defects the growth of the contra-lateral kidney, judged from its parenchymal area, appeared to compensate well for the loss of parenchyma in the one with renal parenchymal defects.

One additional case series study was identified that was of good quality and included data from ten countries.

A multicentre case series study in ten countries investigated the incidence of permanent renal damage in 269 children with acute pyelonephritis/upper urinary tract infection.[88] Of these, 152/269 (57%) had first-time UTI while 117/269 (43%) had recurrent UTI, and 150/269 (56%) children had VUR of which 101/234 (43%) renal units had Grades III–V VUR.

Overall, permanent renal damage developed more often in children with recurrent UTI (73% versus 56% with first-time UTI; $P = 0.004$), with non-*E. coli* infection (86% versus 57% with *E. coli*; $P < 0.0001$), in children 5 years or older (75% versus 36% of children younger than 1 year; $P < 0.001$ – but did not differ between children aged between 1 and 5 years or children 5 years or older); in children who had VUR (72% versus 52% without VUR; $P < 0.001$) or in children with high grades of VUR (77% versus 61% of children with low-grade VUR; $P = 0.01$). There were no differences between boys (64%) and girls (64%).

Boys with permanent renal damage were more likely to have a non-*E. coli* infection (81% versus 57%; $P = 0.01$), to be 5 years or older compared with boys younger than 1 year (83% versus 47%; $P = 0.002$), to have VUR (76% versus 45%; $P < 0.001$) and to have high-grade VUR (83% versus 57%; $P = 0.02$). There were no differences in permanent renal damage with respect to first-time or recurrent UTI in boys.

Girls with permanent renal damage were more likely to have recurrent UTI compared with first-time UTI (72% versus 52%; $P = 0.01$) and to have non-*E. coli* infection compared with an *E. coli* infection. There were no differences among girls with respect to age or presence or grade of VUR. [EL = 3]

NCC-WCH analysis

It was previously believed that there was a high risk of a first-time childhood UTI progressing to clinically significant long-term kidney damage. In investigating the relationship between UTI and long-term damage, the primary concern is with ERF, as the relationship between UTI and other related morbidities is not measurable. Frequency of kidney damage resulting from VUR alone or in combination with UTI is uncertain.

One study estimated that between 10 000 and 15 000 girls would need to be investigated to prevent a single case of ERF.[217] This level of risk was much lower than previously believed. It was found that the estimated risk stated above was based on annual incidence of ERF in the population, rather than cumulative incidence. This resulted in a significant underestimate of risk based on the assumptions used in this study. Further evidence examining the link between childhood UTI and ERF was sought.

Based on analysis undertaken for this guideline, estimates of the risk of developing long-term morbidities following a UTI range from 1/155 to 1/10 000. However, it was found that evidence from renal registries and published estimates showed that the true risk of ERF developing as a result of UTI in childhood is highly uncertain; information from registries is often not specific about the cause of ERF. UTI in childhood often goes undiagnosed (see Appendix C), making it difficult to arrive at an accurate estimate of the true risk.

Given the degree of uncertainty around the key assumptions and data used by the Stark study considered above,[217] no reliable estimate of the risk of UTI leading to ERF can be calculated. The true rate of ERF caused by UTI is unclear. Without reliable estimates of these figures, as well as of lifetime risk, the level of uncertainty in the model in Appendix C is such that no reliable conclusions can be drawn based on the published data alone.

Effectiveness of interventions

The effectiveness of interventions was reviewed and included in acute management (Chapter 5) and the surgical section below (Section 6.5).

Evidence statement – long-term impact of UTI and renal damage

Based on analysis undertaken for this guideline, estimates of the risk of developing ERF following a UTI range from 1/155 to 1/10 000. No high-quality studies were identified that estimated the risk of childhood UTI leading to renal damage or ERF.

6.2 Prevention of recurrence

6.2.1 Introduction

Background

Recurrent UTI is associated with morbidity and all opportunities to prevent it should be explored. Children who have experienced the debilitating and painful effects of UTI and their carers will welcome strategies that can identify predictors and prevent recurrence. While there is still much to be discovered regarding the long-term effects of UTI, there is no question that individual infections are unpleasant and often result in time missed from school, which with recurrence can have a detrimental effect on learning. This section attempts to define predictive factors for recurrent UTI and explore strategies excluding antibiotics that prevent recurrence.

Current strategies often incorporate behaviour modification which is not dependent upon costly interventions. Other strategies include regular drinks of cranberry juice or reducing caffeinated and high-sugar drinks. There is a wide variation in the policies and implementation of strategies used in the prevention of recurrent UTIs. This may reflect differing healthcare systems.

Clinical questions

How should infants and children with recurrent UTI be managed?

What strategies other than antibiotics are helpful in preventing recurrence?

6.2.2 Factors relating to recurrence

Review findings – prediction of future UTI

Eight studies were identified which investigated factors predicting future UTIs in children who had a previous UTI.[72,218–225]

A US cohort study evaluated the relationship between early UTI, VUR and dysfunctional elimination syndrome (DES):[218] 123 questionnaires were completed (73% response rate) for children in the UTI cohort aged 4.3–10 years who had a first-time UTI when younger than 2 years and 125 questionnaires were completed (31% response rate) in the comparison cohort of children who were investigated for fever and who had a negative urine culture during the same period. The groups were similar with respect to demographic and clinical characteristics. The prevalence of DES did not differ between children with UTI and children without (22% versus 21%; $P = 0.82$). In children with UTI, the prevalence of DES did not differ in children with or without VUR (18% versus 25%; $P = 0.52$). Further analysis using different cut-off values did not yield different results.

Thirty-one children had recurrent UTI. Of these, 13 (43%) had encopresis (OR 2.5; 95% CI 1.1 to 5.4; $P = 0.03$), 11 (36%) had DES (OR 2.2; 95% CI 0.99 to 5.0; $P = 0.05$) and 17 (55%) had VUR (OR 2.2; 95% CI 0.9 to 5.0; $P = 0.07$). The only variable that remained significant with recurrent UTI was encopresis ($P = 0.03$). [EL = 2+]

An Australian cohort study evaluated the risk factors that predispose to recurrent UTI in children younger than 6 years presenting at a children's hospital with symptomatic UTI and the role of recurrent UTI in the development of a renal parenchymal defect.[72] At 1 year, 261 (90%) children were evaluated (133 girls and 157 boys). There were 46 recurrent UTIs in 34 children during 12 months of follow-up: 20 children had one recurrence and 14 had two or more recurrences. At the initial UTI, VUR was found in 83/290 (29%) of children and renal parenchymal defects in 113/290 (39%).

In multivariable analysis, recurrence was not associated with gender ($P = 0.08$), fever ($P = 0.59$), VUR ($P = 0.50$), intrarenal VUR ($P = 0.54$), bilateral VUR (0.6) or abnormal initial DMSA ($P = 0.32$). Age younger than 6 months at the time of first UTI (OR 2.9; 95% CI 1.4 to 6.2; $P < 0.01$) and dilating VUR (OR 3.6; 95% CI 1.5 to 8.3; $P < 0.001$) were significant predictors for recurrence.

VUR

VUR was present in 14/34 (41%) with recurrent infection and 65/256 (27%) without recurrent infection. Comparison between groups showed that the presence of VUR was not associated with recurrent infection ($P < 0.05$) but the grade of VUR ($\chi^2 = 12.1$; $P < 0.01$), bilateral VUR ($\chi^2 = 6.1$; $P < 0.05$) and intrarenal VUR ($\chi^2 = 5.2$; $P < 0.05$) were significantly associated with recurrence. High-grade VUR (Grades III–V) was an independent predictor of recurrence (OR 3.6; 95% CI 1.5 to 8.3; $P < 0.001$)

Renal scarring

Repeat DMSA was performed in 173 children at 1 year. Recurrent UTI was significantly associated with renal parenchymal defects seen on first UTI ($\chi^2 = 4.6$; $P < 0.05$) and there was a significant linear trend in the proportion of children with recurrent UTI with increasing grade of DMSA abnormality on entry (χ^2 trend = 9.6; df = 1; $P < 0.01$). Recurrent UTI was also significantly associated with DMSA abnormalities at 1 year ($\chi^2 = 11.5$; $P < 0.001$) and recurrent febrile UTI was significantly associated with DMSA abnormalities at 1 year ($\chi^2 = 10.1$; $P < 0.001$). [EL = 2++]

A case–control study (90 cases, 45 controls) conducted in Switzerland evaluated the role of family history, infrequent voiding, poor fluid intake, functional stool retention and inadequate anogenital hygiene or toilet habits in girls with three or more recurrent UTIs.[219] Of the 90 cases, 60 girls had a history of lower UTI and the remaining 30 had history of mixed UTI, upper in 16 and both upper and lower in 14.

Family history of UTI (42% of cases versus 11% of controls; $P < 0.001$), behavioural abnormalities (81% versus 56%; $P < 0.01$), infrequent voiding (54% versus 24%; $P < 0.001$), poor fluid intake (53% versus 16%; $P < 0.001$) and functional stool retention (30% versus 13%; $P < 0.05$)

were more frequent in girls with recurrent infection than in controls. There were no significant differences between cases and controls for anogenital hygiene or toilet habits. [EL = 2+]

A cross-sectional study conducted in Turkey surveyed the incidence of idiopathic hypercalciuria in 75 children (62 girls and 13 boys) with recurrent UTI.[220] Hypercalciuria was found in 32 children (43%), of whom 23 (72%) were girls and 9 (28%) were boys. Hypercalciuric children were younger (7.2 ± 2.1 years versus 8.7 ± 2.9 years; $P = 0.01$) and had a higher mean calcium/creatinine ratio (0.50 ± 0.21 versus 0.10 ± 0.04; $P = 0.01$) than normocalciuric children. There were no significant differences between groups for voiding dysfunction, pain, haematuria, urolithiasis, family history of urolithiasis or predisposing urinary tract abnormality. [EL = 3]

A cross-sectional study from the USA evaluated the rate of and potential risk factors for recurrent UTI in infants younger than 6 months with UTI and no abnormality on radiographic evaluation.[221] Follow-up data was available for 84 infants (52 girls and 32 boys) and the mean follow-up period was 4.4 years (range 1.9–7.0 years). Sixteen of 84 (19%) had at least one febrile UTI after the negative radiographic evaluation. There were no statistically significant risk factors for recurrent UTI, breastfeeding (less than 4 months) ($P = 0.08$), siblings younger than 14 years ($P = 0.68$), family history of UTI ($P = 0.33$), potty training (less than 2 years) ($P = 0.64$), neurological problems ($P = 0.69$), undiagnosed fevers ($P = 0.08$), constipation history ($P = 0.71$), residence (live in private house) ($P = 0.60$), income less than $50 000 ($P = 0.34$) or circumcision ($P = 0.84$). [EL = 3]

A cross-sectional study conducted in Belgium investigated the possible relationship between recurrent UTI and methods of potty training by comparing the methods used in children with and without recurrent UTI.[222] 4332 questionnaires were completed in children attending the last 2 years of primary school and were stratified into three groups: children with a single UTI 382 (9%), children with recurrent UTI 132 (3%), and children with no history of UTI 3818 (88%). Overall, girls were more likely to have a UTI than boys ($P < 0.001$) and in children with recurrent UTI more boys (51%) than girls (21%) had their first UTI in the first 2.5 years of life ($P < 0.001$).

In children with daytime wetting, 12% had recurrent infection, compared with 2% of children with recurrent infection in children without wetting ($P < 0.001$).

Children with recurrent UTI were more likely to have faecal soiling (9.1%) compared with children with no UTI (2.5%), nocturia at least once a week (10% versus 3%; $P < 0.001$), and not to have started potty training by 18 months (21% versus 31%; $P < 0.05$).

When an attempt to void was unsuccessful the reaction of parents/carers of children with recurrent UTI compared with children with no UTI was to keep the child on the potty until a void was obtained (11% versus 3%; $P < 0.005$), push or strain (13% versus 7%; $P < 0.001$), or turn on the tap (32% versus 22%; $P < 0.001$). [EL = 3]

A case series from Switzerland evaluated the role of family history, infrequent voiding, poor fluid intake, functional stool retention and inadequate hygiene or toilet habits in girls aged 3.9–18 years (median age 6.5 years) referred to a nephrology clinic for evaluation of three or more symptomatic UTIs.[223] Eighty-eight percent had history of cystitis/lower urinary tract infection. Two hundred and twelve behavioural and functional abnormalities were found in 121 girls and no abnormalities were found in 20/141 (14%) of girls with recurrent UTI. Infrequent voiding was found in 63 (45%), poor fluid intake in 60 (43%), functional stool retention in 30 (21%), inadequate genital hygiene in 27 (19%), dysfunctional voiding in 25 (18%) and bladder overactivity in seven (5%).

Two, three or four concomitant abnormalities were found in 66 girls. Girls without abnormalities were significantly younger than girls with abnormalities ($P < 0.05$). Girls with dysfunctional voiding ($n = 25$) were significantly older than other girls with abnormalities ($P < 0.02$). [EL = 3]

Baseline data from a case–control study conducted in Turkey evaluated 30 children with renal parenchymal defects and 67 children without renal parenchymal defects.[224] Children with renal parenchymal defects were more likely to have recurrent UTIs than children without renal parenchymal defects (6.90 ± 2.45 UTI episodes versus 3.35 ± 1.48 UTI episodes; $P < 0.001$). [EL = 2+]

A matched cohort study conducted in the USA investigated the relationship between pinworm infestation and recurrent UTI in girls, but owing to methodological limitations it should not be used to base recommendations on.[225] Forty-one girls (mean age 5.5 years) referred for evalua-

tion of the urinary tract were compared with 58 girls (mean age 6.4 years) who had no history of urinary, vaginal or pinworm infection. Nine of 41 (22%) girls with recurrent UTI had a positive Scotch tape test compared with 3/58 (5%) of controls, and 31/41 (75%) of girls with recurrent UTI had a positive introital enterics culture compared with 25/58 (43%) of controls. [EL = 2–]

Evidence statement – risk factors for recurrence

Infants younger than 6 months at the time of the first UTI, family history of UTI, dilating VUR, infrequent voiding, poor fluid intake and functional stool retention may be associated with an increased risk of recurrent UTI in children, but evidence is limited. (Table 6.1)

Infrequent voiding, poor fluid intake, functional stool retention, inadequate genital hygiene, dysfunctional voiding and bladder overactivity may coexist to varying degrees.

6.2.3 Non-antibiotic strategies for preventing recurrence

Overview of available evidence

No studies were identified which investigated strategies other than antibiotics for preventing recurrence in infants and children with UTI. Studies were identified about predisposing factors for first-time UTI (see Chapter 4) and for recurrent UTI (see Section 6.3). Consensus recommendations based on these reviews were made.

6.2.4 GDG translation and recommendations

GDG translation

There is little evidence supporting strategies to prevent recurrent UTI. However, clinical experience, combined with this low-level evidence, indicates that a thorough assessment of a child's voiding history, bowel management and hygiene can highlight areas which can be addressed and may be effective in the prevention of further infection. Dysfunctional voiding as discussed in the evidence includes many aspects of bladder malfunction, including a learned ability to delay voiding, resulting in poor emptying and high residual urine volume. This can be addressed by improving opportunities for children to void whenever necessary by providing appropriate and readily accessible toilet facilities, and an environment which assists adequate and timely bladder emptying. An holistic approach incorporating strategies that address all these issues would facilitate the best management for the children and help those who deliver this care.

Table 6.1 Summary factors relating to recurrence

Factor	Study					
	Shaikh (2003)[218]	**Panaretto (1999)[72]**	**Stauffer (2004)[219]**	**Bratslavsky (2004)[221]**	**Bakker (2004)[222]**	**Ece (2005)[224]**
n	123	261	90 cases, 45 controls	84	4322	30
Gender		($P = 0.08$)				
Breastfeeding	—	—	—	$P = 0.08$	—	—
Age under 2.5		$P < 0.01$				
Family history of UTI	—	—	< 0.001	0.325	—	—
Constipation	—	—	—	0.714	—	—
Circumcision	—	—	—	0.841	—	—
Dysfunctional voiding[a]	0.05	—	< 0.001	—	$P < 0.001$	—
Poor fluid intake	—		< 0.001	—	—	—
Functional stool retention/encopresis	0.03	—	$P < 0.05$	—	—	—
Inadequate toilet habits	—	—	NS	—	—	—
VUR	0.07	$P = 0.50$	—	—	—	—
Renal parenchymal defect (on initial DMSA)	—	$P < 0.05$			—	$P < 0.001$

[a] Includes infrequent voiding, nocturia.

Recommendations

Dysfunctional elimination syndromes and constipation should be addressed in infants and children who have had a UTI.

Children who have had a UTI should be encouraged to drink an adequate amount.

Children who have had a UTI should have ready access to clean toilets when required and should not be expected to delay voiding.

(For further advice on infants and children with recurrent UTI, see follow-up section.)

6.3 Antibiotic prophylaxis

Introduction

Antibiotic prophylaxis aims to reduce the risk of recurrent, symptomatic UTIs and the subsequent development of pyelonephritic scarring characterised on imaging as renal parenchymal defects. Repeated episodes of acute UTI can be distressing to children, young people and their parents or carers. There is a widespread belief that prophylaxis effectively prevents or reduces acute symptomatic UTIs and prevents the development of new renal scarring in children with VUR. Consequently, the use of prophylaxis generates an additional need to assess the urinary tract for VUR and renal parenchymal defects in healthy children after recovery from the acute illness. Benefits of prophylaxis must be balanced against any risks and inconvenience. This section aims to examine the rationale and evidence for benefit from the widespread use of prophylaxis which is additional to treatment of acute UTIs.

Current practice

In the RCP guideline, it was stated that a low dose of a suitable antibacterial drug should be continued prophylactically until imaging of the urinary tract has been completed.[21]

In the national audit of the RCP guideline, prophylactic antibiotics were initiated in accordance with the RCP guidelines in the majority of children diagnosed with a UTI.[23]

Clinical questions

In infants and children who have had a UTI, how effective is the use of prophylactic antibiotics?

In infants and children on prophylaxis, what are the indications for changing antibiotic?

Description of included studies

A total of ten trials[71,71,226–233] were identified from the two systematic reviews,[234,235] as well as the search.

A new meta-analysis was conducted by NCC-WCH including all the above RCTs, with a subgroup analysis of different target populations as follows:

1. children with asymptomatic bacteriuria (four trials)[226–229]
2. children who have had UTI without VUR or with a small proportion of children with VUR (four trials)[71,230–232]
3. children with VUR (two trials).[71,233]

Prophylactic antibiotics for children with asymptomatic bacteriuria

Four trials were identified for asymptomatic bacteriuria. The Cardiff–Oxford trial[226] (n = 208) investigated girls with bacteriuria screened from schools, and the intervention was co-trimoxazole or other antibiotics for 1–2 weeks followed by optional 3–12 month therapy, compared with antibiotics for symptomatic episode. The Newcastle trial[227] (n = 252) investigated girls with covert bacteriuria identified from screening of schools, and the intervention was a 2 year course of an antibiotics treatment, compared with antibiotics treatment only for symptomatic episode. The Lindberg[228] trial (n = 61) investigated girls with covert bacteriuria with negative imaging whose bacteriuria was not eliminated for the first 6 months, and the intervention was to give nitrofurantoin for 6 months and the course repeated if bacteriuria still remained, compared with antibiotics treatment for symptomatic episode only. The Savage trial[229] (n = 61) investigated girls aged 5–7 years, and the inclusion criteria were initial UTI by $> 10^5$ cfu/ml on three consecutive

occasions without past history of UTI or unwell. Thirty-one percent of the study population had VUR. The intervention was nitrofurantoin or co-trimoxazole for 10 weeks after 2 week acute treatment, which was compared with no treatment after 2 week acute treatment.

Prophylactic antibiotics for children with symptomatic UTI

Four trials were identified looking at children with symptomatic UTI without VUR or with a small proportion of children with VUR, comparing antibiotic treatment with no antibiotic treatment.[71,230–232]

The Montini trial[230] (*n* = 235) included children aged 1–64 months with 66% girls. The inclusion criteria were clinical diagnosis of acute pyelonephritis/upper urinary tract infection and positive DMSA scan. Forty-three percent had VUR. The trial compared co-trimoxazole for 12 months and co-amoxiclav for 12 months with no prophylaxis.

The Smellie trial[231] (*n* = 45) included children aged 2–12 years with 89% girls, Initial UTI was diagnosed by urine culture, and no child with VUR was included. The three-arm trial compared co-trimoxazole for 6–12 months and nitrofurantoin for 6–12 months with no treatment.

The Stansfeld trial[232] (*n* = 45) included children aged 6 months to 14 years. Twenty-two percent had VUR and 93% were girls. Initial UTI was defined as two or more consecutive, significant and consistent urine cultures accompanied by pyuria. The two-arm trial compared co-trimoxazole for 6 months with placebo for 6 months.

The Garin trial[71] (*n* = 105) included children without VUR aged 3 months to 17 years with 83% girls. The inclusion criteria were documented episode of acute pyelonephritis/upper urinary tract infection in a patient between 3 months and 18 years (fever, pyuria and $> 10^5$ cfu/ml) with positive DMSA scan. The two-arm trial compared sulfamethoxazole/trimethoprim or nitrofurantoin for 12 months after 2 week acute treatment with no prophylaxis after 2 week acute treatment.

Prophylactic antibiotics for children with VUR

Prophylaxis for children with VUR was investigated in two trials.[71,233] The Reddy trial[233] (*n* = 43) included newly diagnosed VUR but no further details were given for inclusion criteria. The three-arm trial compared daily antibiotics for 1 year and three times a week antibiotics for 1 year with no antibiotics. The Garin trial[71] (*n* = 113) included children aged 3 months to 12 years with 81% girls. VUR was diagnosed by using MCUG. The trial compared effectiveness of prophylaxis in documented episode of acute pyelonephritis/upper urinary tract infection (fever, pyuria and $> 10^5$ cfu/ml) with positive DMSA scan between sulfamethoxazole/trimethoprim or nitrofurantoin for 12 months after 2 week acute treatment with no prophylaxis after 2 week acute treatment.

Recurrence of symptomatic UTI

There was insufficient evidence of difference in all of the three subgroup analyses between the intervention and control groups (Figure 6.1). It is interesting to note the difference in outcomes between the two arms of the Garin trial. With the same methodology, one group showed a trend to favour treatment, the other to favour control. There is no obvious biological reason for this difference, which suggests that the trial could not reliably detect a difference between an RR of 0.40 and 1.37.

Prevalence of bacteriuria at the end of prophylaxis

There was evidence of reduction in prevalence of bacteriuria at the end of the study for both children with asymptomatic bacteriuria and symptomatic UTI (Figure 6.2).

Incidence of new or deteriorated renal parenchymal defects

There was no evidence of a difference in incidence of new or deteriorated renal parenchymal defects in any of the groups of children (Figure 6.3).

Evidence statement – prophylactic antibiotics

Evidence is limited owing to heterogeneity of trials. Prophylactic antibiotic treatment reduced bacteriuria based on meta-analysis of eight studies including 1103 patients. There is, however, no high-level evidence of a reduction in the incidence of symptomatic UTI based on meta-analysis of five studies including 539 patients or for renal parenchymal defects based on that of four studies which included 638 patients.

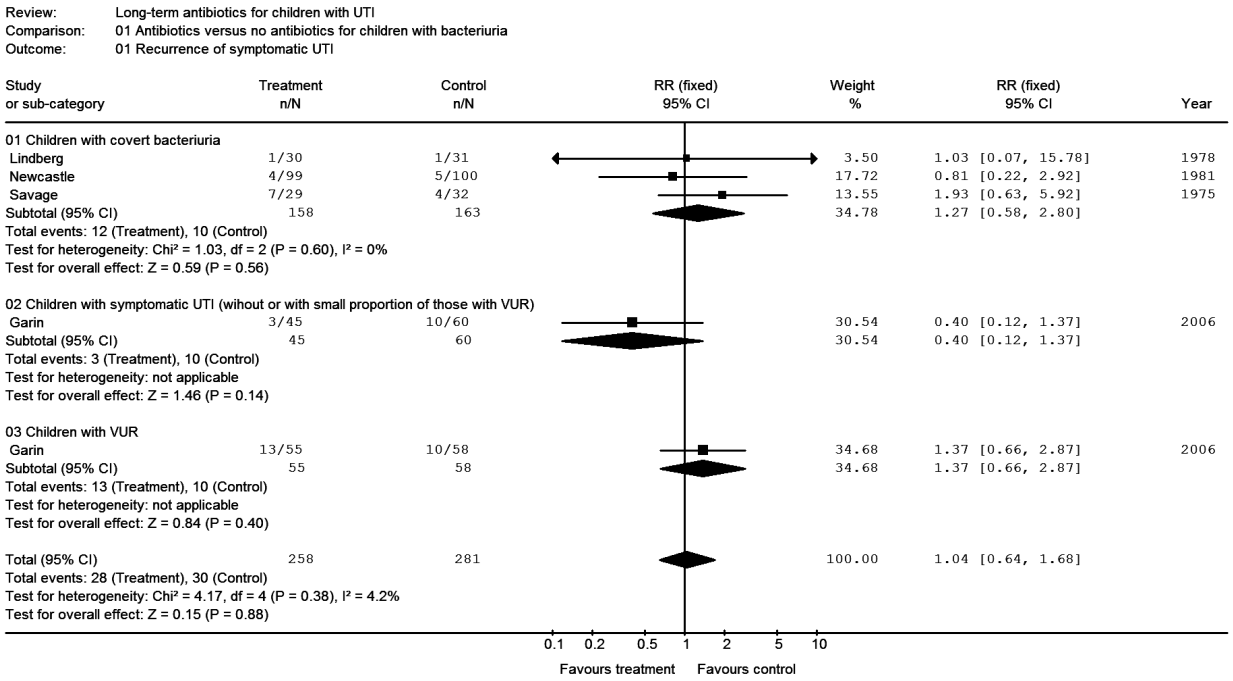


Figure 6.1 Meta-analysis of prophylactic antibiotics (recurrence of symptomatic UTI)

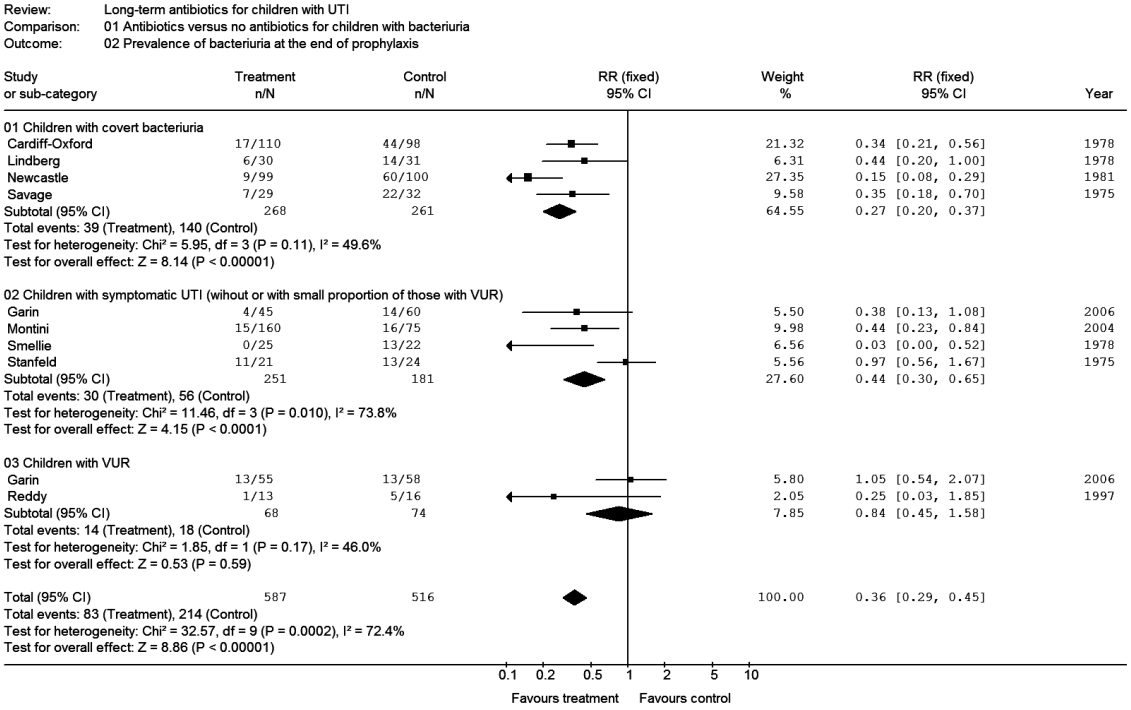


Figure 6.2 Meta-analysis of prophylactic antibiotics (prevalence of bacteriuria at the end of prophylaxis)

GDG translation

Prophylactic antibiotics for symptomatic UTI

While prophylaxis has been commonly used to prevent recurrent UTI, there is no evidence of an effect in reducing the most important outcomes for the patient. Although it is effective in reducing the number of positive urine cultures, there is no benefit through a reduction in the number of symptomatic infections or new renal parenchymal defects. It is inconvenient for the patient,[24] compliance is poor,[266] it carries the risks associated with any medication[267] and patients tend to become colonised with resistant organisms. There is also evidence that widespread use of antibiotics is linked to the development of bacterial resistance in the community.[269]

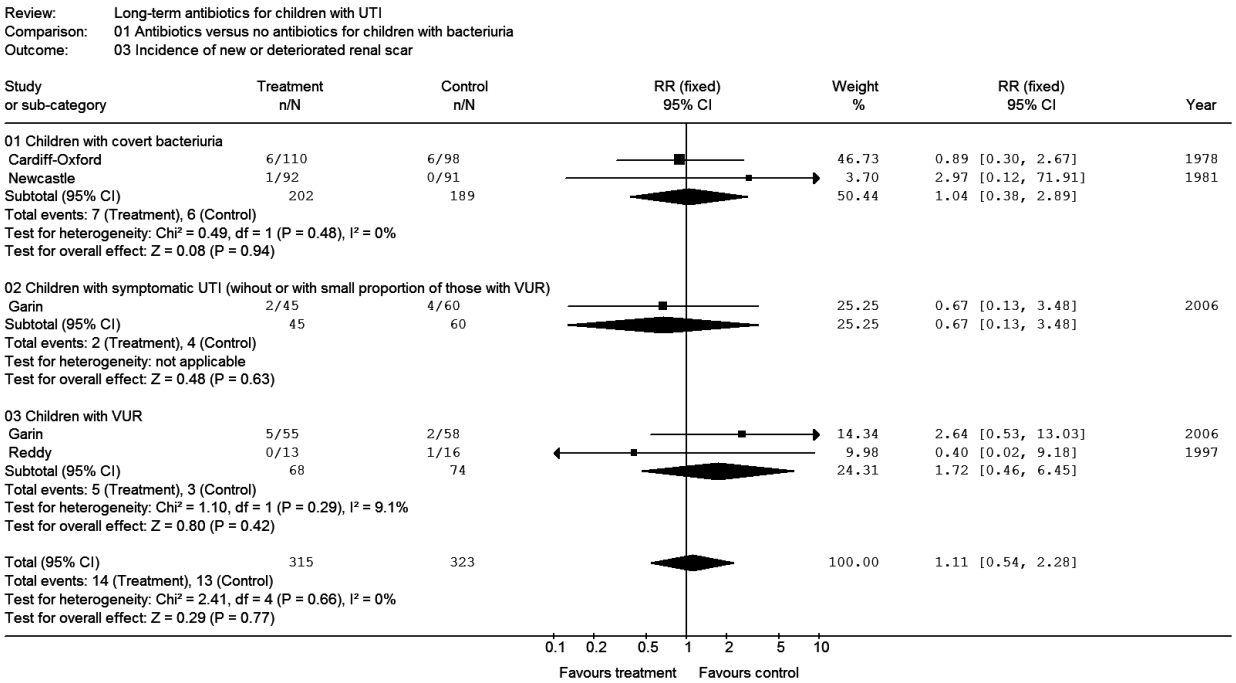


Figure 6.3 Meta-analysis of prophylactic antibiotics (incidence of new or deteriorated renal parenchymal defects)

Since prophylaxis is already in widespread use and is not without risks, disadvantages and costs, there is a case for reducing its use, particularly in healthy children who have recovered from a straightforward UTI. In the event that there are small benefits that might have not been captured in the available evidence, the various drawbacks of this treatment are most likely to outweigh any benefits in children without any identified risk factors such as the majority of children for whom this guideline is intended. There is insufficient evidence to be confident that there is no role for prophylaxis in children with more complex urological conditions beyond the scope of this guideline, and trials in progress may throw further light on this situation.

Asymptomatic bacteriuria in otherwise healthy children

Asymptomatic bacteriuria (ASB) does not present with symptoms but is detected by screening. It is detected in clinical practice when children are followed up after recovery from a UTI and routine urine samples are collected. There are several studies on ASB which describe the risk of VUR and renal parenchymal defects and give information about the natural history. There is relatively good evidence of long-term outcome and influence of treatment from randomised controlled trials. The conclusion from these trials was that there was no evidence of effective prevention of new renal scarring by antibiotic treatment or prophylaxis in children with ASB.

Recommendations

Antibiotic prophylaxis should not be routinely recommended in infants and children following first-time UTI.

Antibiotic prophylaxis may be considered in infants and children with recurrent UTI.

Asymptomatic bacteriuria in infants and children should not be treated with prophylactic antibiotics.

Research recommendations

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.

6.4 Imaging tests

6.4.1 Introduction

The aim of imaging has been to identify children with underlying abnormalities or factors that put them at increased risk of recurrent UTI or renal damage based on the assumption that long-term low-dose prophylactic antibiotic treatment is effective in preventing further UTIs and new renal scarring. This section aims to examine these assumptions critically and to rationalise the recommended imaging based on the available evidence.

Once a urinary tract infection in a child has been confirmed by urine testing, it is customary to request one or more imaging investigations of the urinary tract. This is to look for urinary tract abnormalities that may have predisposed the child to infection (e.g. obstruction or VUR) and for complications of the infection, typically renal scarring, with the objective of being able to modify one or more of these risk factors to the child's advantage.

Current practice

The most recent guidance on the use of imaging following UTI in childhood was published by the Royal College of Physicians (RCP) in 1991.[21] This states that infants should undergo ultrasonography of the urinary tract, a micturating cystourethrogram (MCUG) and renal scintigraphy (Tc-99m-labelled dimercaptosuccinic acid (DMSA)). Additionally, the guidance states that children between 1 and 7 years of age should have an ultrasound scan and a DMSA scan, and those 7 years or older, should have an ultrasound scan with further imaging being directed by the results of this scan.

Children found to have anomalies detected would be subject to additional tests if deemed appropriate.

This guidance was a consensus document which accepted the assumption that infection associated with VUR was responsible for renal parenchymal defects. The implication was that by treating with long-term antibiotic prophylaxis those thought to be at risk of developing new or progressive renal scarring (i.e. those with VUR and those who had renal parenchymal defects on imaging), further scarring and progression to established renal failure (ERF) could be prevented.

Argument

UTI encompasses a spectrum of severity from cystitis to severe parenchymal infection with subsequent fibrosis leading to renal scarring due to pyelonephritic scarring/reflux nephropathy. These abnormalities are seen on imaging as renal parenchymal defects. There is divergent clinical opinion on the risk of uncomplicated UTI and VUR in the development of these renal defects. The imaging recommended in the RCP guidelines does not form part of a child's treatment and therefore can not hasten recovery. In order to justify the use of imaging and prophylaxis after recovery from an acute UTI there should be evidence of clinical effectiveness of these interventions, which are a type of prevention strategy in a population deemed to be at risk of serious renal morbidity.

One view is that a first UTI is a potential cause of significant renal scarring and therefore all children who have had a UTI will benefit from imaging. This depends on the concept that VUR plays a major role in the pathogenesis of UTI and subsequent renal scarring, and that this can be reduced by the use of prophylactic antibiotics.

Current imaging strategies are based on this view and could be considered to be a form of screening. For a screening programme to be successful, several criteria need to be fulfilled: the natural history and risk from the disease should be known, there should be a simple test or marker of disease, there should be an effective treatment and the whole process should be cost-effective.

However, a significant proportion of parenchymal defects in children, identified through imaging, particularly in infants, are congenital and therefore are not susceptible to prevention.[25,31] The benefit of prophylactic antibiotics has not been demonstrated (see previous chapter). Imaging tests are not without risk or cost, including infection, discomfort, radiation, inconvenience and resource use, and these disadvantages have to be balanced against potential benefits in different groups of patients.[141,256]

An alternative view suggests that in most children UTI is uncomplicated and not associated with renal scarring so that a strong case can be made for reserving imaging for a small subgroup of children who are considered to be at highest risk of scarring and underlying abnormalities following UTI. This approach would enable resources to be more selectively targeted on those who may benefit from further management, and obviate the need to image the vast majority of children who have recovered fully following first-time UTI.

The first strategy implies that all children require imaging following UTI, with all the attendant resource implications and associated risks from the procedures. The latter suggests that imaging could be concentrated on a few children whose clinical features indicate that they might benefit. These arguments were rehearsed in a paper in 2001.[40]

6.4.2 Evaluation of the structure of the urinary tract

Introduction

Ultrasound can assess renal size and the presence of collecting system or ureteric dilatation and evaluate the bladder (including emptying). It can indicate obstruction and other congenital abnormalities of the urinary tract and can detect large calculi, all of which may require specific management outside of the remit of this guideline. It is a widely available technique which has the benefit that it does not use ionising radiation and is non-invasive, making it ideally suited for children.

Clinical questions

In infants and children who present with UTI, what proportion have undiagnosed structural renal tract abnormality?

In infants and children who have or have had UTI, what is the most effective test for diagnosing structural abnormality?

Previous guideline

Ultrasound is currently the first-line imaging investigation in children who have had a UTI and is recommended by the most recent (RCP 1991) guidelines on imaging UTI in children.[21]

Review findings – prevalence of structural abnormalities

Ten studies investigated the prevalence of structural abnormalities in children who have had UTI.[52,66,67,77,78,80,116,118,138,236] [EL = 3]

The results of each study are presented in Table 6.2.

Review findings – diagnostic value of tests to detect structural abnormalities

There is no high-quality study directly assessing diagnostic value of imaging tests to evaluate structural abnormalities of the urinary tract in children who have had UTI.

Review findings – clinical effectiveness

There is no high-quality study directly assessing the clinical effectiveness of imaging in the evaluation of structural abnormality of the urinary tract in children who have had UTI.

Evidence statement – renal structural abnormalities

Common abnormalities identified in children who have had UTI include hydronephrosis, obstruction and duplex kidneys. VUR and renal scarring are discussed separately below. The proportion of children with structural abnormalities found by an imaging test among children who have had UTI range from 10% to 75% depending upon characteristics of the children included in each study. There is a tendency that the abnormalities are more likely to be identified in younger children than older children.

There is no high-level evidence on diagnostic value and clinical effectiveness of detecting structural abnormalities of the urinary tract.

Table 6.2 Prevalence of structural abnormalities excluding VUR and renal parenchymal defects

Study	Population	Age	Imaging tests and structural abnormalities
UK			
Ring (1988)[77]	Hospital records of children admitted with UTI (*n* = 110 who had radiographic examinations of 140)	Median 3 months (4 days to 12 months)	Imaging tests: US, MCUG and IVU 46/110 (42%) had abnormalities 8 had ureteropelvic obstruction 3 had primary obstructive megaureter 2 had duplication with megaureter or ureterocele 4 had posterior urethral valve 1 had horseshoe kidney 1 had multicystic kidney
Burbige (1984)[138]	Hospital data from boys treated for initial UTI (*n* = 83)	Boys aged 2 weeks to 14 years (mean age unknown)	Imaging tests: MCUG and IVU 62/83 (75%) had abnormalities 7 (11%) had posterior urethral valves 6 (10%) had ectopic ureterocele (duplex systems) 5 (8%) had ureteropelvic junction obstruction
Smellie (1981)[67]	Hospital data from children presenting with UTI (*n* = 744, 498 without VUR and 246 with VUR)	Children aged 0–12 years (52% younger than 5 years)	Imaging tests: MCUG and IVU 67/498 (13%) of children with no VUR had abnormalities 24 had duplex kidneys 14 had hydronephrosis 103/246 (42%) of children with VUR had abnormalities 20 had duplex kidneys 4 had hydronephrosis
Other countries			
Biyikli (2004)[118]	Neonates treated in hospital for UTI (*n* = 71)	Neonates (mean age 18.1 ± 11.2 days)	Imaging test: US 23% had abnormalities including renal pelvis dilation, hydronephrosis or hyperechogenic kidney.
Cascio (2002)[236]	Hospital records of children admitted with UTI (*n* = 57)	< 8 weeks (mean 32 days)	Imaging tests: US and DMSA (within 72 hours of admission to hospital) and MCUG (6 weeks after acute episode) 35% had abnormalities
Honkinen (2000)[52]	Hospital (36 hospitals) and laboratory (25 labs) data of children with bacteraemic and non-bacteraemic UTI (*n* = 134 bacteraemic children)	1 week to 9.5 years (median age 0.125 years)	Imaging tests: US or IVU, and MCUG 51% of bacteraemic children had abnormalities 12 (9%) had obstruction 46% of non-bacteraemic children had abnormalities 2 (1%) had obstruction
McKerrow (1984)[66]	Hospital data from children referred for investigation (*n* = 572)	Children aged 0–13 years.	Imaging tests: MCUG and IVU 7.5% had obstructions 7% had duplex kidneys 0.9% had deformities
Ginsburg (1982)[116]	Hospital data from infants admitted with acute UTI (*n* = 86 who underwent radiological investigation)	Infants aged 5 days to 8 months (mean age 2.1 months)	Imaging test: IVU 18/86 (21%) had abnormalities including duplication, hydronephrosis and pelviureteric obstruction.
Pylkkanen (1981)[80]	Data from a paediatric outpatient clinic (*n* = 252	Infants and children aged 6–13 years	Imaging tests: MCUG and IVU 26/252 (10%) had abnormalities 2 had unilateral pelviureteral stenosis 1 had unilateral non-obstructive hydronephrosis 1 had papilloma of the bladder 1 had unilateral ureterocele 1 had sarcoma botryoides of the bladder
Drew (1976)[78]	Hospital data from neonates with UTI (*n* = 64)	Neonates (mean age 10 days in term infants and 18 days in preterm infants)	Imaging tests: MCUG and IVU 30/54 (56%) of boys had abnormalities 5/10 (50%) of girls had abnormalities 6 had hydronephrosis 3 had obstruction 3 had megacystis

DMSA = dimercaptosuccinic acid scan; IVU = intravenous urogram; MCUG = micturating cystourethrogram; US = ultrasound; VUR = vesicoureteric reflux.

6.4.3 Evaluation of vesicoureteric reflux

Introduction

Much of the imaging of children following UTI has been focused on the detection of VUR because of the association described between UTI, VUR and the development of renal parenchymal defects.[21]

There are several imaging techniques available to detect VUR, including MCUG, direct and indirect radionuclide cystogram and cystosonography. All have advantages and disadvantages. MCUG is considered the 'gold standard' for the detection of VUR. This is the only imaging modality which can reliably provide information about the urethra. However, while an MCUG is very simple to perform in infants, it has a number of significant complications (infection, urethral trauma, radiation) and children and parents may find it distressing.

Alternative techniques for the detection of VUR include cystosonography (which involves bladder catheterisation but no radiation) and direct and indirect radionuclide cystography (the latter being able to be performed in toilet-trained children without the need for bladder catheterisation).

The radiation dose from MCUG (1 mSv) is equivalent to about 4 months of natural background radiation, although the introduction of dose-reduction techniques can reduce this.

Only studies that investigated VUR in children who had had UTI were searched, and therefore studies that included children without evidence of previous UTI were not considered in this section.

Clinical question

In infants and children who have had a UTI, what is the most effective test for detecting vesicoureteric reflux?

Previous guideline

The Royal College of Physicians guidelines[21] recommended that MCUG should be performed in all infants who have had a UTI.

Review findings – clinical effectiveness

There is no high-quality study directly assessing clinical effectiveness of imaging evaluation of VUR following UTI in children.

Review findings – prevalence of VUR

Twelve studies reported prevalence of VUR following UTI in children.[47,50,52,64,66,76,237–241] The results of each study are presented in Table 6.3.

Review findings – diagnostic values between tests to detect VUR

Conventional ultrasound compared with MCUG

A total of 12 studies were included, out of which 11 were reported in the HTA[143] and one additional study was identified from the search.

A systematic review identified 11 studies evaluating the use of ultrasound for detecting VUR compared with the reference standard of MCUG.[143]

Sensitivity ranged from 10.5% (specificity 89.4%) to 90.9% (specificity 14.6%) and specificity from 14.6% (sensitivity 90.9%) to 93.8% (sensitivity 53.7%).

Likelihood ratios showed significant heterogeneity ($P < 0.001$). LR+ values ranged from 1.0 (LR– ≈ 1.0) to 8.7 (LR– = 0.49) and LR– values ranged from 0.41 (LR+ = 8.2) to 0.98 (LR+ ≈ 1.0). The pooled LR+ was 1.9 (95% CI 1.2 to 2.9) and the pooled LR– was 0.76 (95% CI 0.63 to 0.93).

The median LR+ was 1.4 (IQR 1.1 to 2.5) and the median LR– was 0.79 (IQR 0.58 to 0.98).

An Israeli study compared renal ultrasound with MCUG for detecting VUR in a population of 252 children younger than 5 years.[244] The sensitivity, specificity, positive and negative LRs for ultrasound were 16%, 88%, 1.33 and 0.95, respectively. [EL = II]

The summary results of all 12 studies are presented in Table 6.4.

Table 6.3 Prevalence of VUR

Study	Study type	Population	Age	Imaging tests and VUR prevalence
UK				
McKerrow Scotland (1984)[66]	Case series	Hospital records of children referred to a paediatric surgical outpatient clinic (*n* = 572)	< 13 years (7% > 2 years)	Imaging test: MCUG 31% had VUR
Other countries				
Tsai Taiwan (2004)[64]	Retrospective cohort	Hospital records of children admitted with first UTI (*n* = 114)	1 month to 5 years (median age 6 months)	Imaging tests: MCUG and US 29% of patients (31/114) 21% of kidneys (47/228) Severe VUR in 12% of patients
Chand USA (2003)[76]	Case series	Hospital records of children who underwent MCUG or radionuclide cystogram because of previous UTI (*n* = 9912)	0–21 years	Imaging tests: MCUG or IRC 31% in girls 18%in boys 39% > 2 years 27% 2–6 years 20% 7–11 years 8% 12–21 years
Upadhyay Canada (2003)[237]	Case series	Girls investigated for dysfunctional voiding and concomitant UTI by MCUG (*n* = 58)	4–11 years (mean age 6.7 years)	Imaging test: MCUG 33% had VUR
Zaki Kuwait (2003)[238]	Case series	Hospital records of children admitted for first febrile UTI (*n* = 174)	< 12 years (72 children younger than 1 year, 66 children aged 1–5 years, 36 children older than 5 years)	Imaging test: MCUG 24% in girls 18% in boys 25% < 1 year 18% 1–5 years 27% > 5 years
Howard Hong Kong (2001)[239]	Case series	Hospital records of children who presented with documented UTI and underwent MCUG and DMSA (*n* = 93)	< 5 years	Imaging test: MCUG 25% in girls 45% in boys
Honkinen Finland (2000)[52]	Case series – population surveillance data	Surveillance records of children identified at hospitals or labs with bacteraemic UTI (*n* = 132)	1 week to 9.5 years (median age 0.125 years)	Imaging test: MCUG or IRC 30% of children had VUR
Honkinen Finland (1999)[240]	Cohort	Hospital records of children with positive urine samples who had IVU or ultrasound and MCUG (*n* = 184)	62% younger than 2 years, 37% 2 years or older (range unknown)	Imaging test: MCUG 38% had VUR
Sargent USA (1995)[241]	Case series	Hospital records of children investigated for first UTI (*n* = 309)	Median 48 months in girls and 12 months in boys (range unknown)	Imaging test: MCUG 29% in girls 30% in boys Under 1 year: males 34%, females 46% Children younger than 2 years: males 30%, females 44% Children 2–4 years: males 32%, memales 32% Children 5 years or older: males 29%, females 15%
Messi Italy (1988)[50]	Case series	Hospital records of children with first symptomatic UTI (*n* = 225)	0–14 years (28% younger than 12 months, 28% 1–4 years)	Imaging test: MCUG Overall, 18% had VUR 17% in girls 21% in boys 30% 0–12 months 14% 1–4 years 13% 5–14 years
Jodal Sweden (1987)[47]	Case series	Hospital records of children with first symptomatic UTI (*n* = 1177)	Children younger than 10 years	Imaging test: MCUG 34% in girls 33% in boys

DMSA = dimercaptosuccinic acid scan; IRC = indirect radionuclide cystogram; IVU = intravenous urogram; MCUG = micturating cystourethrogram; US = ultrasound; VUR = vesicoureteric reflux.

Table 6.4 Ultrasound compared with MCUG for detecting VUR

Study	Test details	Definition of positive result	Reference standard; definition of positive result	Unit of analysis	Sensitivity	Specificity	LR+	LR–
Baronciani (1986)[143]	Standard	Presence of VUR; dilation or hydronephrosis	MCUG; presence of VUR	Patients	61.9%	92.5%	8.2	0.41
Evans (1999)[143]	Standard	Presence of VUR (change in pelvic diameter)	MCUG; presence of VUR	Renal units	10.5%	89.4%	1.0	1.0
Foresman (2001)[143]	Duplex	Any abnormality	MCUG; presence of VUR	Patients	49.0%	52.2%	1.0	0.98
Mage (1989)[143]	Standard	Not stated	MCUG; presence of VUR	Patients	53.7%	93.8%	8.7	0.49
Mahant (2002)[143]	Standard	Presence of VUR (dilation)	MCUG; presence of VUR	Patients	40.0%	76.4%	1.7	0.79
Morin (1999)[143]	Standard	Renal change indicative of APN	MCUG; presence of VUR	Patients	90.9%	14.6%	1.1	0.62
Muensterer (2002)[143]	Standard	Abnormal kidney size or dilation	MCUG; presence of VUR ≥ Grade III	Renal units	91.3%	67.5%	2.8	0.15
		Presence of VUR (dilation)	MCUG; presence of VUR	Renal units	50.7%	76.0%	2.1	0.65
		Abnormal kidney size	MCUG; presence of VUR	Renal units	29.0%	91.2%	3.3	0.78
		Abnormal kidney size	MCUG; presence of VUR ≥ Grade III	Renal units	47.8%	89.8%	4.7	0.58
		Presence of VUR (dilation)	MCUG; presence of VUR ≥ Grade III	Renal units	78.3%	74.7%	3.0	0.31
	Standard	Presence of VUR (at least mild dilatation)	MCUG; presence of VUR	Patients	56.8%	80.6%	2.9	0.54
Tan (1988)[143]	Standard	Not stated	MCUG; presence of VUR	Patients	17.6%	84.2%	1.1	0.98
Trave (1997)[143]	Standard	Not stated	MCUG; presence of VUR	Renal units	17.6%	87.1%	1.4	0.95
Verber (1988)[143]	Standard	Presence of VUR or renal parenchymal defects	MCUG (Hypaqure); presence of VUR	Renal units	28.6%	73.5%	1.1	0.97
Zamir (2004)[244]	Standard	Presence of VUR	MCUG; presence of VUR	Patients	16.0%	88.0%	1.3	0.95

APN = acute pyelonephritis; MCUG = micturating cystourethrogram; VUR = vesicoureteric reflux.

Contrast-enhanced ultrasound (cystosonography) compared with MCUG

A total of 16 studies were included, out of which 14 were reported in the HTA[143] and two additional studies were identified from the search (Table 6.5, Figure 6.4).

A systematic review identified 14 studies evaluating the diagnostic accuracy of cystosonography for detecting VUR using MCUG as the reference standard.[143] In all included studies, the study population included children both with and without UTI.

Sensitivity ranged from 56.8% (specificity 84.8%) to 96.3% (specificity 80%). In all but three studies, sensitivity was above 75%. Specificity ranged from 80% (sensitivity 96.3%) to 100% (sensitivity 76.5% and 85.7%).

Likelihood ratios showed significant heterogeneity ($P < 0.001$). LR+ values ranged from 3.8 (LR– = 0.51) to 71.2 (LR– = 0.20) and LR– values ranged from 0.04 (LR+ = 25.6) to 0.51 (LR+ = 3.8). The pooled LR+ was 12.3 (95% CI 8.2 to 18.3) and the pooled LR– was 0.17 (95% CI 0.11 to 0.27).

The median LR+ was 13.7 (IQR 9.1 to 30.8) and the median LR– was 0.16 (IQR 0.11 to 0.23).

One additional study from Japan evaluated the diagnostic potential of voiding urosonography (VUS) (cystosonography) compared with MCUG conducted simultaneously.[245]

Table 6.5 Contrast-enhanced ultrasound compared with MCUG for detecting VUR

Study	Test details	Definition of positive result	Reference standard; definition of positive result	Unit of analysis	Sensitivity	Specificity	LR+	LR–
Alzen (1994)[143]	Air contrast	Not stated	MCUG; presence of VUR	Renal units	90.9%	92.4%	12.0	0.10
Bergius (1989)[143]	Cystosonography (Isopaque)	Presence of VUR ≥ Grade III (air bubbles)	MCUG; presence of VUR ≥ Grade III	Renal units	90.5%	99.6%	134.7	0.11
		Presence of VUR ≥ Grade II or air bubbles	MCUG; presence of VUR ≥ Grade II	Renal units	80.0%	98.9%	71.2	0.20
Berrocal (2001)[143]	Cystosonography (SH U 508A)	Presence of VUR (micro-bubbles)	MCUG (Plenigraf); presence of VUR	Renal units	90.4%	91.4%	10.5	0.11
				Patients	88.2%	88.6%	7.5	0.14
Frutos (2000)[143]	Cystosonography (Levograf)	Presence of VUR (micro-bubbles)	MCUG; presence of VUR	Renal units	90.0%	91.5%	10.6	0.11
Haberlick (1997)[143]	Colour Doppler cystosonography	Presence of VUR (blue-coloured jet)	MCUG; presence of VUR	Renal units	70.0%	91.9%	8.7	0.33
Kessler (1982)[143]	Cystosonography (Cysto-Conray)	Presence of VUR (micro-bubbles and/or dilation)	MCUG; presence of VUR ≥ Grade II	Renal units	76.5%	100.0%	58.5	0.24
Mentzel (2002)[143]	Cystosonography (Levovist)	Presence of VUR	MCUG; presence of VUR	Renal units	90.0%	94.6%	16.6	0.11
Piaggio (2003)[143]	Cystosonography (Levovist)	Not stated	MCUG; presence of VUR	Renal units	56.8%	84.8%	3.8	0.51
Radmayr (2002)[143]	Doppler cystosonography (galactose-based contrast agent)	Presence of VUR (micro-bubbles)	MCUG; presence of VUR	Renal units	95.9%	96.3%	25.7	0.04
Rohden (1995)[143]	Cystosonography (Echovist)	Not stated	MCUG; presence of VUR	Patients	85.7%	100.0%	32.5	0.14
Schneider (1984)[143]	Cystosonography (Conray FL/air)	Presence of VUR (increased separation in the central renal echo complex)	MCUG; presence of VUR ≥ Grade II	Renal units	87.2%	90.0%	8.4	0.15
		Presence of VUR	MCUG; presence of VUR	Renal units	73.0%	90.4%	7.6	0.30
Siamplis (1996)[143]	Cystosonography (air)	Not stated	MCUG; presence of VUR	Renal units	83.3%	97.5%	32.9	0.17
	Cystosonography (fluid)			Renal units	94.4%	94.9%	17.2	0.08
Salih (1994)[143]	Colour Doppler	Presence of VUR (blue-coloured jet)	MCUG; presence of VUR	Renal units	96.3%	80.0%	4.8	0.05
Valentini (2001)[143]	Greyscale cystosonography (Levovist)	Presence of VUR (micro-bubbles)	MCUG; presence of VUR	Renal units	81.0%	94.7%	15.4	0.20
	Colour Doppler cystosonography (Levovist)	Presence of VUR (colour signals)		Renal units	100.0%	93.4%	13.8	0.01
Nakamura (2003)[245]	Greyscale cystosonography (Levovist)	Presence of VUR (micro-bubbles)	MCUG; presence of VUR	Renal units (1 month to 14 years)	86.0%	95.0%	17.2	0.15
				Renal units (24 months)	73.0%	98.0%	36.5	0.28
Xhepa (2004)[246]	Greyscale cystosonography (Levovist)	Presence of VUR (micro-bubbles)	MCUG; presence of VUR	Renal units	93.0%	44.0%	1.7	0.16

MCUG = micturating cystourethrogram; VUR = vesicoureteric reflux.

Boys and girls aged 1 month to 14 years (mean age 2.3 years) with confirmed UTI and follow-up of previously detected VUR underwent simultaneous VUS and MCUG. The sensitivity was 86% and specificity 95%, and the LR+ was 17.20 and LR– 0.15. When a subgroup of children younger than 24 months was analysed the sensitivity decreased to 73% and specificity increased to 98%. The LR+ was 36.50 and the LR– was 0.28 (*n* = 56 or 111 ureterorenal units (one patient with a single kidney was included)).

Another additional study in Albania evaluated the diagnostic efficacy of voiding cystourethrosonography (CUS) (cystosonography) compared with MCUG. Twenty-two children aged 2 months to 14 years (mean age 3.9 years) were referred to hospital for investigation of VUR because of documented acute pyelonephritis/upper urinary tract infection. Sensitivity of CUS for detecting VUR was 93%, and specificity 44%, LR+ was 1.66 and LR– 0.16.[246] [EL = II]

Other tests and combinations of tests

A total of four studies were identified for inclusion in this section, of which three studies were identified from the searches conducted in the HTA[143] and the additional study was from the search conducted for this guideline (Table 6.6).

Two studies reported in the HTA[143] evaluated indirect radionuclide cystography, but they did not provide sufficient information to assess quality. Two studies, one evaluating indirect radionuclide voiding cystography (Tc-99m-MAG3) and one evaluating dynamic micturating scintigraphy (Tc-99m-DTPA) used MCUG as the reference standard.

One study investigated the diagnostic value of the use of dynamic micturating scintigraphy (Tc-99m-DTPA), compared with MCUG, and one study investigated a combined risk score (gender, family history, age, CRP and ultrasound) compared with MCUG.

An additional study conducted in Turkey compared MCUG with direct radionuclide cystography in 25 children with recurrent UTI (13 female, 12 male) aged 1.5 months to 15 years.[247] The sensitivity was 20%, specificity 74%, LR+ 0.77, and LR– 1.08. [EL = III]

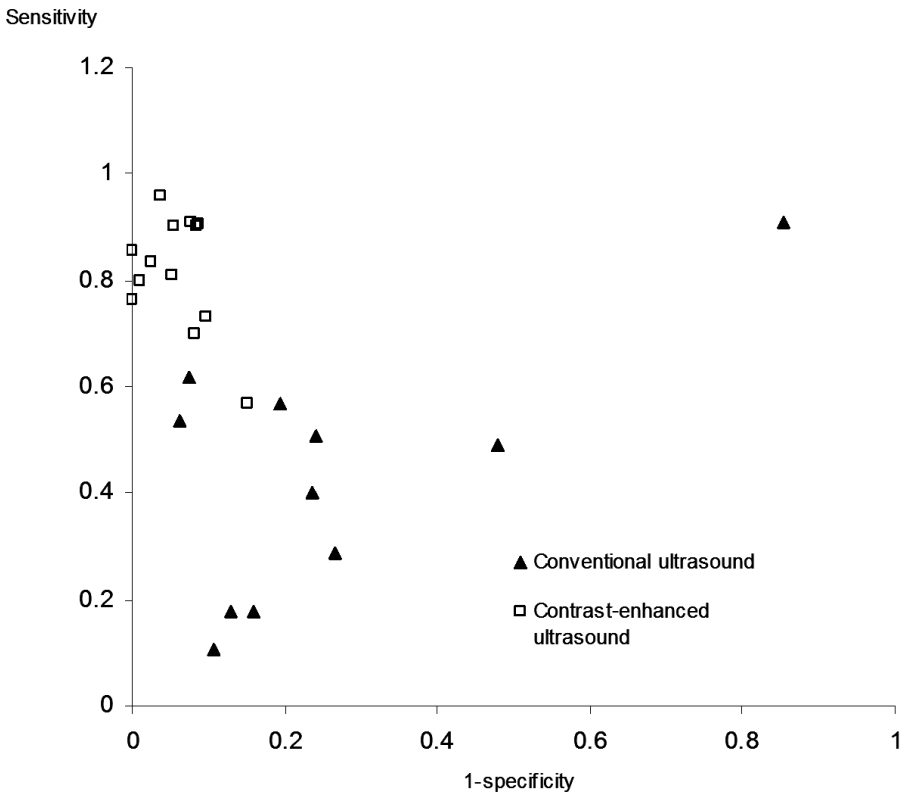


Figure 6.4 Ultrasound (conventional and contrast-enhanced) compared with MCUG for detecting VUR, plotted in ROC space

Table 6.6 Other investigations for VUR

Study	Test details	Definition of positive result	Reference standard; definition of positive result	Unit of analysis	Sensitivity	Specificity	LR+	LR–
Bower (1985)[143]	Indirect radionuclide voiding cystography (Tc-99m-DMSA)	Presence of VUR	Direct radionuclide voiding cystography (Tc-99m-DTPA renal scan and a delayed voiding cystogram); presence of VUR	Renal units	68.4%	97.1%	16.2	0.34
De Sadeleer (1994)[143]	Indirect radionuclide voiding cystography (Tc-99m-MAG3)	Presence of VUR	MCUG; presence of VUR	Renal units	32.6%	100.0%	25.0	0.68
Hedman (1978)[143]	Dynamic micturating scintigraphy (Tc-99m-DTPA)	Not stated	MCUG; presence of VUR	Renal units	61.9%	95.1%	11.2	0.41
Oostenbrink (2000)[143]	Combined risk score: gender, family history, age, CRP and US	≥ 1	MCUG; presence of VUR	Patients	100.0%	15.0%	1.2	0.09
		≥ 6			91.9%	37.9%	1.5	0.24
		≥ 11			81.1%	52.4%	1.7	0.38
		≥ 16			64.9%	71.8%	2.3	0.50
		> 25			51.4%	92.2%	6.3	0.53
		≥ 11	MCUG; presence of VUR > Grade II		89.3%	51.8%	1.8	0.23
		≥ 16			71.4%	70.5%	2.4	0.42
		> 25			57.1%	90.2%	5.6	0.48
Sukan (2003)[247]	Direct radionuclide voiding cystography	Presence of VUR	MCUG; presence of VUR	Renal units	20.0%	74.0%	0.77	1.1

CRP = C-reactive protein; DMSA = dimercaptosuccinic acid scan; MAG3 = mercaptoacetyltrigycerine; MCUG = micturating cystourethrogram; US = ultrasound; VUR = vesicoureteric reflux.

Evidence statement – VUR

Overall, of the children who present with a UTI it is likely that between 30% and 40% have VUR. VUR in girls ranged from 17% to 34% and in boys from 18% to 45%.

The evidence suggests that the most sensitive tests for identifying VUR are MCUG and cystosonography. There is little evidence about the use of direct or indirect radionuclide cystography in children who have had UTI.

One study estimated the cost of both cystosonography and MCUG at £124.50 (see Chapter 8 for details). In the absence of further evidence about treatment outcomes following imaging of the bladder and kidneys, the relative cost-effectiveness of these methods cannot be assessed.

6.4.4 Evaluating renal scarring

Introduction

DMSA scintigraphy involves the intravenous injection of a radiopharmaceutical (dimercaptosuccinic acid) labelled with Tc-99m. DMSA is concentrated in the proximal renal tubules and enables an image of the distribution of functioning renal tissue to be obtained. Images are obtained between 2 and 6 hours after injection. Imaging with DMSA is deferred till several months after UTI to allow for any parenchymal changes from acute infection to resolve. If performed too soon, acute parenchymal defects which may resolve completely and are indicative of acute pyelonephritis/upper urinary tract infection will be detected. These cannot be differentiated from permanent renal parenchymal defects indicating renal scarring.

It is not possible to use imaging tests to differentiate between small dysplastic kidneys due to congenital causes and acquired focal or global scarring. Thus the results of imaging are best referred to as renal parenchymal defects without attributing a cause.

DMSA scintigraphy is currently considered the gold standard for the detection of renal parenchymal defects and was used as such in the HTA assessment.[143]

Clinical questions

In infants and children who have had a UTI, what are the predictors of scarring?

In infants and children who have a UTI, what is the risk of (developing) scarring?

In infants and children who have had a UTI, what is the most effective test for detecting scarring?

Previous guideline

Current guidelines (RCP 1991)[21] recommend the use of DMSA scintigraphy in all children younger than 7 years following UTI to look for evidence of renal parenchymal defects.

Review findings – clinical effectiveness of imaging tests to detect renal scarring

There was no high-quality study that directly compared the impact of different imaging strategies for the evaluation of renal scarring in children who have had UTI on patient outcomes.

Review findings – prevalence and incidence of renal scarring

Prevalence of renal scarring

Seven data sets in six studies investigated the prevalence of renal parenchymal defects presumed to represent renal scarring in children who have had UTI.[42,43,47,80,82,84,92,224,248]

UK studies

One population-based study in the UK reported that 4.7% of girls and 4.3% of boys presenting with their first UTI had renal parenchymal defects on DMSA. Logistic regression showed no independent association of renal parenchymal defects with age or sex. The rate of renal parenchymal defects remained constant throughout the 4 years of the study, and the cumulative rate of UTI was 11.3% of girls and 3.6% of boys.[43] From this study, 0.53% of all girls in a population will develop renal parenchymal defects, and 0.16% of boys. [EL = 3]

A case series study in the UK investigated 105 children who had had UTI and who attended a renal clinic using serial IVUs.[92] 55/105 (52%) of children had VUR and of the infants (younger than 1 year), 8/9 had Grade III VUR. Of the 210 kidneys, 34 (16%) did not have a cystourethrogram, 86 (41%) had no renal parenchymal defects, 30 (14%) had Grade I VUR, 13 (6%) had Grade II VUR and 47 (22%) had Grade III VUR.

Of the kidneys that were affected by VUR, 6/20 (20%) with Grade I VUR were with renal parenchymal defects, 5/13 (38%) of those with Grade II VUR were with renal parenchymal defects and 37/47 (79%) with Grade III VUR were with renal parenchymal defects. Those with Grade II or III VUR were significantly more likely to have renal parenchymal defects than those with no VUR ($P < 0.001$).

Deterioration of existing renal parenchymal defects or new renal parenchymal defect formation was seen in 11 children, nine of whom had Grade III VUR. [EL = 3]

A case series study conducted in the UK reviewed the histories of 52 children aged 1–12 years with bilateral renal parenchymal defects and severe VUR to determine whether an improvement in early management might reduce the risk of renal parenchymal defects.[248] There was a delay in diagnosis or appropriate imaging or effective treatment of urinary infection in 50 of the 52 children. In 41 there was a delay in diagnosis, in 45 a delay in receiving effective treatment, in 25 a delay in diagnosis of VUR without prophylaxis, and investigation of the urinary tract was delayed in 33. Four children of mothers known to have reflux nephropathy were not investigated until they developed a UTI. IVU was used to detect renal parenchymal defects.

Among the 11 children without delay in diagnosis, the types of renal parenchymal defect seen were moderate in ten children and severe in one child. Among the 24 children in whom there was up to a 6 month delay, 11 had moderate renal parenchymal defect types and 13 severe. Among the 17 children in whom there was more than a 6 month delay, six had moderate renal parenchymal defect types and 11 severe.

There was a significant association between the type of renal parenchymal defect and timing of diagnosis ($\chi^2 = 6.32$; $P < 0.01$) and also a significant dose-dependent association ($\chi^2 = 7.43$; df = 1; $P < 0.001$). [EL = 3]

Studies in other countries

A population-based study in Sweden found the annual incidence of renal parenchymal defects (detected by IVU) in girls and boys with UTI to be 9.3/100 000 with a ratio of 2:1. From this study, 0.18% of girls and 0.11% boys in a population would be expected to have renal parenchymal defects.[82] [EL = 3]

Another study, which appeared to be population based, gave rates of renal parenchymal defects of 6.4% (detected by IVU).[84] [EL = 3]

Baseline data from a case–control study conducted in Turkey evaluated 97 children with recurrent UTI who underwent an MCUG and DMSA. Thirty children were found to have renal parenchymal defects and 67 children had no renal parenchymal defects.[224] Children with renal parenchymal defects had more frequent recurrent UTIs than children without renal parenchymal defects (6.90 ± 2.45 UTI episodes versus 3.35 ± 1.48 UTI episodes; $P < 0.001$) and were more likely to be younger at their first UTI (2.61 ± 1.52 years versus 3.52 ± 2.17 years; $P = 0.04$). Mean age, gender, length of follow-up, and ratio of UTI with *E. coli* and with other bacteria were similar in children with and without renal parenchymal defects ($P > 0.05$). [EL = 3]

A case series study in Sweden treated 1177 (225 boys, 952 girls) children younger than 10 years with bacteriologically verified symptomatic first-time UTI.[47] Of children without demonstrable VUR, renal parenchymal defects developed in 5%. Of the total number of children with renal parenchymal defects, 25% did not have VUR, 5% had Grade I VUR, 28% had Grade II VUR and 42% had Grade III VUR. IVU was used to detect renal parenchymal defects. [EL = 3]

A case series study in 252 in infants and children in Finland with symptomatic and asymptomatic UTI at a paediatric clinic found that 164/252 (65%) children had upper UTI, 88/252 (35%) children had lower UTI or asymptomatic UTI and12/252 (5%) had renal parenchymal defects.[80] Localisation of UTI was made by clinical diagnosis, and renal parenchymal defects were detected by using IVU at 2 weeks after the initiation of antibiotic therapy. All the children with renal parenchymal defects had had acute pyelonephritis/upper urinary tract infection. Of the infants and children with VUR, 40% had renal parenchymal defects. [EL = 3]

A case series study in Sweden investigated the epidemiology of symptomatic UTI in 596 children and reported that renal parenchymal defects were found in 13% of boys (18/156) and 4.5% of girls (20/440).[42] [EL = 3]

Incidence of new/progressive renal parenchymal defects

Six studies investigated new or progressive renal parenchymal defects in children who have had UTI.[95,97,98,226,249,250]

UK studies

A case series study in the UK investigated 120 children (aged 2 weeks to 12 years) who had a UTI and underwent an IVU.[98] New renal parenchymal defects (seen on second IVU) were found in 87 kidneys of 74/120 (62%) children (8 boys, 66 girls), of whom 58 had normal kidneys initially and 16 had renal parenchymal defects initially.

Of the children who developed new renal parenchymal defects, 46/58 (79%) were unilateral and 12/58 (21%) were bilateral. Of the 16 children who developed progressive renal parenchymal defects, 13 had unilateral renal parenchymal defects initially and 3 had bilateral renal parenchymal defects.

Of the children who developed renal parenchymal defects, 51% had previously had a UTI and 91% had VUR. New renal parenchymal defects developed in children with all grades of VUR: one or more renal parenchymal defects developed in 15 kidneys with no VUR, 11 in kidneys with Grade I VUR, 25 in kidneys with Grade II VUR, and 36 in kidneys with Grade III VUR. [EL = 3]

A case series study in the UK of children aged 3 and 4 years investigated up to what age children remain at risk of developing a new renal parenchymal defect from a UTI.[95] Overall, 5/355 (1.4%)

children developed renal parenchymal defects in the follow-up period (2–11 years) and all were girls in the 3-year-old group.

One child who developed renal parenchymal defects had no further UTIs after the original scanning, and the other children who developed renal parenchymal defects had three or more UTIs between original and follow-up scanning. [EL = 3]

From an initial screening program in the UK involving 16 800 girls aged 4–12 years, 248 with covert bacteriuria were randomised to receive antibiotic treatment (127) or no treatment (121).[226] During follow-up, 9/110 (8%) girls in the treatment group and 8/98 (8%) in the untreated group had a symptomatic infection accompanied by frequency, dysuria or loin pain and fever and were given antibiotics.

At follow-up MCUG (4 years later), 17/110 (15%) of the girls who had received treatment and 44/98 (45%) of the girls who had received no treatment had bacteriuria ($P < 0.001$). No new renal parenchymal defects were seen in girls who had normal kidneys at the initial X-ray examination. Of the girls with renal parenchymal defects at the initial X-ray, new and/or deepening renal parenchymal defects were found in 12/44 (27%): 6/28 (21%) in the girls who had received treatment and 6/16 (38%) in the girls who had received no treatment. [EL = 3]

Studies in other countries

A case series study in Sweden investigated 107 girls who were continuously monitored following their first childhood UTI – median age at first recognised UTI was 4.3 years (0.1–14.7 years).[97] All received at least two urographies (mean number of investigations 4.3). The first was performed after the initial UTI and the repeat urographies as recurrences occurred. All patients had a last urography after puberty. At the initial urography, renal parenchymal defects were seen in 38 of 107 patients (36%), unilateral in 31 and bilateral in 7. At the last urography there were 51 patients with renal parenchymal defects.

New renal parenchymal defects occurred in 18 patients where both kidneys were previously normal. The median age at detection was 9.9 years.

In 23 patients with established renal parenchymal defects the degree of renal parenchymal defect remained unchanged during follow-up. In 28, renal parenchymal defects progressed: 10 developed more severe renal parenchymal defects (increased renal parenchymal defects of existing lesions), 5 with unilateral renal parenchymal defects developed new renal parenchymal defects on the other kidney, and 13 acquired new renal parenchymal defects in previously normal kidneys. VUR was present in 67 patients of whom 51 had renal parenchymal defects. [EL = 3]

A case series study in the USA reviewed records of 1426 patients with acute pyelonephritis/upper urinary tract infection and VUR to assess renal parenchymal defects.[249] 192/1426 (2.1%) children had established renal parenchymal defects at initial presentation. Of these children, 30 developed additional/progressive renal parenchymal defects while being monitored continuously for UTI and one child developed new renal parenchymal defects where previously there had been no evidence of renal parenchymal defects. [EL = 3]

An Australian case series study investigated the prevalence of renal parenchymal defects in children 2 years after the child's first recognised UTI and analysed the relationship of these defects with acute illness variables, primary VUR and recurrent infections.[250] The children were recruited when they presented at the emergency department of a hospital and were followed up. Repeat DMSA scans were performed on 150/193 (78%) children, of whom 54 (36%) had Grade III–V VUR. Those lost to follow-up were younger, had fewer hospitalisations, lower prevalence of VUR and, overall, had a significantly lower risk of initial renal parenchymal defects, either as subjects ($\chi^2 = 6.59$; $P = 0.01$) or their individual kidneys ($\chi^2 = 4.60$; $P = 0.03$).

On initial DMSA carried out during the acute phase of illness, 75/150 (50%) had an acute renal parenchymal defect. Defects persisted 2 years later in 20 of the 75 children. During the study period, 15 (10%) children had further UTIs diagnosed. No new defects were detected in the 150 children, including those with recurrent UTI.

Children 2 years or older at their first UTI ($P < 0.001$) and girls ($P = 0.023$) were more likely to have persistent renal parenchymal defects, but this is probably due to the significant differences in the age distribution. The median age for boys with initial renal parenchymal defects was

3.6 months (range 0.75–31 months) compared with 11.5 months (range 1.7–59 months) in girls ($P < 0.001$).

There were no associations found between the presence (Grade II $P = 0.72$) or severity of VUR (Grades III–V $P = 0.34$), recurrent infection ($P = 1.0$) or hospitalisation ($P = 0.08$) and renal parenchymal defects. Prevalence of persistent defects after UTI for all study participants was 20/150 (13.3%; 95% CI 8.3% to 19.8%). [EL = 3]

Review findings – diagnostic values between tests to detect renal parenchymal defects

Dynamic renal imaging compared with DMSA scan for detecting renal parenchymal defects

A systematic review identified two studies evaluating the diagnostic accuracy of dynamic scintigraphy (MAG3) using DMSA scintigraphy as the reference standard (Table 6.8).[143] One study investigated renal units, where sensitivity of MAG3 was 88%, specificity 88%, LR+ 7.1 and LR– 0.15. The second study investigated MAG3 by patient and found a sensitivity of 82%, specificity of 95%, LR+ of 12.6 and LR– of 0.21.

Ultrasound compared with DMSA scan for detecting renal parenchymal defects

A systematic review identified six studies reporting eight data sets for detecting renal parenchymal defects (Table 6.9).[143] Three additional studies were identified from the search.

Three studies reported renal parenchymal defect results by renal units. Two studies reported sensitivities of 86% and 82%, specificities of 98% and 87%, LR+ values of 35.9 and 5.8 and LR– values of 0.14 and 0.23. The third study showed much poorer results for the performance of ultrasound in detecting renal parenchymal defects and showed sensitivity of 3%, specificity of 97%, LR+ of 1.3 and LR– of 0.99. The reasons for the discrepancies in results are unclear. A further three studies reported renal parenchymal defect results by patient. Sensitivity ranged from 23% to 67%, and specificity from 80% to 99%. [EL = II]

A study conducted in the UK investigated the use of ultrasonography in the evaluation of renal parenchymal defects.[251] 465 children (930 kidneys) aged 3 months to 16 years with proven UTI who presented to a radiology department and who underwent ultrasound and DMSA scan on the same day at least 3 months after UTI were included.

The sensitivity of ultrasound to detect focal scarring in kidneys was 5%, specificity 98.3%, LR+ 2.50 and LR– 0.97. The sensitivity of ultrasound to detect diffuse scarring in kidneys was 47%, specificity 92%, LR+ 5.88 and LR– 0.58.[EL = II]

A study conducted in Taiwan evaluated the use of ultrasonography and CRP level in 45 children (31 boys and 14 girls) aged 9 days to 10 years (mean age 1.5 ± 0.2 years, median age 0.3 years) with febrile UTI who fulfilled criteria for acute pyelonephritis/upper urinary tract infection.[191] The sensitivity of ultrasound to detect renal parenchymal defects was 59%, specificity 61%, LR+ 1.51 and LR– 0.67 ($P = 0.11$; OR 2.3; 95% CI 0.82 to 7.65). The sensitivity of CRP > 70 mg/l to identify renal parenchymal defects was 81%, specificity 74%, LR+ 3.12 and LR– 0.26 ($P < 0.0001$; OR 11.9; 95% CI 3.72 to 38.11). The sensitivity of ultrasound and CRP > 70 mg/l combined to

Table 6.8 Dynamic renal imaging compared with DMSA scan to detect renal parenchymal defects

Study	Test details; time	Definition of positive result	Reference standard; definition of positive result; time	Unit of analysis	Sensitivity	Specificity	LR+	LR–
Gordon (1992)[143]	Dynamic including micturating (Tc-99m-MAG3); follow-up	Not stated	Tc-99m-DMSA on follow-up; presence of renal parenchymal defect; follow-up	Renal units	88.0%	88.3%	7.1	0.15
Pickworth (1992)[143]	Dynamic including micturating (Tc-99m-MAG3); not stated	Presence of renal parenchymal defect or VUR	Tc-99m-DMSA; not stated; not stated	Patients	82.4%	94.7%	12.6	0.21

DMSA = dimercaptosuccinic acid scan; MAG3 = mercaptoacetyltrigrycerine; VUR = vesicoureteric reflux.

identify renal parenchymal defects was 52%, specificity 81%, LR+ 2.74 and LR– 0.59 ($P < 0.01$; OR 4.7; 95% CI 1.47 to 14.95). [EL = III]

A study conducted in Turkey compared the efficacy of DMSA and renal ultrasonography in detecting renal parenchymal defects in 62 children (18 boys, 44 girls) aged 6 months to 15 years (mean age 5 years) diagnosed with primary VUR between 1997 and 2003 following a documented UTI.[252] Of 90 refluxing units, 33% had Grades I–II VUR, 41% had Grade III VUR and 26% had grade IV–V VUR. DMSA detected renal parenchymal defects in 32/58 units with bilateral VUR and in 20/33 units with unilateral VUR. Ultrasonography detected renal parenchymal defects in 22/58 units with bilateral VUR with a sensitivity of 69%, specificity of 100% and an LR– of 0.31

Table 6.9 Ultrasound compared with DMSA scan for detecting renal parenchymal defects

Study	Test details; time	Definition of positive result	Reference standard; time	Unit of analysis	Sensitivity	Specificity	LR+	LR–
Acute US compared with acute DMSA								
MacKenzie (1994)[143]	Ultrasound; acute (within 48 hours)	Any abnormality	DMSA; within 28 days	Patients	52.5%	80.4%	2.6	0.60
Trave (1997)[143]	Ultrasound; acute (mean 2.6 days after recruitment)	Not stated	DMSA; mean 3.9 days after admission	Renal units	3.4%	97.3%	1.3	0.99
Wang (2005)[191]	Ultrasound; on admission	Presence of renal parenchymal defect	DMSA; within 1 week	Patients	59.0%	61.0%	1.51	0.67
	Ultrasound (on admission) + CRP	Presence of renal parenchymal defect	DMSA; within 1 week	Patients	52.%	81.0%	2.74	0.59
Acute US compared with late DMSA scan								
Barry (1998)[143]	Ultrasound; 1–3 months	Presence of renal parenchymal defect	DMSA; after 3 months	Renal units	86.%	97.7%	35.9	0.14
Late US compared with acute DMSA scan								
Moorthy (2004)[251]	Ultrasound; after 3 months	Presence of diffuse renal parenchymal defect	DMSA; acute changes	Renal units	47.%	92.0%	5.88	0.58
Late US compared with late DMSA scan								
Moorthy (2004)[251]	Ultrasound; after 3 months	Presence of focal renal parenchymal defect	DMSA; after 3 months	Renal units	5.0%	98.3%	2.50	0.97
Temiz (2006)[252] Bilateral VUR	Ultrasound; follow-up	Presence of renal parenchymal defect	DMSA: follow-up	Renal units	69.0%	100.0%	0.31	N/A
US and DMSA scan timing not stated								
LeQuesne (1986)[143]	Ultrasound; not stated	Presence of renal parenchymal defect or signs of VUR	DMSA; not stated	Renal units	81.5	87.2	5.8	0.23
Mucci (1994)[143]	Ultrasound; not stated	Not stated	DMSA; not stated	Patients	22.7	99.4	27.4	0.77
Scherz (1994)[143]	Ultrasound; not stated	Presence of renal parenchymal defect	DMSA; after 3 months	Patients (asymptomatic)	100.0	95.7	14.0	0.13
				Patients (symptomatic)	60.0	78.6	2.7	0.52
				Patients (all)	66.7	84.6	4.1	0.41

CRP = C-reactive protein; DMSA = dimercaptosuccinic acid scan; US = ultrasound; VUR = vesicoureteric reflux.

(LR+ was not estimable), and in 9/33 with unilateral VUR with a sensitivity of 45%, specificity of 100% and LR– of 0.55 (LR+ not estimable). Ultrasound did not detect any defects when DMSA was normal. [EL = III]

MRI compared with DMSA scan for detecting renal parenchymal defects

A total of three studies were identified, one from the HTA search[143] and the others from the search conducted for this guideline (Table 6.10).

A systematic review identified one study evaluating the use of magnetic resonance imaging (MRI) techniques. The study used DMSA scintigraphy as the reference standard and reported results by renal units.[143]

The study evaluated three MRI sequences. Sensitivity ranged from 81% to 100% and specificity from 78% to 91%.

A further study conducted in Ireland compared DMSA scintigraphy with MRI for detecting renal parenchymal defects in 37 children (19 boys and 18 girls) aged 4 months to 13 years (mean age 4.5 years) presenting for radiological investigation after a first UTI.[253]

The sensitivity of MRI in detecting renal parenchymal defects on a kidney-by-kidney basis where each kidney was graded as normal or abnormal for renal parenchymal defects was 77%, specificity 87%, LR+ 5.92 and LR– 0.26. The sensitivity of MRI in detecting renal parenchymal defects on a zonal basis where each kidney was divided into six zones and each zone was assessed for the presence or absence of renal parenchymal defects was 75%, specificity 98%, LR+ 37.5 and LR– 0.26. [EL = Ib]

A study conducted in Turkey compared MRI with DMSA scintigraphy for localising UTI and detecting renal parenchymal defects in 20 children (15 females, 5 males).[254] Children were aged 2–14 years (mean age 7.3 ± 3.4 years) and had symptomatic UTI (including dysuria, enuresis, costovertebral pain, fever of < 37.5 °C and/or a positive urine culture). The sensitivity of MRI to demonstrate renal lesions was 91%, specificity 89%, LR+ 8.27 and LR– 0.10.

IVU compared with DMSA scan for detecting renal parenchymal defects

A systematic review identified four studies evaluating the diagnostic accuracy of IVU for detecting renal parenchymal defects using a scintigraphic technique as the reference standard

Table 6.10 MRI compared with DMSA scan for detecting renal parenchymal defects

Study	Test details; time	Definition of positive result	Reference standard; definition of positive result; time	Unit of analysis	Sensitivity	Specificity	LR+	LR–
Chan (1999)[143]	MRI (gadolinium-enhanced STIR); follow-up	Presence of renal parenchymal defect	Scintigraphy (Tc-99m-DMSA); presence of renal parenchymal defect; follow-up	Renal units	93.8%	81.3%	4.6	0.11
	MRI (STIR or T1-W); follow-up				100.0%	78.1%	4.3	0.04
	MRI (T1-W not gadolinium); follow-up				81.3%	90.6%	7.5	0.23
Kavanagh (2005)[253]	MRI	Presence of renal parenchymal defect; normal/abnormal	Scintigraphy (Tc-99m-DMSA); presence of renal parenchymal defect; not stated	Renal units	77.0%	87.0%	5.9	0.26
				Renal zones (6 zones per kidney)	75.0%	98.0%	37.5	0.26
Kovanlikaya (2004)[254]	MRI	Presence of renal parenchymal defect	Scintigraphy (Tc-99m-DMSA); presence of renal parenchymal defect; not stated	Renal units	91.0%	89.0%	8.3	0.10

DMSA = dimercaptosuccinic acid scan; MRI = magnetic resonance imaging.

(Table 6.11).[143] Only one of these studies used an appropriate spectrum of patients and this study reported sensitivity of 22% and specificity of 98%.

Acute DMSA compared with follow-up DMSA scan for detecting renal parenchymal defects

Two studies were identified to address this question. One study was included in the HTA[143] and another was identified from the search.

A study included in the HTA compared findings on acute-phase DMSA scan (mean 3.9 days from the acute episode) with presence of renal parenchymal defects on late-phase DMSA scan (mean 1.1 years from the acute episode) in 314 children. The results showed sensitivity of 55.4% and specificity of 82.3%, while LR+ was 3.1 and LR– was 0.54. [EL = III]

A study conducted in France compared a semi-quantitative uptake score on acute DMSA scintigraphy (reference standard) with a quantitative automatic index to predict renal parenchymal defects on follow-up DMSA.[255] Both the intensity and severity and the size and extent of the uptake defect were considered. Forty-three children (85 kidneys – one child had a single kidney), three boys and 40 girls, aged 11 months to 15.5 years (mean age 5.8 ± 3.6 years) with acute pyelonephritis/upper urinary tract infection and who had a DMSA performed at the acute stage were evaluated.

On the first DMSA scan, 59 kidneys were normal and 26 kidneys were abnormal. At the follow-up DMSA scan, the 59 normal kidneys remained normal and, of the 26 abnormal kidneys, 14 kidneys had improved and 12 kidneys remained unimproved.

When the intensity and severity threshold of 70% was used, a cut-off value of 0.45 was able to predict renal parenchymal defects with a sensitivity of 85% and specificity of 78%. [EL = III]

Evidence statement – renal parenchymal defects

The prevalence of renal parenchymal defects in children who have had a UTI is about 5% on both IVU and DMSA scan. There were more boys with renal parenchymal defects in first-time UTI than girls. Children who have VUR are more likely to have renal parenchymal defects than those without.

There is insufficient information about the impact of diagnostic tests on outcome for detecting renal parenchymal defects to draw any conclusions about either clinical effectiveness or cost-effectiveness. No other test (including MRI) has been found to detect more renal parenchymal defects than DMSA scans. DMSA scan has been regarded as the gold standard method for detecting renal parenchymal defects. It is the most sensitive test for the detection of renal scarring in children who have had a UTI but the long-term implications of this finding are unquantified.

Table 6.11 IVU compared with scintigraphy for detecting renal parenchymal defects

Study	Test details; time	Definition of positive result	Reference standard; definition of positive result; time	Unit of analysis	Sensitivity	Specificity	LR+	LR–
McLorie (1980)[143]	IVU; not stated	Presence of renal parenchymal defect	Scintigraphy (Tc-99m-DMSA); presence of renal parenchymal defect; not stated	Renal units	82.8%	100.0%	58.8	0.19
Merrick (1980)[143]	IVU; not stated	Not stated	Scintigraphy (Tc-99m-GH or Tc-99m-DMSA); not stated; not stated	Renal units	85.5%	100.0%	171.3	0.15
Pickworth (1992)[143]	IVU; not stated	Not stated	Scintigraphy (dynamic including micturating, Tc-99m-MAG3); presence of renal parenchymal defect or VUR; not stated	Patients	59.1%	100.0%	74.0	0.42
Stokland (1998)[143]	IVU; follow-up	Presence of renal parenchymal defect	Scintigraphy (Tc-99m-DMSA); presence of renal parenchymal defect; follow-up	Renal units	21.5%	98.0%	10.0	0.80

DMSA = dimercaptosuccinic acid scan; IVU = intravenous urogram; MAG3 = mercaptoacetyltriglycerine; VUR = vesicoureteric reflux.

6.4.5 GDG translation and recommendations for imaging tests

This chapter has clearly shown the most accurate imaging tests for assessing various aspects of the paediatric urinary tract following UTI. These are the same investigations that the RCP guidelines suggest[21] and in summary are:

- ultrasound for the structure of the urinary tract
- MCUG (or cystosonography) for the detection of VUR; indirect radionuclide cystography is a reasonable alternative for older toilet-trained children
- DMSA for the detection of renal parenchymal defects.

Although UTI is relatively common in children, affecting at least 3.6% of boys and 11.3% of girls, the risk of developing renal scars (5% on IVU and DMSA) is low and the risk that these will alter quality of life, blood pressure or renal function is much lower than this (see Section 3.3 on epidemiology). Widespread use of imaging after UTI has not led to a measurable reduction in the incidence of ERF, using data from several large national and international registries.[86] The long-term significance of a renal parenchymal defect detected on DMSA is unknown (see Section 6.1 on the long-term impact of UTI).

After reviewing the evidence for the risk of UTI leading on to ERF and the evidence for the benefit of antibiotic prophylaxis, the GDG has formed a view that routine imaging of all children after a first UTI is inappropriate because it is neither clinically effective nor cost-effective. NHS resources used for imaging after recovery from UTI in childhood should be reserved for a more targeted group of children than is currently the case.

In addition, the widespread use of antenatal ultrasound has decreased the number of infants and children who present with UTI and a significant underlying urinary tract anomaly.[27]

The most useful strategy for the reduction of morbidity from UTI in children and the prevention of acquired renal parenchymal defects is prompt diagnosis and treatment of UTI,[96] particularly in infants and young children in whom the diagnosis can easily be missed.

As the GDG is not recommending antibiotic prophylaxis following first-time UTI, even in children who have VUR, it is unnecessary to routinely evaluate for VUR by imaging (see Section 6.3). This is especially so given that the most useful tests for detecting VUR are invasive, run the risk of introducing infection and use ionising radiation (MCUG).[268] There is a subgroup of children with recurrent acute pyelonephritis/upper urinary tract infection in whom there is some evidence (see Sections 6.3 and 6.5) that imaging may specifically influence management.

The general indications for early imaging during UTI are as follows:

- failure to improve on appropriate antibiotic treatment; although there are several causes for this, early ultrasound is recommended to look for dilatation of the renal collecting system and ureters which may indicate obstruction
- the presence of an abdominal mass, poor urine flow, septicaemia or raised creatinine may indicate obstruction and early ultrasound is recommended
- tests for localisation in the rare situations where this is clinically important.

In all other circumstances, delayed imaging in line with Tables 6.13, 6.14 and 6.15 is recommended. The rationale for focusing on the subgroups who are younger than 6 months, who have had atypical illness or who have recurrent UTIs has been derived from a careful evaluation of the risks and benefits in each group as indicated in the outcomes of the case series presented earlier in this chapter and in the epidemiology section. These can be summarised as follows:

- infants presenting with UTI in the first few months of life have a higher likelihood of obstruction and major structural abnormalities than older children
- renal parenchymal defects are associated with recurrent acute pyelonephritis/upper urinary tract infection ,
- children with atypical UTI have a higher risk of significant structural abnormalities and significant renal parenchymal defects.[270]

Further imaging over and above those suggested below can be considered in unusual subgroups of children following UTI, for example where there is a strong family history of ERF, VUR and

recurrent infection which may reflect familial and genetic risk factors or because of high levels of concern within the family.

Discussion

There is no intrinsic value in carrying out imaging investigations or in the unmasking of minor renal anomalies that do not affect treatment decisions simply because a child has had a UTI. This practice does not represent a good use of NHS resources.

Furthermore, if future studies confirm the view that routine use of imaging and prophylaxis are of no benefit to healthy children after first-time uncomplicated UTI but bear significant risks and costs, economic modelling will not be required to show that a reduction in routine imaging is a cost-effective change in management of children who have recovered from a UTI.

Timing of DMSA scan

There were no good studies addressing the optimum timing for DMSA scan to demonstrate long-term renal damage. Changes of acute pyelonephritis/upper urinary tract infection have been described in the section on localisation (Section 4.7). Longitudinal studies showed changes in renal parenchymal defects over time. Most of the studies that described the timing of DMSA scans to detect renal parenchymal defects stated that they had been carried out after 3 months or more. There is a possibility that conducting DMSA scans too early would pick up clinically insignificant renal parenchymal defects (acute changes). There is also a possibility of losing the connection between the acute episode and the DMSA findings if the DMSA scan is conducted too late. Therfore the GDG has recommends that this test should usually be carried out at between 4 and 6 months. The long-term significance of persistent renal parenchymal defects seen on DMSA scans is unknown.

Recommendations

Infants and children with atypical UTI (see Table 6.12) should have ultrasound of the urinary tract during the acute infection to identify structural abnormalities of the urinary tract such as obstruction as outlined in Tables 6.13, 6.14 and 6.15. This is to ensure prompt management.

Table 6.12 Definitions of atypical and recurrent UTI

Atypical UTI includes:
- seriously ill (for more information refer to 'Feverish illness in children' (NICE clinical guideline 47)
- poor urine flow
- abdominal or bladder mass
- raised creatinine
- septicaemia
- failure to respond to treatment with suitable antibiotics within 48 hours
- infection with non-*E. coli* organisms.

Recurrent UTI:
- two or more episodes of UTI with acute pyelonephritis/upper urinary tract infection, or
- one episode of UTI with acute pyelonephritis/upper urinary tract infection plus one or more episode of UTI with cystitis/lower urinary tract infection, or
- three or more episodes of UTI with cystitis/lower urinary tract infection.

For infants aged younger than 6 months with first-time UTI that responds to treatment, ultrasound should be carried out within 6 weeks of the UTI, as outlined in Table 6.13.

For infants and children 6 months or older with first-time UTI that responds to treatment, routine ultrasound is not recommended unless the infant or child has atypical UTI, as outlined in Tables 6.14 and 6.15.

Infants and children who have had a lower urinary tract infection should undergo ultrasound (within 6 weeks) only if they are younger than 6 months or have had recurrent infections.

A DMSA scan 4–6 months following the acute infection should be used to detect renal parenchymal defects as outlined in Tables 6.13, 6.14 and 6.15.

If the infant or child has a subsequent UTI while awaiting DMSA, the timing of the DMSA should be reviewed and consideration given to doing it sooner.

Routine imaging to identify VUR is not recommended for infants and children who have had a UTI, except in specific circumstances as outlined in Tables 6.13, 6.14 and 6.15.

When micturating cystourethrogram (MCUG) is performed, prophylactic antibiotics should be given orally for 3 days with MCUG taking place on the second day.

Infants and children who have had a UTI should be imaged as outlined in Tables 6.13, 6.14 and 6.15.

Table 6.13 Recommended imaging schedule for infants younger than 6 months

Test	Responds well to treatment within 48 hours	Atypical UTI[a]	Recurrent UTI[a]
Ultrasound during the acute infection	No	Yes[c]	Yes
Ultrasound within 6 weeks	Yes[b]	No	No
DMSA 4–6 months following the acute infection	No	Yes	Yes
MCUG	No	Yes	Yes

[a] See Table 6.12 for definition.
[b] If abnormal consider MCUG.
[c] In an infant or child with a non-*E. coli* UTI, responding well to antibiotics and with no other features of atypical infection, the ultrasound can be requested on a non-urgent basis to take place within 6 weeks.

Table 6.14 Recommended imaging schedule for infants and children 6 months or older but younger than 3 years

Test	Responds well to treatment within 48 hours	Atypical UTI[a]	Recurrent UTI[a]
Ultrasound during the acute infection	No	Yes[c]	No
Ultrasound within 6 weeks	No	No	Yes
DMSA 4–6 months following the acute infection	No	Yes	Yes
MCUG	No	No[b]	No[b]

[a] See Table 6.12 for definition.
[b] While MCUG should not be performed routinely it should be considered if the following features are present:
- dilatation on ultrasound
- poor urine flow
- non-*E. coli* infection
- family history of VUR.

[c] In an infant or child with a non-*E. coli* UTI, responding well to antibiotics and with no other features of atypical infection, the ultrasound can be requested on a non-urgent basis to take place within 6 weeks.

Table 6.15 Recommended imaging schedule for children 3 years or older

Test	Responds well to treatment within 48 hours	Atypical UTI[a]	Recurrent UTI[a]
Ultrasound during the acute infection	No	Yes[b c]	No
Ultrasound within 6 weeks	No	No	Yes[b]
DMSA 4–6 months following the acute infection	No	No	Yes
MCUG	No	No	No

[a] See Table 6.12 for definition.
[b] Ultrasound in toilet-trained children should be performed with a full bladder with an estimate of bladder volume before and after micturition.
[c] In a child with a non-*E. coli* UTI, responding well to antibiotics and with no other features of atypical infection, the ultrasound can be requested on a non-urgent basis to take place within 6 weeks.

For advice on use of DMSA scan in localising UTI, see Chapter 4.

Research recommendations

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.

Further research on MRI for localising UTI could be considered.

6.5 Surgical intervention for VUR

Introduction

Children with VUR have traditionally been considered to be more likely to get UTI, and to have an increased risk of developing renal damage. Therefore in every child where it was diagnosed, VUR was corrected with re-implantation surgery. An alternative treatment with antibiotic prophylaxis was then developed with the aim to keeping the child free from infections until the VUR resolved or the risk of developing new renal parenchymal defects diminished.

The spontaneous resolution of VUR has been clearly described, with the large majority of VUR disappearing but sometimes taking 10 years to do so. During the past decade, with the advent of prenatal diagnosis of kidney malformations, it has become clear that a significant proportion of the kidney damage seen in relation to VUR is congenital and part of the same malformation as the VUR.

Diagnosis of VUR is most often by MCUG requiring catheterisation which is unpleasant for children and their parents/carers, carries iatrogenic risks and exposes the child to radiation. The American Academy of Paediatrics Committee[257] recommends an MCUG for all children aged 2 months to 2 years after a first-time febrile UTI, under the assumption that prophylaxis and/or surgical intervention are beneficial to children who are found to have VUR.

Prophylactic antibiotics have not been shown to reduce the number of recurrent infections and can lead to bacterial resistance. Parents/carers and children can also be non-compliant (see Section 6.3 above on antibiotic prophylaxis).

Current indications for surgery in the UK are symptomatic breakthrough UTIs despite medical management and/or increased renal parenchymal defects. Surgical interventions incur the risk of anaesthetic and postoperative complications. The open cross trigonal ureteric advancement procedure devised by Cohen remains the favoured operation because of its greater than 95% success rate and low incidence of postoperative ureteric obstruction, but it does require bladder drainage post-operatively.[258] The extravesical antireflux operation originally described by Lich and Gregoir is another open procedure, unsuited to dilated ureters and, as with the Cohen procedure, may require up to a week in hospital.

A recent development is the submucosal Teflon injection (STING),[259] which is the endoscopic treatment of VUR. This involves an injection of a substance, initially Teflon but now most often Deflux (a polymer of dextran), under the bladder mucosa in the base of the refluxing ureteric orifice. Successful correction of VUR with a single injection is reported as 75%, and can be done as a day case.

The economic and psychological costs of both diagnosing and treating VUR are considerable. The rationale for diagnosing and treating VUR in children who have had UTI has therefore recently come into question.

Clinical question

How does surgical management of VUR compare with conservative management?

Review findings – treatment options for VUR

A systematic review[235] evaluated the benefits and harms of various treatment options for primary VUR. Seven studies were identified comparing the effectiveness of long-term antibiotic prophylaxis for 1–24 months and ureteric re-implantation by surgery.

Antibiotic prophylaxis versus surgical management (outcome of UTI)

Seven trials compared prophylaxis with surgical management with the outcomes of UTI. The frequency of recurrent UTI ranged from 0% to 42% in the antibiotic-only group and from 20% to 22% in the surgical management group.

By 2 years there was no reduction in the risk of UTI in the surgical management versus the antibiotic-only group (RR 1.07; 95% CI 0.55 to 2.09). By 5 years there were no significant differences in the risk of UTI between the groups (RR 0.99; 95% CI 0.79 to 1.26).

The risk of febrile UTI reported by the European and US arms of the International Reflux Study was significantly lower in the surgical management group (8–10%) than in the antibiotic-only group (22%) (RR 0.43; 95% CI 0.27 to 0.70). The overall incidence of symptomatic UTI (reported only by the European arm) showed no significant difference between the groups (RR 0.95; 95% CI 0.67 to 1.35)

Antibiotic prophylaxis versus surgical management (outcome of renal parenchymal abnormality)

Seven trials compared prophylaxis with surgical management with the outcomes of renal parenchymal abnormality (Table 6.16).

The risk of renal parenchymal abnormality at 5 years using DMSA was investigated in the European arm of the International Reflux Study, where no evidence of differences were found between the antibiotic-only group and the surgical management group (RR 0.97 95% CI 0.58 to 1.62).

The European and US arms differentiated between renal parenchymal defects and renal parenchymal thinning on IVU. There was no evidence of differences at 5 years (RR 1.28; 95% CI 0.84 to 1.94) or at 10 years (RR 0.90; 95% CI 0.46 to 1.75).

Evidence statement

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.

GDG translation

The available evidence was both poor quality and limited hence the recommendations were formulated by consensus through the clinical expertise of the GDG members based on limited available evidence. Several international trials are currently underway comparing the outcomes of the STING in high-grade dilating VUR with prophylaxis and placebo (and some may also have an open surgical group). One RCT was identified comparing endoscopic submucosal ureteric injection (STING) with prophylaxis. Studies evaluating the long-term benefits of the STING are pending but in children where surgical treatment of VUR is judged to be necessary this procedure might be an option.

Recommendation

Surgical management of VUR is not routinely recommended.

Research recommendation

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.

Table 6.16 Prophylaxis versus surgery, outcome of renal parenchymal abnormality

	Duration			
	2 years		**4–5 years**	
Unit of analysis	Patients	Individual kidneys	Patients	Individual kidneys
New renal parenchymal abnormality	2 trials, RR 1.06 (95% CI 0.33 to 3.42)	2 trials, RR 1.03 (95% CI 0.31 to 3.37)	4 trials, RR 1.09 (95% CI 0.79 to 1.49)	2 trials, RR 0.85 (95% CI 0.24 to 3.09)
Progressive abnormality	1 trial, RR 7.00 (95% CI 0.45 to 108.26)	2 trials, RR 1.56 (95% CI 0.24 to 10.08)	3 trials, RR 0.99 (95% CI 0.69 to 1.42)	2 trials, RR 0.84 (95% CI 0.50 to 1.41)
Total new and progressive	1 trial, RR 9.00 (95% CI 0.61 to 133.08)	2 trials, RR 1.54 (95% CI 0.24 to 9.95)	3 trials, RR 1.05 (95% CI 0.85 to 1.29)	2 trials, RR 0.84 (95% CI 0.53 to 1.34)

6.6 Follow-up

Introduction

Historically, follow-up has played an important part in the understanding of the natural history and effects of various forms of management of UTI, VUR and renal damage.

The concept of follow-up for children with urine infection emerged following the discovery that many children who have had UTI had recurring UTIs and underlying renal and urological anomalies. These included characteristic focal renal parenchymal defects or small kidneys seen on IVU and VUR seen on MCUG. Progression of renal parenchymal defects was observed on serial imaging. Some cases, particularly those with bilateral renal parenchymal defects or small kidneys, developed significant hypertension and renal impairment. These conditions had serious implications for morbidity and mortality in later childhood and adult life. Pregnancies complicated by acute pyelonephritis/upper urinary tract infection, hypertension, proteinuria and anaemia were also reported. The presence of proteinuria persisting after resolution of acute infection is a marker for chronic and progressive kidney disease. Children rarely have proteinuria in the absence of fever and the presence of more than 20 mg/mmol (protein creatinine ratio) may be significant.

Follow-up appointments were used for a range of strategies including:

- organisation and explanation of imaging tests and conveying the results
- advice on diagnosis and treatment of recurrent UTI
- screening the urine for covert infection
- advice on prevention of recurrence
- management of prophylaxis
- reinforcing advice and preventative strategies
- advice on the risks and consequences of renal parenchymal defects and monitoring the presence of VUR by sequential imaging
- referral for surgery to correct VUR if medical management failed
- advice on familial renal disease including VUR
- blood pressure monitoring for children with renal anomalies
- assessment of renal function and proteinuria as markers of chronic kidney disease (CKD)
- a need to understand the natural history of this condition
- a need to understand the effects of various interventions.

The exact details of follow-up varied with time, place, access to imaging and individual preference.

Modern health care takes a more focused approach, giving patients and families more information and choice, devolving care locally whenever possible, minimising interventions to those that have been shown to be effective as far as possible, and having a more formal and structured approach to research.

However careful the follow-up, it cannot ensure prompt treatment of recurrent infection as this rarely occurs at the time of a routine clinic appointment. The patient, primary care system and local hospital all need to be involved in the process of recognising the symptoms, establishing the diagnosis and ensuring prompt treatment.

The role of this section is to draw on the evidence of this guideline to consider what follow-up is worthwhile and what is no longer appropriate. It is also complementary to the advice of the Renal National Service Framework (NSF), which recommends that patients with CKD should receive appropriate follow-up and assessment. This includes any child with a congenital or acquired renal parenchymal defect. The potential benefits of such follow-up need to be set in perspective against other more common, potentially preventable but serious health problems.

Clinical questions

What are the indications for follow-up?

What follow-up assessments are required for children with damaged kidneys?

Overview of available evidence

There was no direct evidence to address any particular follow-up strategies for children who have had UTI. The evidence from all systematic reviews undertaken in this guideline was used.

GDG translation

Giving advice and information has been a major part of the follow-up process. Follow-up may not be necessary if advice has already been given in a written format.

The use of follow-up to order and explain imaging tests and impart the results is largely inappropriate in the light of the reduction of imaging tests proposed. When imaging is indicated, in the majority of cases, this information can be provided both verbally and in writing at the time of diagnosis and treatment of the acute infection. Normal results can be explained by letter.

When an abnormality is detected or a child has CKD, the child and family may benefit from a discussion with an appropriate paediatric specialist to explain the condition and any associated risks in more detail. Suitable long-term arrangements should be made, such as monitoring within primary or secondary care.

Children who have recurrent infections may benefit from specialist advice and management to reduce the risk of recurrence. Recurrent attacks of acute pyelonephritis/upper urinary tract infection are of particular concern. Some families are particularly anxious because of a family history of VUR or other serious renal problems and need sufficient time combined with accurate information about the condition and its mode of inheritance.

Recommendations

Infants and children who do not undergo imaging investigations should not routinely be followed up.

The way in which the results of imaging will be communicated should be agreed with the parents or carers or the young person as appropriate.

When results are normal, a follow-up outpatient appointment is not routinely required. Parents or carers should be informed of the results of all the investigations in writing.

Infants and children who have recurrent UTI or abnormal imaging results should be assessed by a paediatric specialist.

(See recurrence section earlier in this chapter)

Assessment of infants and children with renal parenchymal defects should include height, weight, blood pressure and routine testing for proteinuria.

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.

Infants and children who have bilateral renal abnormalities, impaired kidney function, raised blood pressure and/or proteinuria should receive monitoring and appropriate mamagement by a paediatric nephrologist to slow the progression of chronic kidney disease.

Infants and children who are asymptomatic following an episode of UTI should not routinely have their urine re-tested for infection.

Asymptomatic bacteriuria is not an indication for follow-up.

7 Information and advice to children, young people and parents/carers

Introduction

Urinary tract infection is a common bacterial infection which often causes illness in infants and young children. For some young people this may continue into adulthood.

Urinary tract infection is sometimes regarded as unimportant. However, a severe infection can make a child extremely unwell and may sometimes have serious consequences, and even minor infections can be distressing.

Awareness of childhood urinary tract infection in the general population and its symptoms and signs is key to reducing the risk associated with childhood urinary tract infections and it ensures that parents and carers act quickly and appropriately when their child is unwell by seeking help and taking their child to their GP.

Clinical question

What advice should be given to children and their parents/carers when they have had a UTI?

Review findings – parents' and carers' understanding and experiences

A study conducted in the UK assessed parents' and carers' understanding of UTI in their child and identified any delay perceived in the diagnosis, along with identifying how helpful parents/carers had found any information they had been given.[260] Fifty-two parents/carers of children younger than 2 years being investigated in one outpatient department following proven UTI between 1998 and 2000 were evaluated. All children were new referrals and were at their first clinic visit.

Eighty-seven percent of parents/carers felt that they had been given an explanation about the need to test for UTI. Fifty-two percent received a leaflet about childhood UTIs and all parents/carers who received a leaflet found it helpful. Forty percent of parents/carers felt that clean catch was the easiest method for collecting urine from their child, while 37% used urine collection bags and 23% used urine collection pads.

Content analysis of the qualitative data identified some key themes:

- **Delays in requesting urine samples** – some parents/carers felt there had been a delay between their child becoming unwell and a urine sample being requested.
- **Difficulties in urine collection** – mainly around bag collection methods which some parents/carers said produced unnecessary discomfort for their child, while others felt it was difficult to keep the bag in place.
- **Information** – some parents/carers were happy with the information they received, however, the majority requested more information and more detailed advice.
- **Empowering** – following the initial event, parents/carers in this study seemed to understand more about the diagnosis and felt in a better position to deal with future episodes of UTI in their children. Some parents/carers suggested that their experience taught them what to do in the future.
- **Organisational problems** – a number of parents/carers expressed frustration at organisational aspects in terms of limited GP resources in the weekend, several hospital appointments for investigations and receiving different information from different healthcare professionals. [EL = 3]

In one UK study, parents of children aged 1–18 months volunteered to collect urine at home by pads, bags and clean catch in a randomised order, on one day.[155] Forty-four parents attempted collections (29 boys, median age 4 months, range 1–18 months). No samples were obtained from one baby with diarrhoea, and no other child had a urine infection. Parents found the pads and bags easy to use and preferred them to clean catch collections for both sexes. The pad was considered comfortable whereas the bag was distressing, particularly on removal, often leaking and leaving red marks. Some found extracting the urine from the pad or emptying it from the bag to be awkward. Most parents complained that clean catch collections were time-consuming and often messy; nine gave up after prolonged attempts. Five parents whose infants voided immediately ranked it best. The median collection time was 25 minutes for each method but parents resented constraining their children this long for clean catch collections. [EL = 3]

GDG translation

Key issues

Because urinary tract infection is a common illness for many children, advice needs to be given to all parents and carers, children and young people equally, in much the same way as other advice is given on common childhood illnesses such as measles, chickenpox and meningitis.

The best time to provide advice to parents/carers is while their child is still very young and being seen regularly by a midwife, health visitor and/or GP. This will ensure that parents/carers are made aware of the symptoms and signs to look for and that they act quickly and appropriately. Professional childcarers should also be made aware of the symptoms and signs of childhood urinary tract infections and the need to ensure that the child in their care receives prompt treatment.

Children and young people themselves should also be able to access information in a format they can understand.

Information considerations should include:

- age-appropriate format
- in appropriate language (plain English or in an appropriate foreign language)
- comprehensive advice regarding appropriate treatment choices
- providing an advice sheet about childhood urinary tract infection in antenatal/postnatal information
- information should be accessible to parents/carers, children and young people with additional needs such as physical, sensory and/or learning disability, and to parents/carers, children and young people who do not speak or read English
- where advice can be accessed – hospital, GP surgery, school, youth club, nursery, playgroup, etc.
- clear explanatory diagrams should be included.

Advice/information should be given on:

- symptom recognition and testing:
  - what the signs/symptoms of urinary tract infection are in the various age groups
  - when to seek medical help
  - how to collect urine samples
  - types of tests used to establish a urine infection.
- treatment options:
  - information should be provided which covers treatment in a clear and comprehensible way for all individuals
  - parents/carers, children and young people should be able to understand the type of treatment necessary, having been partners in the decision-making process, and being enabled to make appropriate choices fully aware of all the options.
- prevention – general advice on what a urinary tract infection is, how common it is and 'best practice' for prevention
- investigations – if any urinary tract investigations are considered, it is necessary to explain to children, young people and parents/carers:
  - the reason(s) for investigations
  - the details and practical aspects of the investigation(s) proposed
  - how the results will be given.

- prognosis – information to children, young people and parents/carers needs to include:
  - risk of recurrent UTI, how to recognise it and what to do
  - risk of renal or urinary tract abnormality
  - the implications of any abnormalities found
  - the reason for long-term follow-up if required.

A good foundation is the *Understanding NICE Guidance* (UNG) document, which provides information for parents, carers, children and young people about what NICE has said. It is available to download from the NICE website (www.nice.org.uk/CG054) or printed copies can be ordered by phoning the NHS Response Line on 0870 1555 455 (quote reference number N1305).

Understanding NICE Guidance can also be used as a starting point for writing a document reflecting more local practice.

Recommendations

Healthcare professionals should ensure that when a child or young person has been identified as having a suspected UTI, they and their parents or carers as appropriate are given information about the need for treatment, the importance of completing any course of treatment and advice about prevention and possible long-term management.

Healthcare professionals should ensure that children and young people, and their parents or carers as appropriate, are aware of the possibility of a UTI recurring and understand the need to seek prompt treatment for any suspected reinfection.

Healthcare professionals should offer children and young people and/or their parents or carers appropriate advice and information on:

- prompt recognition of symptoms
- urine collection, storage and testing
- appropriate treatment options
- prevention
- the nature of and reason for any urinary tract investigation
- prognosis
- reasons and arrangements for long-term management if required.

8 Economic evaluation of management of UTI

Diagnosis and treatment of UTI in the short and long term

Published evidence

A systematic review of the economic evidence relating to the diagnosis and treatment of urinary tract infections was identified as part of a health technology assessment (HTA) on the diagnosis and management of UTI.[143] The review identified only one study that met the inclusion criteria for economic evaluations. The review concluded that the findings of this one study were of limited value for the NHS setting as results were not expressed in quality-adjusted life years (QALYs), some parameter estimates were based on data from the USA and may not be valid in the context of the NHS, probabilistic sensitivity analysis for exploring uncertainty was not undertaken and it did not consider the full range of diagnostic strategies available in an NHS setting. However, the economic model identified in the review did provide a basis for developing the subsequent economic model developed specifically for the health technology assessment.

The cost-effectiveness model developed for the health technology assessment attempted to identify the optimal strategy for the diagnosis and treatment of UTI in the NHS to prevent long-term complications believed to be associated with the illness. It should be noted from the outset that this economic model was based on clinical evidence of the risk of developing established renal failure (ERF) that is now considered to be out of date by the Guideline Development Group (GDG) and on specific assumptions which are not accepted as correct by the GDG (see discussion below). Therefore the economic model is described here to provide an account of the economic evidence which has been developed in the UK to date, although the GDG did not consider it to be adequate to support decision making. An update of the economic model to include more recent clinical evidence (specifically on the risk of ERF) and more realistic assumptions was considered for this guideline. However, because it was not possible to estimate the true risks of ERF, it was not possible to produce a more up-to-date economic model at this time.

The economic model developed specifically for the HTA examines the health outcomes and costs for a range of diagnosis and treatment strategies over the long term. Health outcomes in the model are expressed in terms of decrements in a patient's quality-adjusted life expectancy, with costs estimated from an NHS perspective and discounted in line with NICE technical guidance (6% for costs). Probabilistic sensitivity analysis was undertaken to explore the uncertainty in the values used in the model.

Data used in the HTA economic model

Where possible, data used in the model were taken from the results of meta-analysis of published clinical studies, although in some cases where such evidence was not available, values were estimated from alternative sources. The prevalence of laboratory-proven infection in children presenting with symptoms suggestive of a UTI was estimated at 22.9%, although this number is highly variable between studies, and for the prevalence of vesicoureteric reflux (VUR) in children who have had UTI was estimated at 28.8%. The short-term model also includes estimates for the performance of diagnostic tests, performance of imaging techniques and costs and effects of illness and treatment. In addition, the long-term model includes estimates of recurrence of UTI, the likelihood of pyelonephritic scarring and ERF, and the costs and effects of illness and treatment.

The model considers 79 diagnostic strategies, based on the evidence for diagnostic test performance. The only sequential testing considered is where the second test was considered as a

reference standard (laboratory culture for UTI, MCUG for VUR). Options to treat none (with no diagnostic test) and treat all (with no diagnostic test) were considered, as were strategies to treat all children with antibiotics while undertaking alternative imaging tests for VUR, but no tests for UTI. Other combinations include dipstick urine tests followed by laboratory cultures, imaging tests or both.

Health outcomes in the model are presented as decrements in QALYs, from a baseline value of full health, that are the result of the initial UTI as well as the development of ERF after having had a UTI. Costs are taken from published studies with relevant UK costs (for 2003), other published sources such as the *British National Formulary* or from NHS service providers.

Discussion of the HTA model

The authors presented their results in terms of net monetary benefit (NMB). This allows for the expected costs and benefits (measured in decrements in QALYs) to be compared using a standard unit of measurement, in this case monetary value, when given the maximum willingness-to-pay (WTP) per QALY. The expected NMB is calculated as the expected total number of QALYs generated multiplied by the WTP per QALY; the expected costs of the strategy are then subtracted from this figure. For example, when the WTP for an additional QALY is zero, the NMB is equal to the expected cost subtracted from zero. The strategy with the greatest NMB at a given level of WTP is then identified as the cost-effective strategy.

The results of the model are highly dependent on two factors: the characteristics of the cohort modelled (sex and age) and the WTP of the provider. As the maximum WTP per QALY is not known, sensitivity analysis using estimates ranging from £0 to £50,000 (in increments of £1,000) was undertaken to estimate the cost-effective strategy at each value. Additionally, owing to uncertainty in the value of model parameters, further analysis was undertaken to estimate the likelihood that a given strategy would be the cost-effective strategy. Results are presented in Tables 8.1 and 8.2.

The model consists of a short-term and long-term element. The short-term element considers the optimal diagnostic strategy for UTI and VUR, while the long-term element considers the cost and quality of life decrement for children depending upon down which path of the decision tree they proceed. Assumptions used in the short- and long-term models were discussed at length by the

Table 8.1 Strategies with greatest net monetary benefit reported in the HTA[143] for the diagnosis and treatment of UTI in children at a threshold willingness-to-pay of £20,000 per QALY, by age and sex; the probability that the strategy is optimal is given in parentheses

Age	Boys	Girls
< 1 year	Nitrate, AND leucocyte followed by MCUG (0.274)	Nitrate OR Leucocyte positive, plus lab culture, followed by MCUG (0.169)
1 to < 2 years	Nitrate, AND leucocyte followed by MCUG (0.22)	Nitrate, AND leucocyte followed by MCUG (0.296)
2 to < 3 years	Treat all, no diagnostic test (0.755)	Nitrate, AND leucocyte followed by MCUG (0.213)
> 3 years	Treat all, no diagnostic test (0.79)	Treat all, no diagnostic test (0.722)

Table 8.2 Strategies most likely to be cost-effective reported in the HTA[143] at a threshold willingness to pay of £20,000 per QALY, by age and sex; the probability that the strategy is optimal is given in parentheses

Age	Boys	Girls
< 1 year	Treat all, no diagnostic test (0.398)	Nitrate, AND leucocyte, followed by MCUG (0.254)
1 to < 2 years	Treat all, no diagnostic test (0.532)	Nitrate, AND leucocyte, followed by MCUG (0.296)
2 to < 3 years	Treat all, no diagnostic test (0.755)	Treat all, no diagnostic test (0.315)
> 3 years	Treat all, no diagnostic test (0.79)	Treat all, no diagnostic test (0.722)

GDG in their deliberations of the evidence. The GDG had specific concerns about the applicability of the results of the model within the context of this guideline. These concerns related to:

- the level of risk assumed in the model for a first-time UTI in childhood leading to ERF
- the level of disutility inherent in the invasive tests included in some diagnostic strategies
- the wider implications of empirical antibiotic treatment, including the disutility from treatment and the development of personal and population resistance to antibiotics.

Therefore, it was the view of the GDG that, due to the use of highly questionable assumptions, the HTA model does not estimate the likely cost-effectiveness of specific management strategies for UTI in children. The GDG, however, recognised the absence of critical data to adequately update this. For these reasons, the diagnosis and treatment strategies recommended in the guideline do not reflect the results of the economic evaluation reported here.

Additional economic analysis undertaken for the guideline

The cost-effectiveness of diagnostic and treatment strategies for UTI focusing on the short term has been evaluated in adults, but not in children. The HTA examined the question of the most appropriate diagnostic and imaging tests for UTI in children.[143] This economic analysis assumed a clear relationship between urine infection, VUR and scarring and took a long-term perspective with regard to outcomes. Clinical evidence reported in this guideline suggests that the strength of the link between urine infection in childhood and ERF may be different than previously believed.

Consideration was given by the GDG to the development of a decision-analysis model to examine the cost-effectiveness of the diagnosis and treatment of UTI in children over the short term. A model was proposed for the guideline to examine the period during which the acute symptoms of a UTI may be present; that is 7 days for an uncomplicated infection and 14 days in the case of an upper urinary tract infection (acute pyelonephritis). The model was to give consideration to the following strategies for urine testing and treatment for UTI, either alone or in appropriate combinations:

- no treatment
- empirical treatment
- urine dipstick testing
- microscopic urine analysis for pyuria and/or bacteriuria
- laboratory culture of a urine sample, with or without identification of the organism.

During the development of this model, it was established that much of the data on the clinical effectiveness of the various diagnostic strategies required was either unavailable or of poor quality and that no robust results could be generated. In particular, it was difficult to find key data on the diagnostic accuracy and effectiveness of some urine tests, including microscopy and urine dipsticks, that was stratified by age in a manner that the GDG felt would be clinically useful (for full details on the evidence for urine testing and its shortcomings, refer to Section 4.6). Cost data to be used in the model that was proposed were to be taken from the previous economic analysis described above and are presented in Table 8.3. Cost data would have been adjusted for inflation where appropriate.

During the development of the guideline, it became clear that there would be insufficient data to enable a reliable estimate of the cost-effectiveness of urine testing strategies to be made. There are a number of important but highly uncertain parameters needed to populate the model and any attempt at modelling would produce highly speculative results in the absence of evidence to inform those parameters. In order to arrive at such an estimate, a model such as the one proposed would be required to examine:

- the likelihood that a child presenting with symptoms suggestive of a UTI had a genuine UTI
- the clinical effectiveness of the diagnostic tests in terms of the number of cases of UTI correctly diagnosed
- the incremental cost of each diagnostic strategy
- the incremental effectiveness of each diagnostic strategy expressed as an appropriate outcome, such as QALYs.

Synthesis of this data could then lead to an estimate of the cost-effectiveness of the strategies tested.

Costs

Table 8.3 is replicated from the HTA reported above.[143] The prices quoted are for 2003. The HTA did not report the costs of a DMSA scan. The cost of a DMSA scan is around £200–300 in 2007 (published private medical practice prices). The cost of urine collection pads and bags was obtained from the NHS Purchasing and Supply Agency in May 2007 and is reported in Table 8.4.

Table 8.3 Cost inputs into the model; adapted from Table 34 on p. 116 of the HTA[143]

Name	Details	Value (£)	Source
Diagnostic tests	Nitrite	0.13	BNF
	Leucocyte esterase	0.13	BNF
	Nitrite/leucocyte esterase	0.15	BNF
	Pyuria	8.00	Molyneux
	Bacteriuria	8.00	Molyneux
	Pyuria/bacteriuria	16.00	Molyneux
	Dipslide culture	2.60	Fenwick
	Laboratory culture	2.60	Fenwick
Imaging	Conventional ultrasound	25.84	York Hospital
	Contrast-enhanced ultrasound	124.05	York Hospital
	MCUG	124.05	York Hospital
Administration of tests	GP-administered tests (GP time)	6.77	PSSRU
	Hospital-based tests (outpatient visit)	86.00	PSSRU
Costs of treatment	Cost of low-dose long-term prophylaxis (per month)	2.43	BNF
	Cost of acute antibiotic treatment	6.58	Fenwick
	Additional cost of pyelonephritic treatment	17.26	Claxton
	Cost of UTI untreated	18.00	PSSRU
	Cost of pyelonephritic attack untreated	125.00	Claxton

The reported cost of a glucose test has been removed from the table as the reported test is not in use for this purpose in the NHS.

Table 8.4 Published price excluding VAT of urine collection pads and bags; source: NHS Purchasing and Supply Agency, 2007

Product	Price					
	1 to 99	100+	1 to 49	50+	1 to 39	40+
Baby urine collection bag 200 ml paediatric 200 ml	0.94	0.90				
Baby urine collection bag 100 ml newborn 24 hour			3.25	3.11		
Baby urine collection bag 100 ml premature sterile	1.14	1.09				
Baby urine collection bag 200 ml paediatric sterile	0.87	0.83				
Baby urine collection bag 100 ml newborn sterile	1.10	1.06				
Baby urine collection bag 100 ml paediatric 24 hour			2.65	2.53		
Baby urine collection bag 100 ml newborn sterile	1.00	0.94				
Baby urine collection bag 47 ml premature boy and girl 25 cm × 6 cm			1.23	1.15		
Baby urine collection bag 120 ml girl 25 cm × 9 cm	0.69	0.65				
Baby urine collection bag 120 ml boy 25 cm × 9 cm	0.69	0.66				
Newcastle urine collection pack 2 urine collection pads 5 ml syringe and urine specimen container					0.58	0.54

Appendix A

Declarations of interest

GDG member	Description of Interest	Industry/organisation
Joydip Banerjee	None	
Su-Anna Boddy	None	
David Grier	None	
Lyda Jadresic	None	
James Larcombe	Chapter author for UTI in children: evidence-based reviews	*British Medical Journal*
Julie Marriott	None	
Jeni Senior	None	
Kjell Tullus	None	
Kate Verrier-Jones	In 1996 paid for lecture and publication	SmithKline Beecham
	1998 Evian Health Award for leaflet for parents on diagnosis of UTIs in early childhood	Evian Water
	1997 Work with Bayer to set up a workshop on the diagnosis of UTIs in early childhood	Bayer
	2000 Support for a clinical effectiveness project on improving the diagnosis of UTIs in early childhood in primary care.	Bayer
	Seconded to NHS Connecting for Health. Dealing with clinicians and IT suppliers to develop the new electronic patient record.	National Programme for IT
	Commissioned to write a commentary on a paper about the value of micturating cystography in children who have had UTIs	*Archives of Disease in Childhood*
Sue Vernon	Attendance at the European Society of Paediatric Urology nurses meeting	Ontex
	Provided *ad hoc* advice to Ontex regarding the development of the Newcastle urine collection pads	Ontex UK
	Met with an NHS logistics authority to discuss pads.	
Craig Williams	Educational grant for microbiology meeting	Gilead Sciences
	Educational grant for website www.flemingforum.org.uk	Pfizer, MSD, bioMérieux
	Research grant	Pfizer

NCC-WCH staff	Description of Interest	Industry/organisation
Michael Corkett	None	
Rosie Crossley	None	
Anita Fitzgerald	None	
Monica Lakhanpaul	None	
Rintaro Mori	None	
Jeff Round	None	
Samantha Vahidi	None	

Appendix B

Clinical questions

What is the definition of UTI in infants and children?

What is the epidemiology of UTI in the UK?

In infants and children who have a UTI, what is the risk of (developing) scarring?

In infants and children who present with UTI, what proportion have undiagnosed structural renal tract abnormality?

In infants and children who have or develop a renal scar, what is the risk of future renal-related morbidity?

In infants and children, what are the predisposing factors for a UTI?

In infants or children, what signs or symptoms would give rise to the suspicion of UTI?

In infants and children with suspected UTI, which method of urine collection is most effective?

How should a urine sample be transported to ensure its reliability?

In infants and children with suspected UTI, which is the most diagnostically accurate urine test for detecting UTI?

In infants and children with suspected UTI, which is the most effective diagnostic test?

In infants and children with UTI, which is the most effective antibiotic treatment?

In infants and children with suspected UTI, how does oral antibiotic treatment compare with intravenous antibiotic treatment?

In infants and children with UTI, which is the most effective symptomatic treatment in addition to antibiotics?

In infants and children who have had a UTI, how effective is the use of prophylactic antibiotics?

In infants and children on prophylaxis, what are the indications for changing antibiotic?

In infants and children with suspected UTI, what is the most effective test for assessing the localisation of UTI?

In infants and children who have or have had UTI, what is the most effective test for diagnosing structural abnormality?

In infants and children who have had a UTI, what is the most effective test for detecting vesicoureteric reflux?

In infants and children who have had a UTI, what are the predictors of scarring?

In infants and children who have had a UTI, what is the most effective test for detecting scarring?

What strategies other than antibiotics are helpful in preventing recurrence?

What are the indications for follow-up?

How should infants and children with recurrent UTI be managed?

What follow-up assessments are required for children with damaged kidneys?

How does surgical management of VUR compare with conservative management?

What advice should be given to children and their parents/carers when they have had a UTI?

Appendix C

Estimated risk of ERF for children who have had UTI

It has long been assumed that the risk of a first-time childhood UTI progressing to long-term kidney damage is significant. In investigating the relationship between UTI and long-term damage, we are primarily concerned with established renal failure (ERF), as the relationship between UTI and other potential morbidities is ambiguous and, in most cases, not measurable. Whether kidney damage results from VUR alone or in combination with UTI remains uncertain.

Stark[217] has argued that the number of patients who have a single UTI in childhood who then go on to have ERF is small, and that the risk of ERF following a UTI is low. From this position, he argues that the investigations undertaken to diagnose VUR and kidney scarring in children who have experienced a first-time UTI are unwarranted. He estimates that between 10 000 and 15 000 girls would need to be investigated to prevent a single case of ERF.

Estimating risk

The assumptions used in the model developed by Stark result in a much lower risk that a first-time UTI in childhood will lead to ERF than was previously assumed. Accepting the risk presented by Stark would lead to a significant change in clinical practice in the NHS and it is important that such a change in practice be supported by robust evidence. The question that must be addressed is whether we can identify with confidence the true level of risk that a patient with a first-time UTI will develop ERF as a direct result of that infection.

In order to examine whether this is the case, a model was developed using the assumptions made by Stark to assess the risk of a first UTI in childhood leading to ERF at any time. The model is represented graphically by the Venn diagram in Figure C.1.

There is a population of patients with UTI (b+d+e+g), a population of patients with ERF (a+b+c+d) and a population of patients with pyelonephritic scarring/reflux nephropathy (b+c+e+f). The proportion of patients in which we are interested is (b+d) / (b+d+e+g) – that is, the risk of a patient developing ERF given that they have had a UTI. Using the figures given by Stark, the risk is calculated as about 1/10 000, where:

Lifetime risk of UTI (b+d+e+g) = 80 000 per million population (pmp)

Incidence of ERF (a+b+c+d) = 87 pmp

ERF attributable to pyelonephritic scarring/reflux nephropathy (b+c) = 9% (0.09)

To calculate the risk, Stark makes two key assumptions. Firstly, that in all cases of ERF attributable to pyelonephritic scarring/reflux nephropathy the patient has had a UTI (c = 0), and secondly, that pyelonephritic scarring/reflux nephropathy is the only mechanism by which UTI can lead to ERF (d = 0). The proportion of patients with pyelonephritic scarring/reflux nephropathy that do not go on to develop ERF (e+f) is not of importance. The proportion of ERF attributable to pyelonephritic scarring/reflux nephropathy, where c = 0, is

(b) × (a+b+c+d) = 0.09 × 87 pmp = 8 pmp

Therefore the risk of UTI leading to ERF, where d = 0 is:

(b) / (b+e+g) = 8 pmp / 0.08 = 100 pmp = 1/10 000

During the development of the model, questions were raised about a number of the crucial assumptions made by Stark, primarily the estimate of ERF incidence and the links between pyelonephritic scarring/reflux nephropathy and ERF and between UTI and pyelonephritic scarring/reflux nephropathy. These assumptions and their implications for the results of the model are examined below.

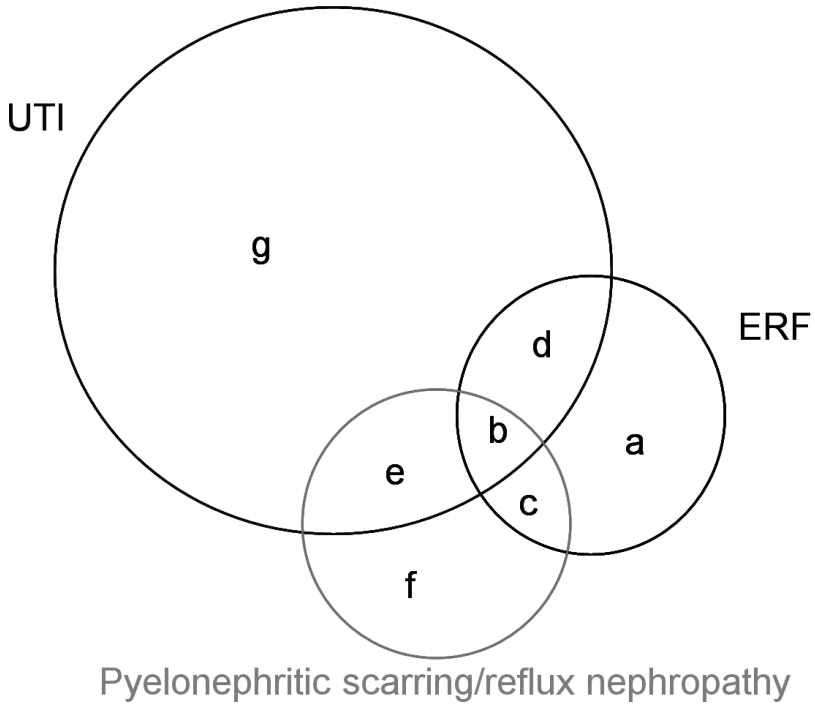


Figure C.1 Venn diagram showing associations between UTI and ERF

Estimating the incidence of ERF

Stark assumes that the statistical risk of a person developing ERF in their lifetime will be very close to the mean incidence of ERF during that person's lifetime. Rate of acceptance for renal replacement therapy (RRT) is used as proxy for the rate of ERF in the absence of accurate data on the number of people that develop ERF. In the initial analysis undertaken for the guideline, this assumption was not challenged. However, the estimate of 87 pmp used by Stark for incidence was an estimate of annual incidence and reflects not the likelihood of an individual developing ERF during their lifetime but the likelihood of them developing ERF in a given year. Annual incidence has been used where cumulative incidence was the appropriate measure.

In the absence of a reliable published estimate of the true lifetime risk of developing ERF, a table was constructed to model a cohort of 1 000 000 patients to determine the number that would develop ERF in their lifetime. Estimates of risk shown in Table C.1 are reported as annual incidence per million population for females and applied to the proportion of the cohort at risk (those who were alive and who had not already developed ERF). It is worth noting that males have a greater lifetime risk of ERF than females. The lifetime risk for males younger than 60 years is nearly 3800 pmp compared with about 2500 pmp in females. Data for females is used in this analysis to allow comparison with the previous estimate by Stark, but simply substituting the data for males, or for the total population, into the above model will alter the estimate of risk accordingly.

Table C.1 shows how the lifetime estimate of developing ERF was calculated, using data for females from the European Dialysis and Transplant Association (EDTA). The estimated lifetime risk of developing ERF from this calculation is nearly 6000 pmp. This represents a much greater risk of developing ERF than that presented by Stark, with significant implications for the model. Substituting the whole lifetime estimate based on the data from the EDTA into the formula (a+b+c+d), lifetime risk for females developing ERF as a result of having had a childhood UTI is estimated at about 1/155. The age group of interest is represented by those patients younger than 60 years, as it is believed that ERF that occurs after this age is unlikely to be attributable to a childhood UTI. In this group, the risk of developing ERF is approximately 2500 pmp. For that group of patients younger than 60 years, the risk of UTI leading to ERF is about 1/355. Estimates

of risk then range from 1/155 to 1/10 000, and the considerable uncertainty in other model parameters must also be explored to illustrate why no reliable estimate of risk can be achieved based on the available data.

The causal relationship between UTI and ERF

Uncertainty in two other key assumptions in the analyses by Stark and the GDG call into question the strength of the relationship between UTI and ERF and need to be addressed. These are the relationship between pyelonephritic scarring/reflux nephropathy and UTI, and the proportion of ERF that can be attributed to pyelonephritic scarring/reflux nephropathy. These are addressed below.

UTI and pyelonephritic scarring/reflux nephropathy

In all of the analyses presented to date it is assumed, in those cases of ERF where pyelonephritic scarring/reflux nephropathy is believed to be the cause, that all patients have also had a UTI. However, no evidence has been presented in support of this assumption. In the analysis by Stark, this assumption is not explicitly stated, although it is evident from the results. In making this assumption, the risk of a UTI leading to ERF is overestimated – in fact, if the converse is true and no patients with ERF caused by pyelonephritic scarring/reflux nephropathy had a UTI in childhood (unlikely though it is), then the risk of UTI leading to ERF is non-existent. It is not possible, based on current evidence, to estimate the true proportion of patients in whom ERF is attributed to pyelonephritic scarring/reflux nephropathy and who have had a UTI in childhood.

In the absence of a reliable estimate of this relationship, it is not possible to make a reliable estimate of overall risk. This can be illustrated using the lifetime risk data in the above table. If the proportion of pyelonephritic scarring/reflux nephropathy that is associated with UTI is assumed to be 0 the risk of UTI leading to ERF is equal to 0, although when the proportion of pyelonephritic scarring/reflux nephropathy that is associated with UTI is assumed to be 1 the risk that UTI will lead to ERF in females is 1/155. The range of risk estimates generated is so great, that in the absence of accurate data on the link between pyelonephritic scarring/reflux nephropathy and UTI, no conclusions can be drawn about the true risk of UTI leading to ERF.

Table C.1 Cumulative incidence of ERF: females (source: EDTA)

Age band	Number at start	Mortality rate per million per year	Number at end	Number at risk	Annual incidence of ERF per million	Number with ERF (new)	Cumulative ERF
0–1	1000000	4940	995060	997530	8.5	8	8
1–4	995051.5	240	994096.3	994573.9	8.5	34	42
5–9	994062.5	106	993535.6	993799	8.5	42	85
10–14	993493.4	106	992966.8	993230.1	8.5	42	127
15–19	992924.6	248	991693.4	992309	8.5	42	169
20–24	991651.2	248	990421.6	991036.4	38.2	189	358
25–29	990232.3	436	988073.6	989152.9	38.2	189	547
30–34	987884.6	436	985731	986807.8	38.2	188	736
35–39	985542.6	952	980851.4	983197	38.2	188	923
40–44	980663.6	952	975995.6	978329.6	38.2	187	1110
45–49	975808.8	2509	963567.3	969688	98.8	479	1589
50–54	963088.2	2509	951006.3	957047.3	98.8	473	2062
55–59	950533.5	5918	922407.2	936470.4	98.8	463	2525
60–64	921944.6	5918	894664.3	908304.4	98.8	449	2973
65–69	894215.6	16701	819544.1	856879.8	224.3	961	3934
70–74	818583.1	16701	750227.3	784405.2	224.3	880	4814
75–79	749347.6	51252	557319.8	653333.7	169.2	553	5367
80–84	556767.1	51252	414089.9	485428.5	169.2	411	5777

Pyelonephritic scarring/reflux nephropathy and ERF

In addition to the uncertainty around the link between UTI and pyelonephritic scarring/reflux nephropathy, there is also uncertainty over the proportion of ERF that can be attributed to pyelonephritic scarring/reflux nephropathy. Stark assumes this rate is 9%, using an approximate average of published estimates that are based on data from various renal registers, including European and the US ones. In many cases renal registry data is not classified in such a way that a reliable estimate of those cases of ERF attributable to pyelonephritic scarring/reflux nephropathy can be made. In contrast to the estimate of 9% assumed by Stark, the current proportion of ERF that is attributed to pyelonephritic scarring/reflux nephritis in the United States Renal Data System 2003 report is 0.46 per cent, or roughly one in every 200 cases of ERF. The EDTA estimates that 8% of all cases of ERF in England and Wales can be attributed to a more generic classification of pyelonephritis. It is not clear what proportion of this is pyelonephritic scarring/reflux nephropathy. The wide range of estimates for the likelihood of pyelonephritic scarring/reflux nephropathy being attributable as the cause of ERF introduces further uncertainty in the model.

This uncertainty further decreases the reliability of any estimate of the risk of UTI leading to ERF. Again, using lifetime risk data in the above table, if it is assumed that 8% of ERF cases are attributable to pyelonephritic scarring/reflux nephropathy, the risk of UTI leading to ERF is 1/155. When 0.50% of cases of ERF are attributed to pyelonephritic scarring/reflux nephropathy, then the risk is approximately 1/2800. Once again, the range is sufficiently wide to prevent a reliable estimate from being made based solely on the currently available data.

Implications

Given the degree of uncertainty around the key assumptions and data used by Stark, and in turn by the GDG, no reliable estimate of the risk of UTI leading to ERF can be calculated. It is not clear what the true rate of ERF caused by pyelonephritic scarring/reflux nephropathy is, nor is it clear what proportion of these cases have had a UTI in childhood. Without reliable estimates of these figures, as well as of lifetime risk, the level of uncertainty in the model is such that no reliable conclusions can be drawn based on the data alone.

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Notes
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All entries refer to urinary tract infections, particularly in children, unless otherwise noted. There is, therefore, no index entry for children.
Page numbers in **bold** refer to major discussions.
vs denotes comparisons.

Other NICE guidelines produced by the National Collaborating Centre for Women's and Children's Health include:

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